NICE National Institute for Health and Care Excellence

Single Technology Appraisal

daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pre-meeting briefing

Daratumumab for treating relapsed and refractory multiple myeloma after a proteasome inhibitor and an immunomodulatory agent (ID933)

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

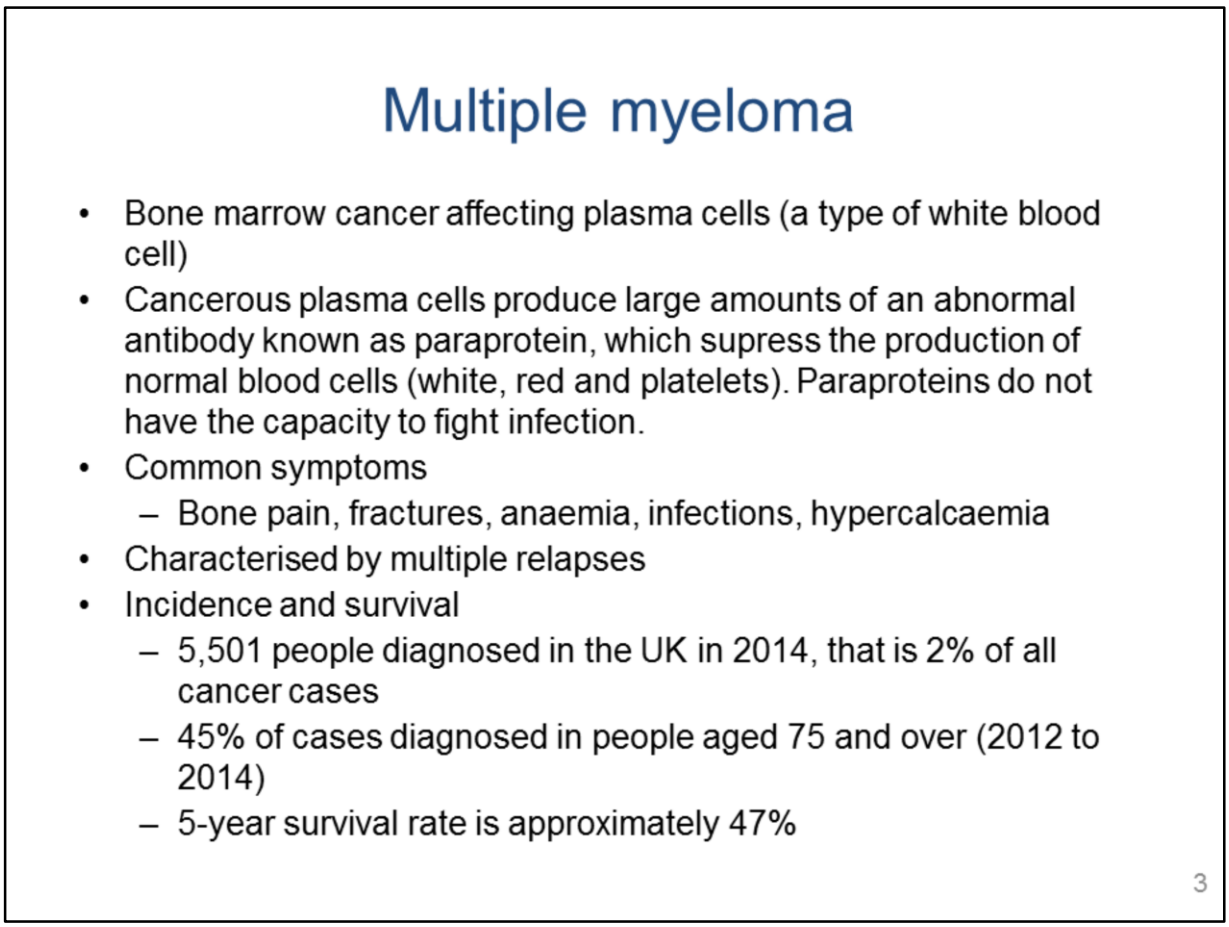
Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

Summary

- Company positions drug 4th line
- Uncertainties
  - ERG believes company's economic model not fit for purpose
  - Evidence from single arm studies phase 2 or earlier
  - ERG believes not appropriate to pool data from these 2 studies
  - Matching adjusted indirect comparison very sensitive to number and choice of covariates
  - Model does not adjust for subsequent treatments
- Innovation
  - Daratumumab monotherapy is a first-in-class drug with a manageable safety profile

2



Defining refractory and relapsed MM

This appraisal is proposed for treating MM for people with relapsed and/or refractory disease.

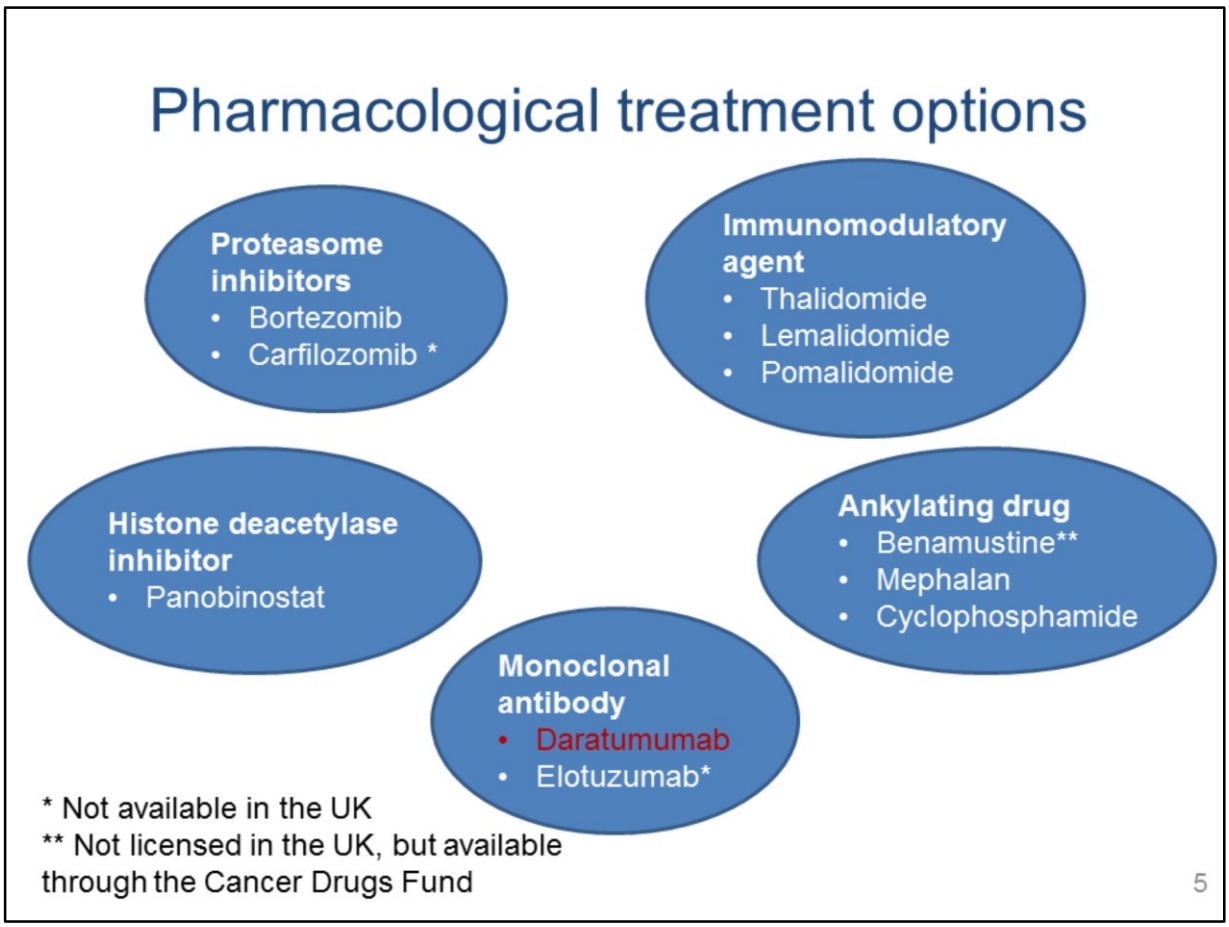
From International Myeloma Working Group - “Relapsed and refractory” myeloma is defined as progression of therapy in patients who achieve minor response (MR) or better, or who progress within 60 days of their last therapy. Relapsed myeloma is defined as disease in a myeloma patient who has previously been treated and has evidence of progressive disease as defined as a 25% increase from nadir (lowest point/count) in the serum or urine paraprotein.

Factors associated with response to treatment and/or survival

- Response declines with each successive line for treatment, age and also depends on cytogenetics
- Stage of disease – International Staging System (ISS) based on serum beta$_2$-microglobulin and albumin
- Revised criteria also include levels of serum lactate dehydrogenase and high-risk chromosomal abnormalities detected by interphase fluorescent in situ hybridization (FISH)

4

Source: Staging and prognostic studies in multiple myeloma, Rajkumar S. V. et al 2017


Pharmacological treatment options
Proteasome inhibitors
• Bortezomib
• Carfilozomib *
Immunomodulatory agent
• Thalidomide
• Lemalidomide
• Pomalidomide
Histone deacetylase inhibitor
• Panobinostat
Ankylating drug
• Benamustine**
• Mephalan
• Cyclophosphamide
Monoclonal antibody
• Daratumumab
• Elotuzumab*
* Not available in the UK
** Not licensed in the UK, but available through the Cancer Drugs Fund
5

Daratumumab (Darzalex®)

Marketing authorisation	Adults with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor (e.g. bortezomib) and an immunomodulatory agent (i.e. thalidomide analogues such as lenalidomide and pomalidomide) and who have demonstrated disease progression on their last therapy. Regulators previously granted daratumumab orphan drug status (in 2013). (n.b. FDA limits daratumumab to 4th line or later).
Mechanism	Human monoclonal antibody that binds to CD38 protein on surface of multiple myeloma tumour cells, and inhibits growth of CD38-expressing tumour cells
Administration	Intravenous infusion
Dose	• 16 mg/kg of body weight • Weekly for weeks 1 to 8; every 2 weeks for weeks 9 to 24; and every 4 weeks from week 25 onwards
Cost	Acquisition cost (excluding VAT) £360.0 for 100mg vial; £1,440.0 for 400mg vial. Average cost of a course of treatment (list price) £68,862 excluding administration costs, £74,531 including administration costs.

6

Source: company submission; pg 24 table 2; pg 29-30; pg 32 table 3

Proteasome inhibitor: blocks proteasomes from breaking down proteins (e.g. bortezomib, carfilzomib)

Immunomodulatory agent: can modify or regulate immune functions, reduce growth of myeloma cells (e.g. thalidomide, revlimid, pomalidomide)

Patient and professional feedback

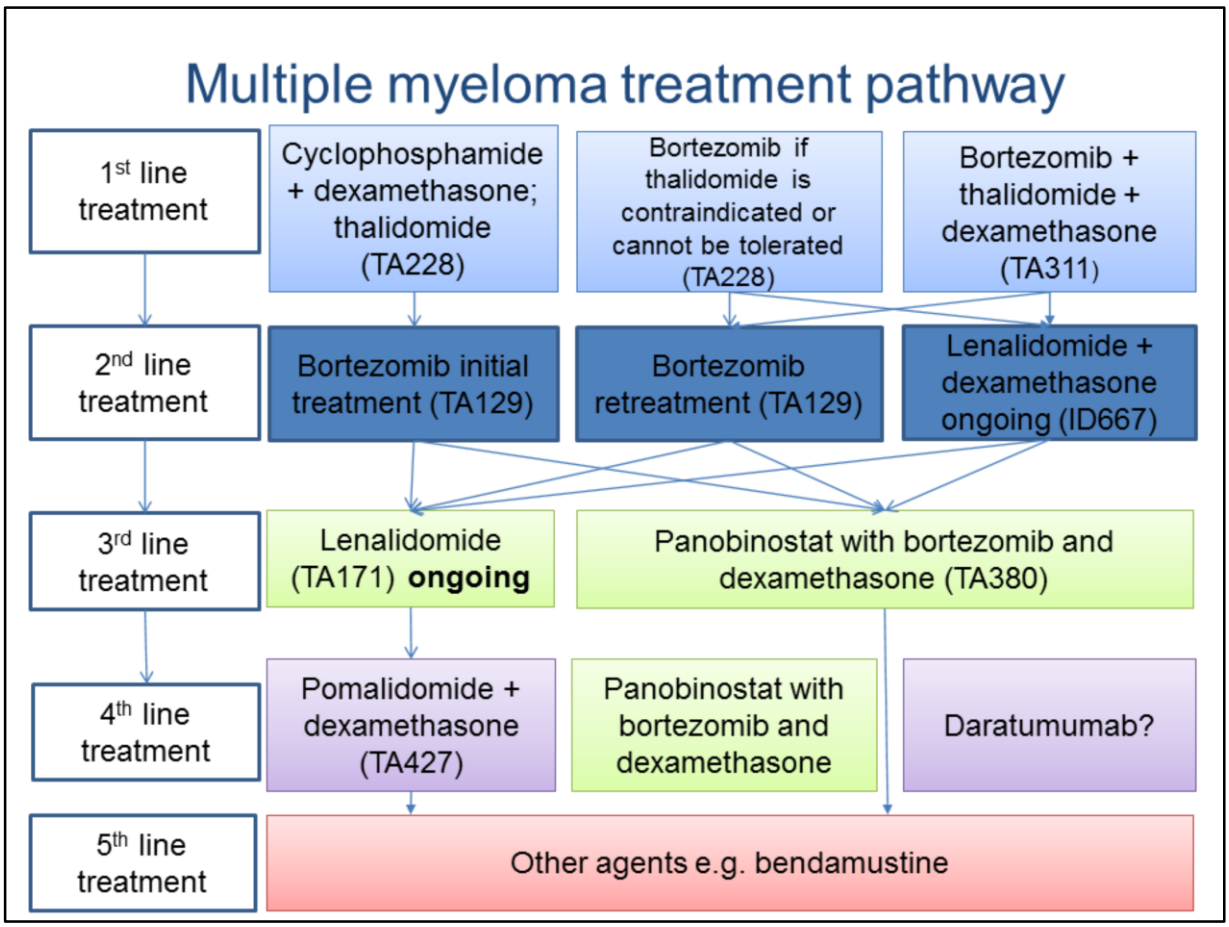
- Daratumumab improves length of survival and quality of life for people whose disease previously has not responded to treatment
- Treatment options are limited for relapsed and refractory multiple myeloma
- Over time, disease becomes resistant to treatment and this has a big impact on physical and emotional wellbeing
- Carers' emotional wellbeing, social life, work life are impacted and this can be greater for those caring for people with relapsed and refractory disease
- Treatment is administered similarly to other monoclonal antibody therapies and severe reactions to treatment are uncommon
- Treatment administered intravenously requires time in hospital and may require an overnight stay for the first infusion
- Lenalidomide + dexamethasone is not used past third-line therapy in current practice and so is not an appropriate comparator

7

Comments from consultees

This section summarises comments from:

- Myeloma UK
- UK Myeloma Forum



Adapted from TA311 – previously untreated MM

The company placed daratumumab as a forth line therapy in line with the use in the available trial data, based on a heavily pre-treated population, 98% received lenalidomide and 84% were refractory to lenalidomide. The MA for daratumumab does not specify the line of treatment, it could be used earlier in the treatment pathway.

Panobinostat + bortezomib + dexamethasone is recommended as 3rd line in TA380, the company's submission states that due to toxicity concerns in current practice it is most commonly used as a 4th line therapy.

Decision problem - population

NICE scope	Company submission	Company justification for difference
People with relapsed and refractory multiple myeloma that has previously been treated with a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy	Same as NICE scope. Daratumumab monotherapy as a treatment for people who have received 3 or more prior therapies.	Available trial data for daratumumab monotherapy.

9

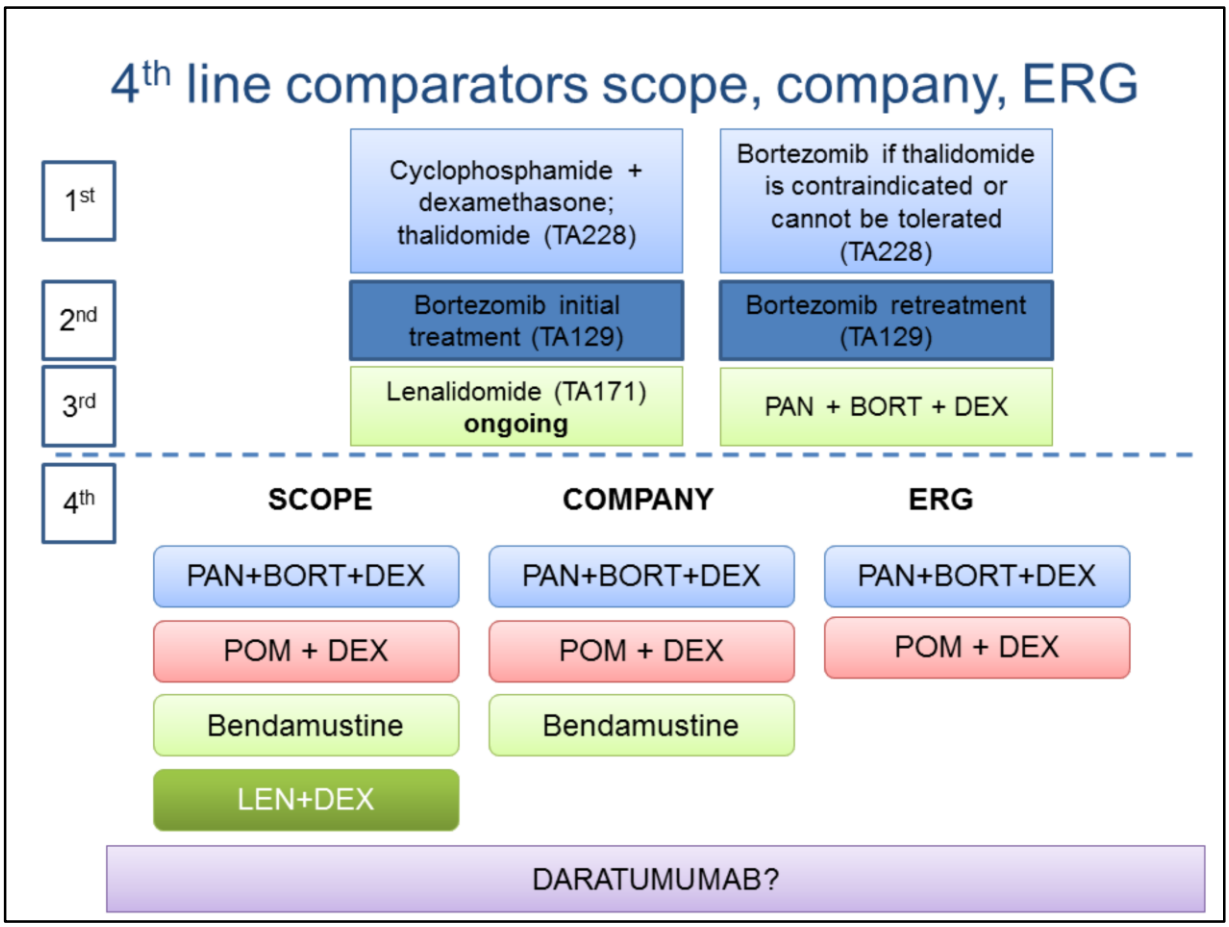
Source: Company submission pg 22 table 1

Decision problem – comparators

Lenalidomide plus dexamethasone not included in submission

NICE scope	Company submission	Company justification for difference
1. Panobinostat with bortezomib and dexamethasone 2. Pomalidomide with dexamethasone 3. Bendamustine (not appraised by NICE but funded via the Cancer Drugs Fund; no marketing authorisation in the UK for this indication) 4. Lenalidomide with dexamethasone	1. Panobinostat with bortezomib and dexamethasone 2. Pomalidomide with dexamethasone 3. Bendamustine (not appraised by NICE but funded via the Cancer Drugs Fund; no marketing authorisation in the UK for this indication)	• In current practice, LEN + DEX is used earlier in the treatment pathway (i.e. third-line) • Trial data for LEN+DEX is based on use earlier in the treatment pathway compared with trial data for daratumumab
ERG comments		
• LEN +DEX is not a comparator – used earlier than 4th line • Unlikely that bendamustine would be used in preference to daratumumab		

10


4th line comparators scope, company, ERG
1st
Cyclophosphamide + dexamethasone; thalidomide (TA228)
Bortezomib if thalidomide is contraindicated or cannot be tolerated (TA228)
2nd
Bortezomib initial treatment (TA129)
Bortezomib retreatment (TA129)
3rd
Lenalidomide (TA171) ongoing
PAN + BORT + DEX
4th
SCOPE
COMPANY
ERG
PAN+BORT+DEX
PAN+BORT+DEX
PAN+BORT+DEX
POM + DEX
POM + DEX
POM + DEX
Bendamustine
Bendamustine
LEN+DEX
DARATUMUMAB?

Decision problem – outcomes

Definition of time to treatment discontinuation unclear

NICE scope	Company submission
• Progression-free survival • Overall survival • Response rates • Time to next treatment • Adverse effects of treatment • Health-related quality of life	• Progression-free survival • Overall survival • Response rates • Time to next treatment • Adverse effects of treatment • Health-related quality of life • Time to treatment discontinuation
ERG comments	
• Time to treatment discontinuation estimated post hoc using patient-level data from MMY2002 and GEN501 • The estimation of TTD lacks transparency and clarity • Using these data in the model carries 'potentially high risk'	

12

Source: Company submission pg 22-23 table 1; ERGR pg 62

ERG found that adjusting this outcome in the economic model had considerable impact on the results.

Company's definition of TTD: TTD is time to treatment discontinuation and not time to progression. Data were taken from *post hoc* analyses of the patient level data (difference between start and stop date of DARA-treatment).

Clinical evidence

2 key clinical trials – phase I/II non-controlled; no RCTs

MMY2002 (n=124)	GEN501 (n=72)
Phase II, randomised multicentre, open-label, 2-part study	Phase I/II, multicentre, open-label, 2-part study
• ≥ 3 prior lines of therapy OR • refractory to a PI and IMiD	• Relapsed and refractory to ≥ 2 previous lines of therapy
Part 1 (2 treatment arms) • Daratumumab 16mg/kg (licenced dose) weekly for weeks 1−8 • Daratumumab 8mg/kg every 4 weeks *Part 2* • Daratumumab 16mg/kg	*Part 1* • Dose escalation of daratumumab from 0.0005mg/kg to 24 mg/kg *Part 2 (2 treatment arms)* • Daratumumab 8mg/kg • Daratumumab 16mg/kg
Outcomes: **overall response rate**[1] (1°), OS, TTR, PFS, TTP, DoR, safety measures	**Outcomes**: **safety** (1°), frequency and severity of adverse events, pharmacokinetics, ORR, TTR, DoR, PFS, OS

[1] Defined as partial response or better

13

Source: Company submission pg 65-70 Key: TTR, time to response; DoR, duration of response

Only phase II non-controlled trial data are available for daratumumab (no RCTs)

Two key trials

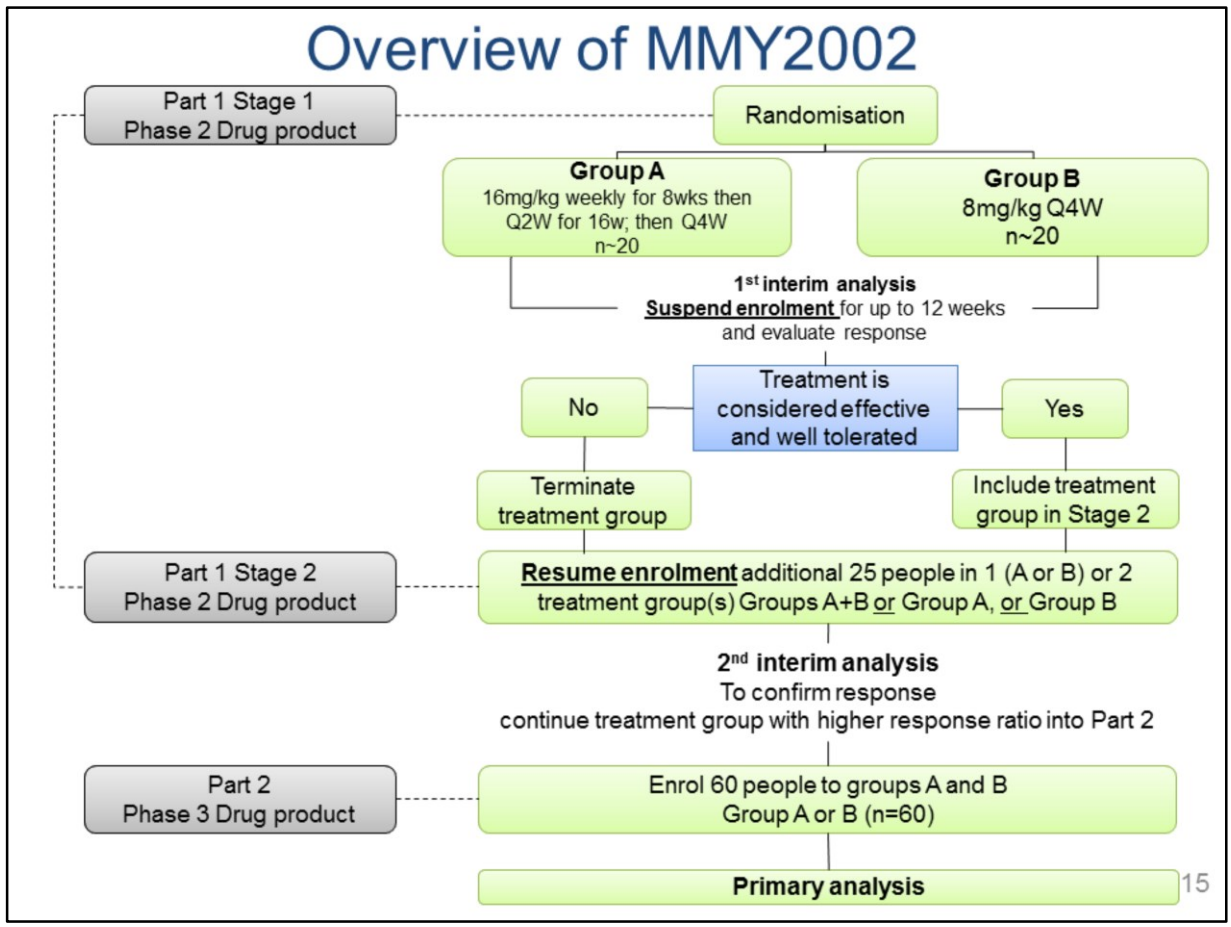
- **MMY2002** Phase II, randomised 1:1 ratio. Number of participants was 124 (106 received daratumumab 16mg/kg 41 part1 and 65 part 2) The licenced dose is 16mg/kg.
    - Primary outcome: ORR the proportion with partial response (PR) as defined by the IMWG criteria or better.
    - Secondary outcomes: OS, TTR, PFS, TTP, DoR, Safety including TEAEs, vital sign measurements, ECGs, physical examinations and lab tests.
    - ***Data cut offs: **Jan 2015** primary analysis median follow-up 9.3 mnths (0.5 to 14.4) **December 2015** median follow-up 20.7 mnths (0.5 to 26.3)
    - Locations US, Canada and Spain.
- **GEN501** Phase I/II. Number of participants 72 (42 received dartumumab 16mg/kg)
    - Primary outcomes: Safety, frequency and severities of adverse events.
    - Secondary outcomes: Pharmacokinetics, ORR, TTP, DoR, PFS, OS.
    - ***Data cut offs: **Jan 2015** primary analysis part 2 median follow-up 10.2 mnths (1.2 to 16.0) **December 2015** median follow-up 20.5 mnths (1.2 to 27.1)
    - Locations US, Denmark, Netherlands and Sweden.

Treatment discontinuation was mostly due to disease progression in both trials.

ERG comments on study design

- ERG noted that FDA requires 'that single-arm studies enrolling people with refractory tumours, and for whom there is no available therapy, provide an accurate assessment of ORR'
- But, 'clinical benefit in tumour response does not necessarily lead to benefit in overall survival'
- Overall survival is potentially confounded by treatments that follow daratumumab

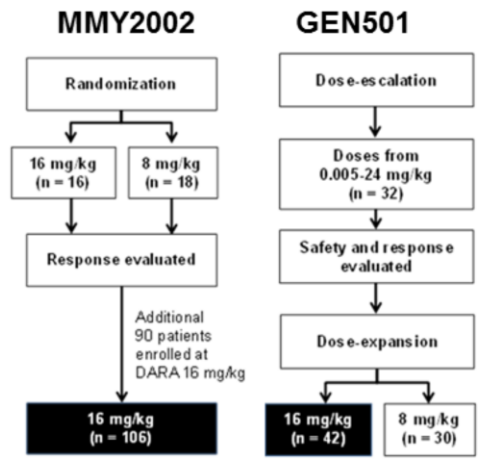
14



Source: company submission pg 67

Pooled analysis of MMY2002 and GEN501 part 2

Post-hoc meta-analysis across MMY2002 and GEN501 part 2 pooling data from daratumumab 16mg/kg arms



16 mg/kg
N = 148

16

Clinical evidence

2 key clinical trials – phase I/II non-controlled

	MMY2002 n=124	GEN501 n=72
Type	Phase II, randomised multicentre, open-label, 2-part study	Phase I/II, multicentre, open-label, 2-part study
Median prior lines of therapy	5	4
Proportion refractory to their last treatment	97%	76%
Primary outcome	Overall response rate	Safety

ERG comment

The ERG considers the pooled analysis of MMY2002 and GEN501 to be inappropriate given the differences between the trials.

17

The trials were carried out in parallel, both are 2-stage, single arm studies; the ERG noted that it is not appropriate to capture time to event data, such as PFS and OS using observational data

Baseline characteristics

Cytogenetic profile and ISS staging not assessed in GEN501

Study	MMY2002	GEN501 Part 2	Pooled analysis
Trial arm	Daratumumab 16 mg/kg		
Age (years), median (range)	63.5 (31, 84)	64.0 (44, 76)	64.0 (31-84)
Male, n%	52 (49)	27 (64)	78 (53)
Time since initial diagnosis, median years (range)	4.8 (1.1, 23.8)	5.8 (0.8, 23.7)	5.1 (0.8-23.8)
Number of lines of prior therapy, median (range)	5 (2, 14)	4 (2, 12)	5 (2-14)
≥4 prior lines of therapy, n (%)	87 (82)	26 (62)	113 (76)
Cytogenetic profile, n (%)	N=95 t(4;14): 9 (9.5) del17p: 16 (16.8) del13q: 30 (31.6) amp1q21: 23 (24.2) other: 43 (45.3)	Not assessed	-
ISS staging, n (%)	I: 2 (11.1) II: 8 (44.4) III: 8 (44.4)	Not assessed	-

Key: ISS, International Staging System

18

Source: company submission table 12 pg 73-75; table 22 pg 90-91

Baseline characteristics

Heavily pre-treated highly refractory population; some prior treatments not routinely funded in the UK

Study	MMY2002	GEN501 Part 2	Pooled analysis
Trial arm	Daratumumab 16 mg/kg		
Prior PI, n (%):	106 (100)	42 (100)	148 (100)
Bortezomib	105 (99)	42 (100)	147 (99)
Carfilzomib	53 (50)	8 (19)	61 (41)
Prior IMiD, n (%)	106 (100)	40 (95)	146 (99)
Lenalidomide	105 (99)	40 (95)	145 (98)
Pomalidomide	67 (63)	15 (36)	82 (55)
Thalidomide	47 (44)	19 (45)	66 (45)
Refractory to last line of therapy, n (%)	103 (97)	32 (76)	135 (91)
Refractory to PI/IMiD, n (%)	101 (95)	27 (64)	128 (87)
Proteasome inhibitor only	3 (3)	3 (7)	6 (4)
Immunomodulatory agent only	1 (1)	4 (10)	5 (3)
Refractory to PI + IMiD + alkylating agent, n (%)	79 (75)	21 (50)	100 (68)

19

Key: IMiD, immunomodulatory agent; PI, proteasome inhibitor.

Source: company submission table 12 pg 73-75; table 22 pg 90-91

Results

Overall response – most achieved stabilisation of disease or better

	MMY2002	GEN501 Part 2	Pooled analysis
	Daratumumab 16mg/kg (n=106)	Daratumumab 16mg/kg (n=42)	Daratumumab 16mg/kg (n=148)
Data cut-off	Jan 2015	Dec 2015	
ORR, n (%)	31 (29.2)	15 (35.7)	46 (31.1)
Clinical benefit rate, n (%)	36 (34.0)	19 (45.2)	55 (37.2)
BOR, n (%):			
sCR	3 (2.8)	0	3 (2)
CR	0	4 (9.5)	4 (2.7)
VGPR	10 (9.4)	3 (7.1)	13 (8.8)
PR	18 (17.0)	8 (19.0)	26 (17.6)
MR	5 (4.7)	4 (9.5)	9 (6.1)
SD	46 (43.4)	22 (52.4)	68 (45.9)
PD	18 (17.0)	0	18 (12.2)
NE	6 (5.7)	1 (2.4)	7 (4.7)

Key: CR, complete response; Dec, December; Jan, January; MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

20

Source: company submission pg 77; table 23 pg 92

ORR

MMY2002 29% ORR daratumumab 16 mg/kg

GEN501 36% ORR daratumumab 16 mg/kg

Note: Analysis based on 9 January 2015 data cut-off for MMY2002 and the 8mg/kg arm of GEN501 Part 2, 31 December 2015 data cut-off for the 16mg/kg arm of GEN501 Part 2.

Survival analysis PFS each trial and pooled

	MMY2002	GEN501 Part 2	Pooled
	Daratumumab 16mg/kg (n=106)	Daratumumab 16mg/kg (n=42)	Daratumumab 16mg/kg (n=148)
Number of events, n (%)	75 (70.8)	27 (64.3)	102 (68.9)
Median PFS, months (95% CI)	3.7 (2.8, 4.6)	6.2 (4.2, 11.6)	4.0 (2.8, 5.6)

Key: CI, confidence interval; PFS, progression-free survival.

Notes Analysis based on 9 January 2015 data cut-off for MMY2002 and the 8mg/kg arm of GEN501 Part 2, 31 December 2015 data cut-off for the 16mg/kg arm of GEN501 Part 2.

21

Source: company submission table 17 pg 84; table 26 pg 100

MMY2002

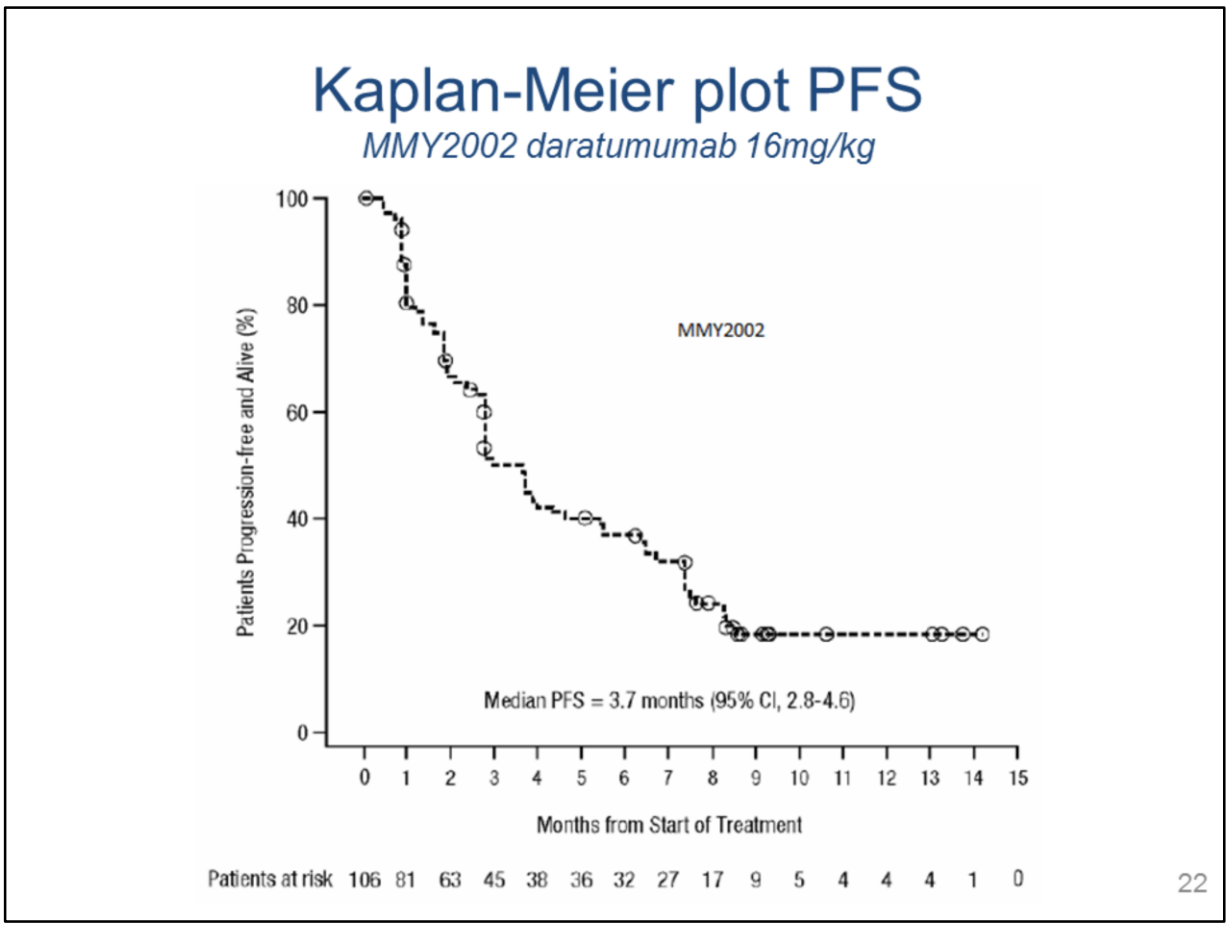
Median PFS daratumumab 16mg/kg 3.7 months

1 year PFS rate 18%

GEN501

Median PFS daratumumab 16mg/kg 6.2 months

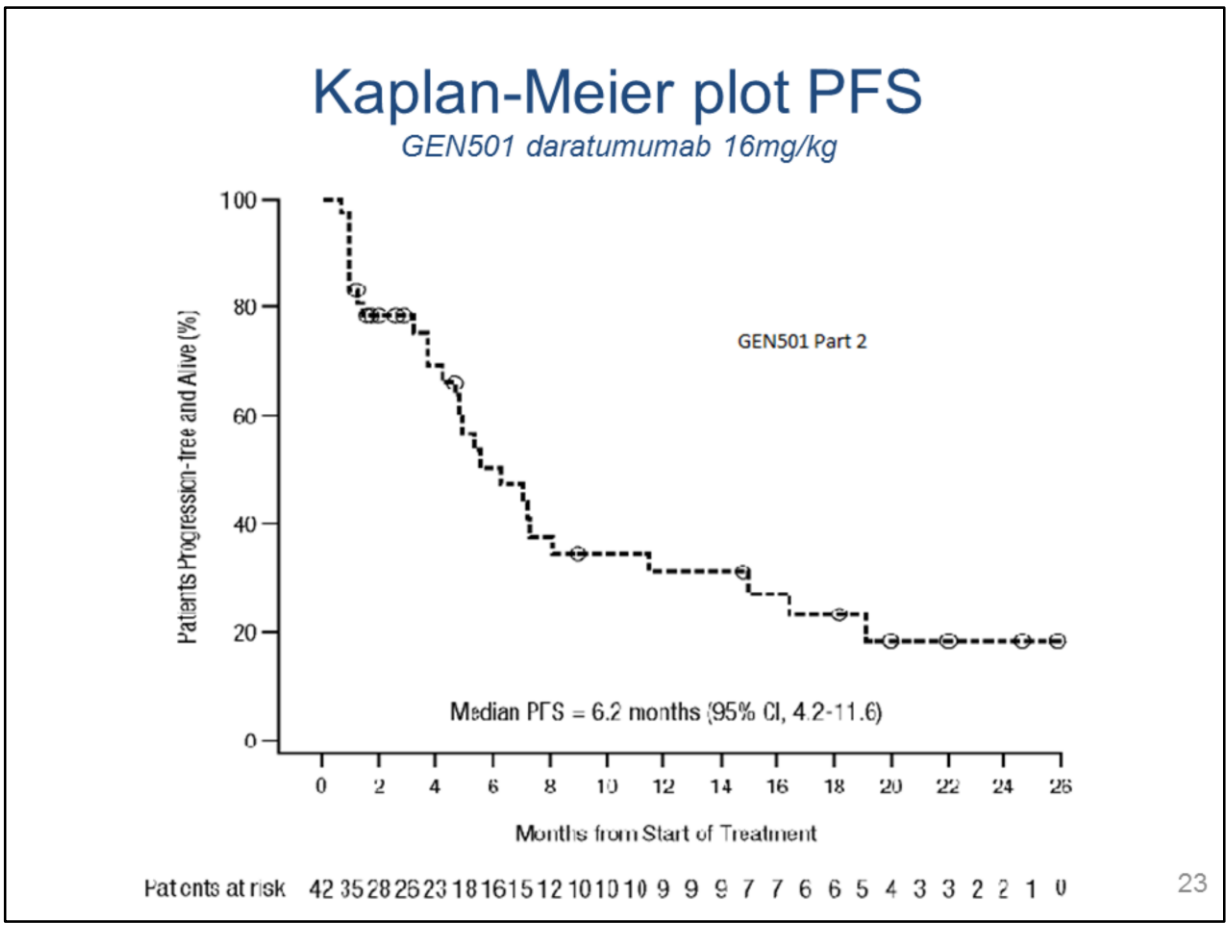
1 year PFS rate 31%



Source: company submission figure 12 pg 85

Key: CI, confidence interval; PFS, progression-free survival.

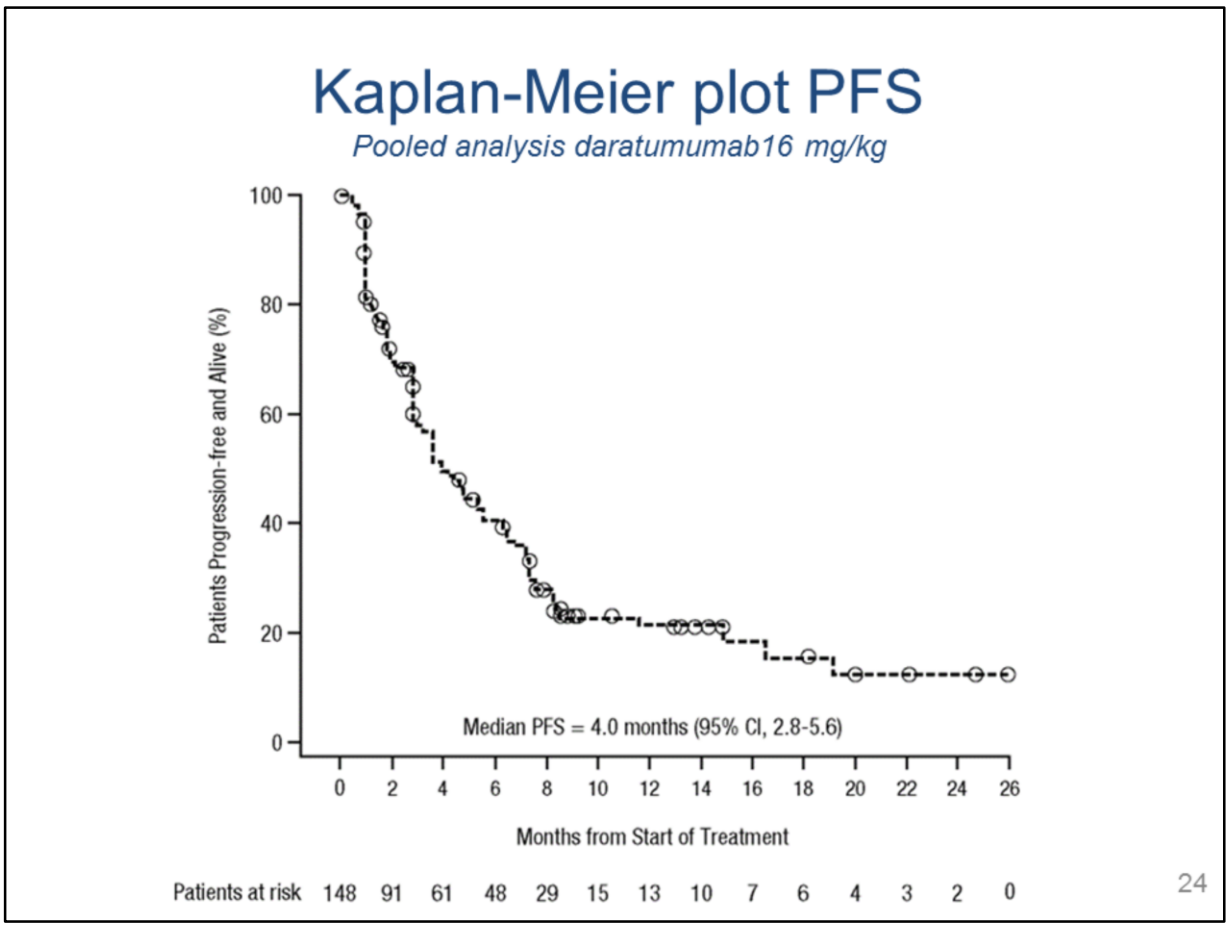
Notes: Circles represent censoring; analysis based on 9 January 2015 data cut-off for MMY2002.



Source: company submission figure 12 pg 85

Key: CI, confidence interval; PFS, progression-free survival.

Notes: Circles represent censoring; analysis based on 31 December 2015 data cut-off for GEN501 Part 2.



Source: company submission figure 19 pg 101

Key: CI, confidence interval; PFS, progression-free survival.

Notes: Circles represent censoring; pooled analysis based on 9 January 2015 data cut-off for MMY2002, 31 December 2015 data cut-off for GEN501 Part 2.

Survival analysis OS

GEN501 median OS not reached

	MMY2002	GEN501 Part 2	Pooled analysis
	Daratumumab 16mg/kg (n=106)	Daratumumab 16mg/kg (n=42)	Daratumumab 16mg/kg (n=148)
Number of events, n (%)	57 (53.8)	16 (38.1)	73 (49.3)
Median OS, months (95% CI)	18.6 (13.7, not reached)	Not reached, (18.7, not reached)	20.1 (16.6, not reached)

Key: CI, confidence interval; Dec, December; OS, overall survival.

25

Source: company submission pg 81 to 82; table 25 pg 97

GEN501

Median OS had not been reached for the latest data cut off (31 December 2015) in the daratumumab 16mg/kg arm

median follow-up was 20.5 months

2 year OS 57%

MMY2002

Median OS 18.6

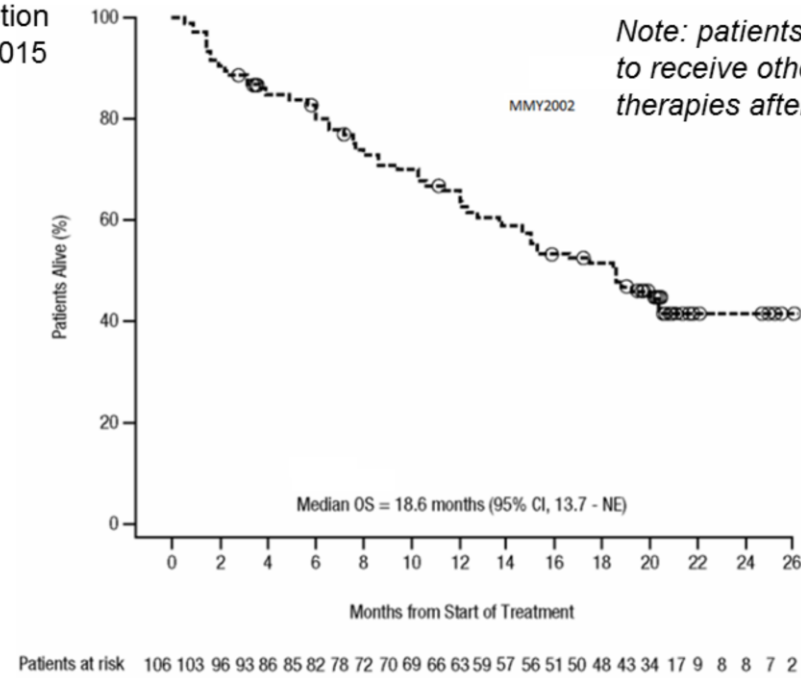
The latest data cut off was 31 December 2015

Kaplan-Meier plot OS

MMY2002 daratumumab16 mg/kg

Start date: September 2013

Primary completion date: January 2015



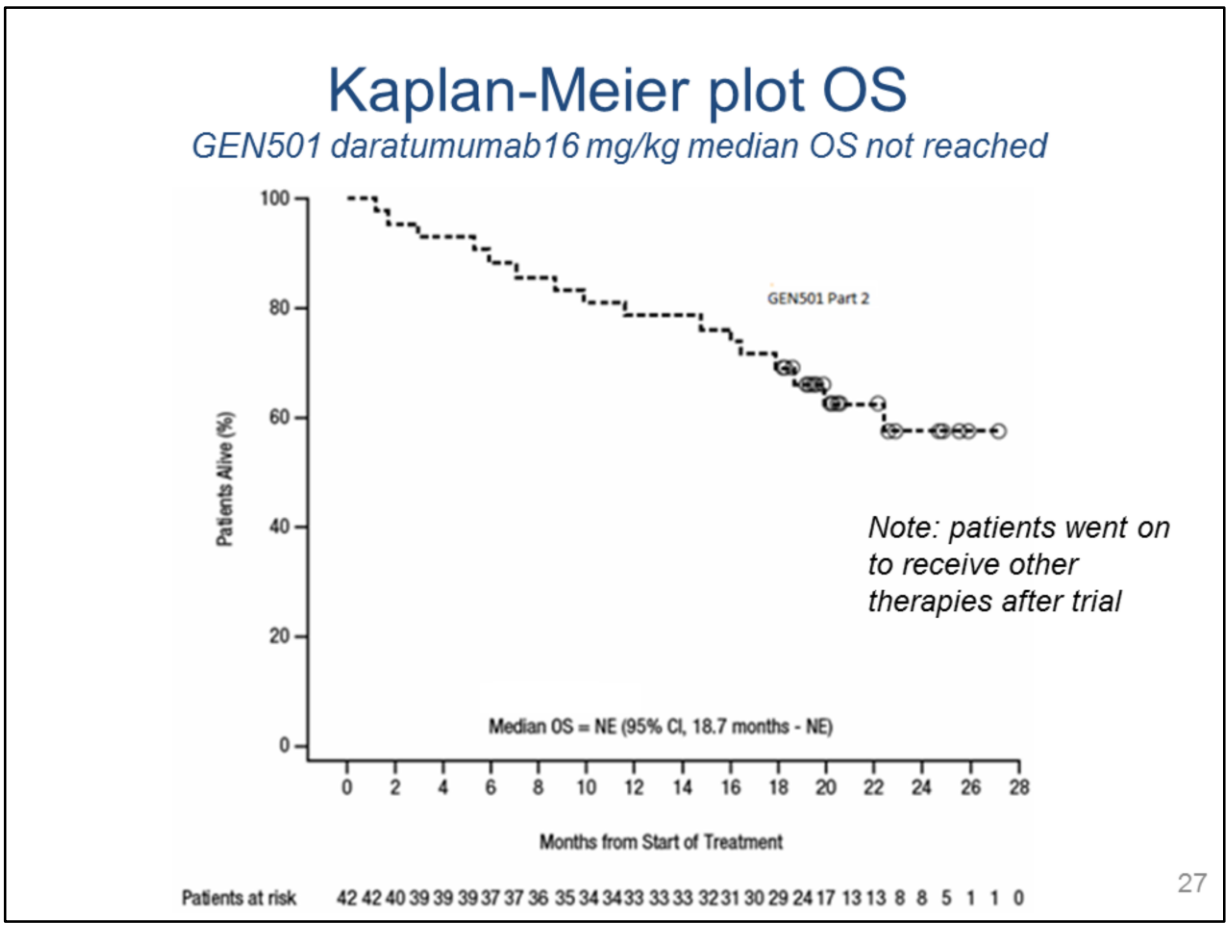
26

Source: company submission figure 11 pg 83

median OS 18.6 months

Key: CI, confidence interval; NE, not evaluable; OS, overall survival.

Notes: Circles represent censoring.



Source: company submission figure 11 pg 83

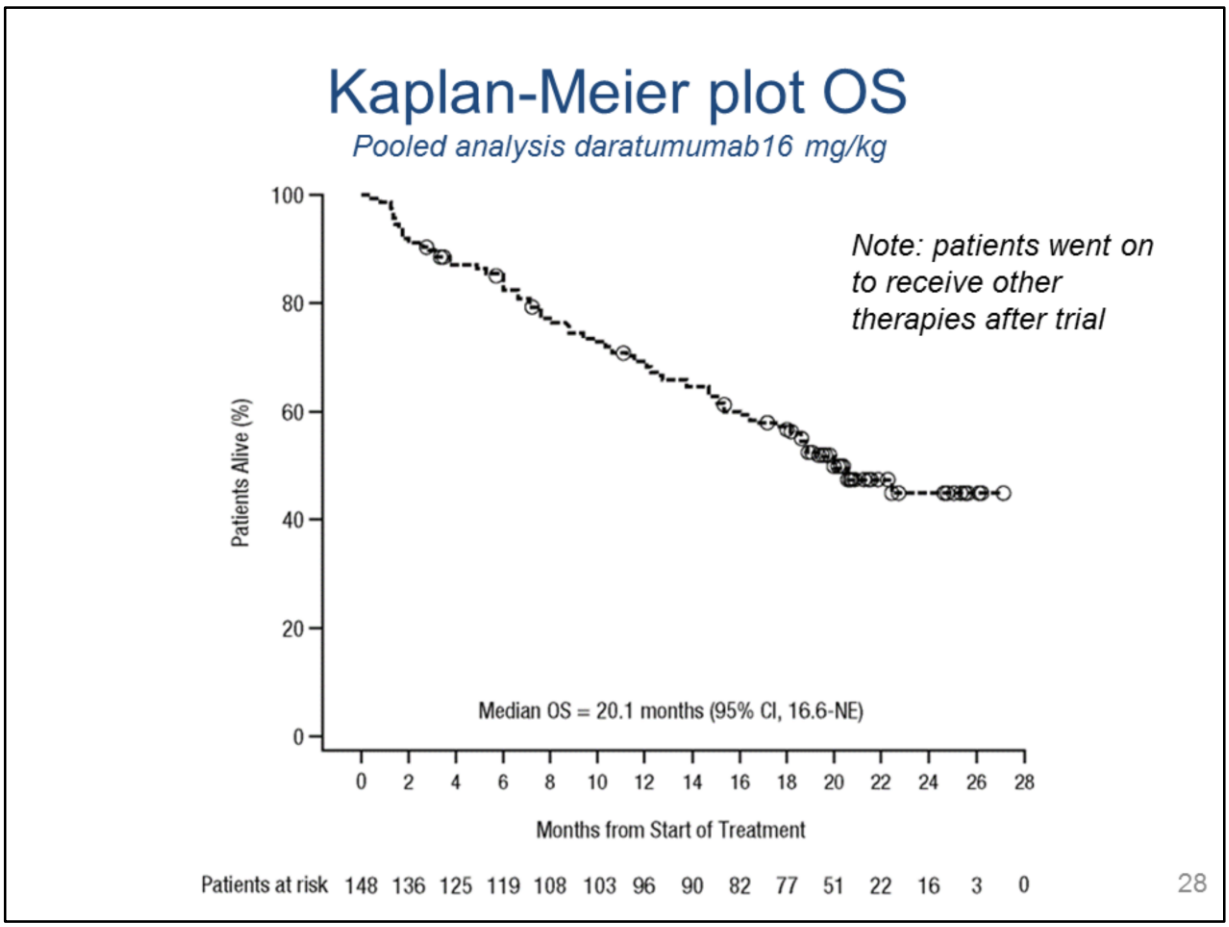
Median OS had not been reached for the latest data cut off (31 December 2015) in the daratumumab 16mg/kg arm

median follow-up was 20.5 months

2 year OS 57%

Key: CI, confidence interval; NE, not evaluable; OS, overall survival.

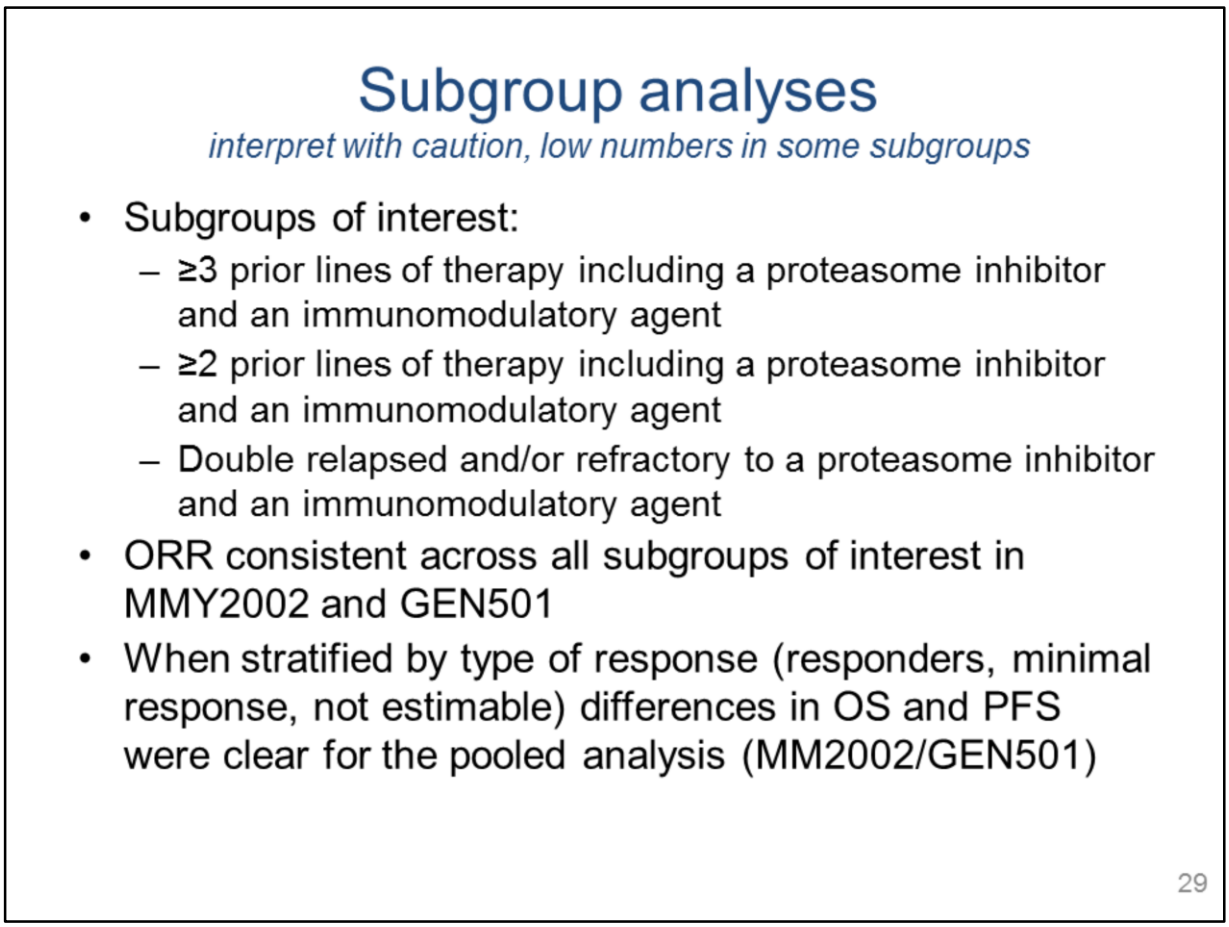
Notes: Circles represent censoring.



source: company submission pg 98

Key: CI, confidence interval; NE, not estimable; OS, overall survival.

Notes: Circles represent censoring.



Source: company submission pg 87 and appendix 5

Subgroup analyses should be interpreted with caution due to low numbers in some subgroups

- **MMY2002** – ORR consistent across all subgroups
- **GEN 501** – ORR consistent across all subgroups
- **Pooled analysis** – ORR consistent across all subgroups. There are clear differences in OS when the cohort is stratified by type of response (pg 98)

Adverse reactions (pooled analysis)

Well tolerated, clinically manageable side effects, TEAE profile consistent with advanced MM

	Daratumumab 16mg/kg (n=148)
Any treatment emergent adverse event	147 (99.3)
Drug-related	117 (79.1)
Any serious TEAE	48 (32.4)
Drug-related	13 (8.8)
Maximum severity of any TEAE	
Grade 1	9 (6.1)
Grade 2	55 (37.2)
Grade 3	56 (37.8)
Grade 4	17 (11.5)
Grade 5	10 (6.8)
DC due to TEAE	6 (4.1)
Drug-related	0
Death due to TEAE	3 (2.0)
Drug-related	0

Key: DC, discontinuation; Dec, December; TEAE, treatment-emergent adverse event.

30

Source: company submission pg 104

Daratumumab well tolerated, clinically manageable side effects

No deaths and no discontinuation of tr due to drug toxicity

3 deaths attributed to TEAEs (HIN1 infection, pneumonia and aspirational pneumonia)

Indirect and mixed treatment comparisons

- Company presented indirect treatment comparisons, given no randomised head-to-head evidence comparing daratumumab with any other treatment

Treatment/ comparator	Source	Evidence level	Method
Daratumumab	Pooled MMY2002/GEN501	Pooled IPD	-
POM+DEX	MM-003	Aggregate data	Matching-adjusted indirect comparison
PANO+ BORT+DEX	PANORAMA 2	Aggregate data	Matching-adjusted indirect comparison
Bendamustine	International myeloma foundation	IPD	Multivariate regression

Key: OS, overall survival; PFS, progression free survival; BORT/DEX, bortezomib plus dexamethasone; IPD, individual patient-level data; POM+DEX, pomalidomide plus dexamethasone

31

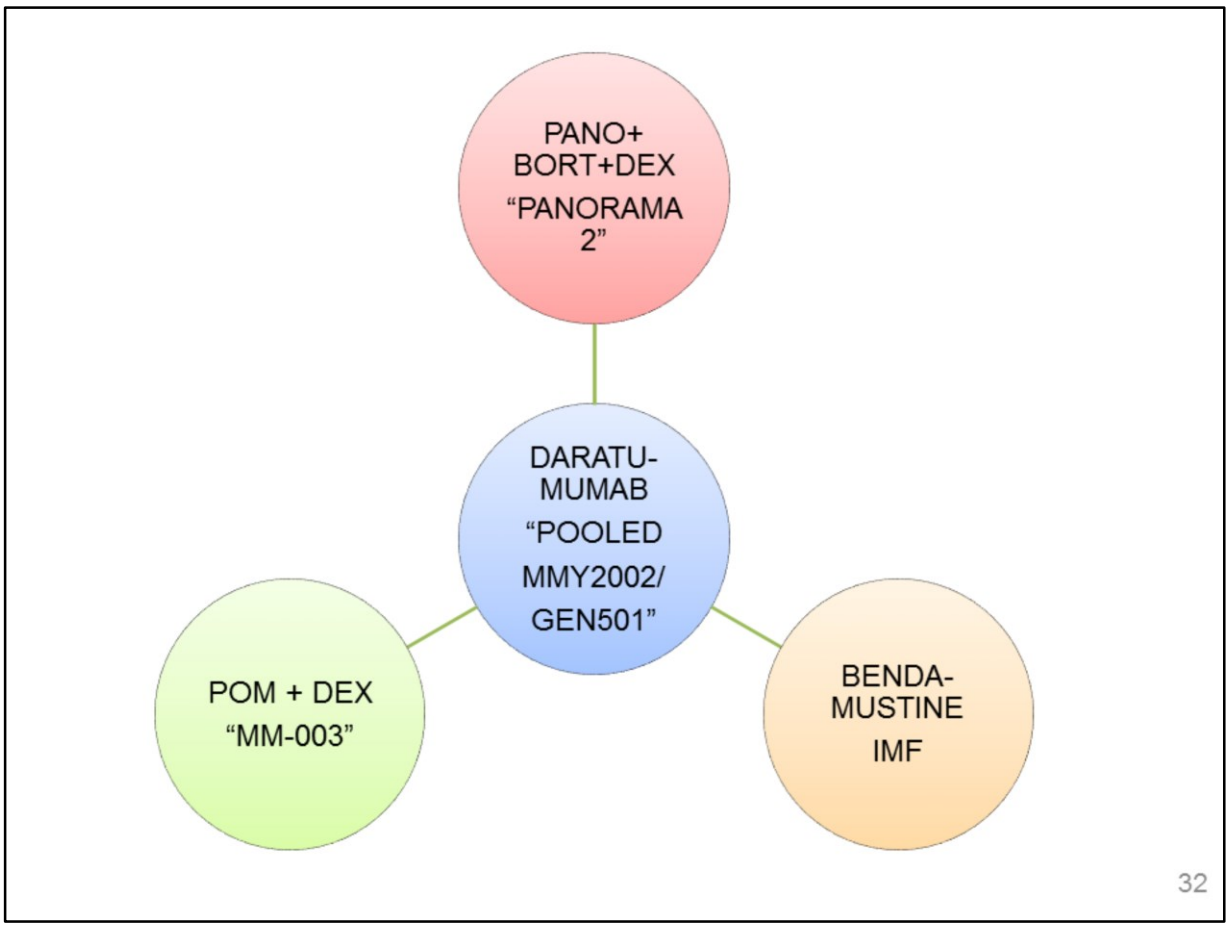
Source: company submission pg 116-119 table 33

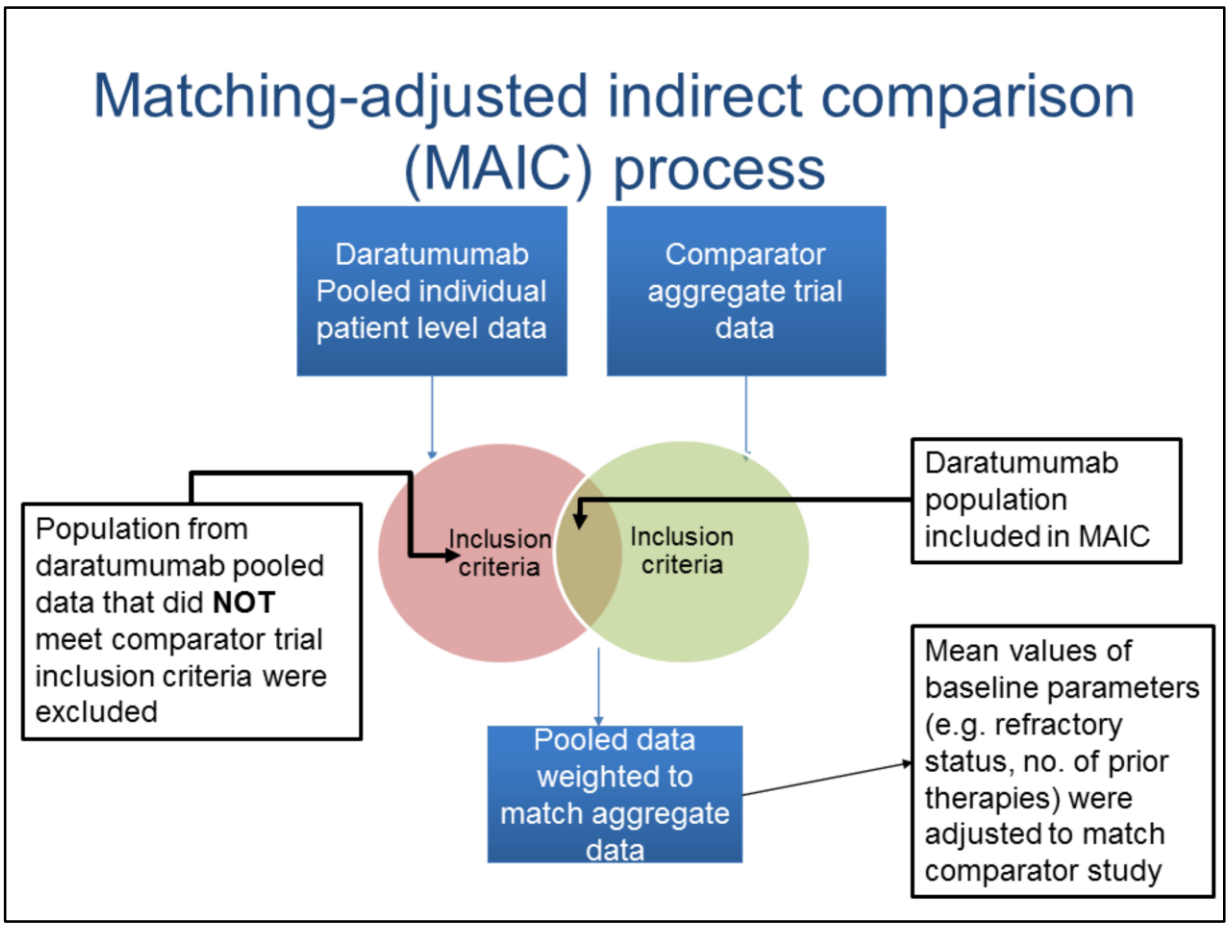
MAIC using Signorovitch et al. methodology

A **MAIC approach** was used for daratumumab vs **pom+dex** and daratumumab vs **pano+bort+dex** given the lack of common comparator and variation across trial populations between MMY2002/GEN501 and MM-003/PANORAMA 2

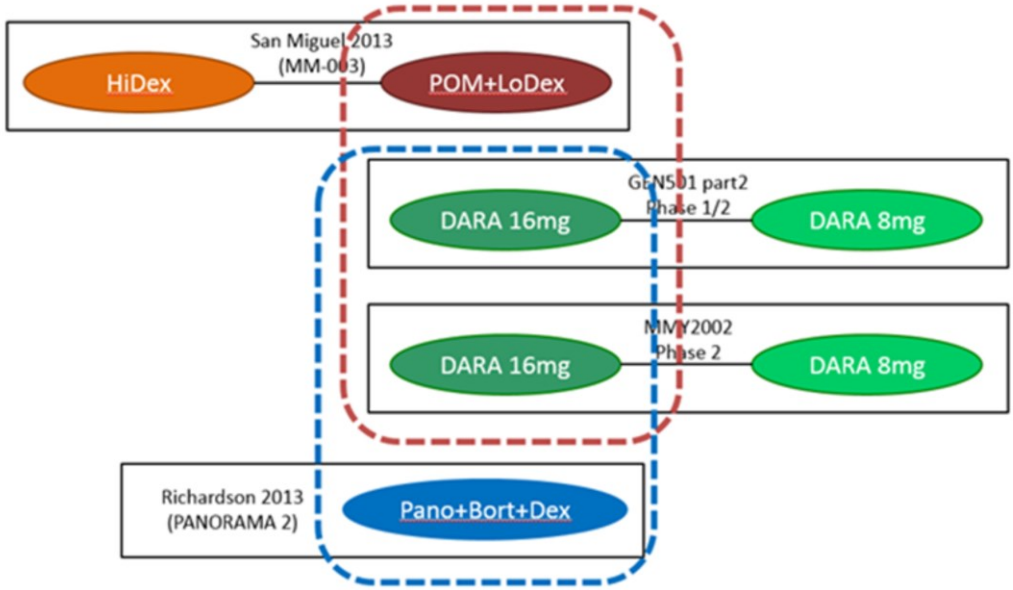
- IPD from MMY2002/GEN501 was compared to aggregate data from the comparator trials
- Used to calculate difference in OS and PFS between daratumumab and comparators
- An approach similar to propensity score weighting was used for patients who had no overlap in characteristics

For **daratumumab vs bendamustine-based therapies** a multivariate regression analysis using IPD from MMY2002 and GEN501 (Part 2) and the real-world IMF cohort was carried out.


PANO+
BORT+DEX
"PANORAMA
2"
DARATU-
MUMAB
"POOLED
MMY2002/
GEN501"
POM + DEX
"MM-003"
BENDA-
MUSTINE
IMF
32


Matching-adjusted indirect comparison (MAIC) process
Daratumumab Pooled individual patient level data
Comparator aggregate trial data
Population from daratumumab pooled data that did **NOT** meet comparator trial inclusion criteria were excluded
Inclusion criteria
Inclusion criteria
Daratumumab population included in MAIC
Pooled data weighted to match aggregate data
Mean values of baseline parameters (e.g. refractory status, no. of prior therapies) were adjusted to match comparator study

Source of evidence forming MAIC



34

Summary data for comparators in indirect comparisons

	POM+DEX	PANO+BORT+DEX	Bendamustine
Study	MM-003	PANORAMA 2	IMF cohort
Comparison analysis	MAIC	MAIC	Multivariate regression
Type of study	RCT phase III, active controlled open label	Phase II, 2 stage, single-arm, open-label	Retrospective observational chart review of the IMF
Population	≥2 cycles of bort+len, refractory to previous treatment Median 5 previous treamtent	≥2 previous treatments including immunomodulatory agent, refractory to bortezomib Median 4 previous treatments Less heavily pre-treated than MMY2002	≥3 previous treaments refractory to IMiD and PI
Arm 1	POM + low dose DEX (n=302)	PANO+BORT+DEX (n=55)	Eligible people at IMF sites (n=550)
Arm 2	High-dose DEX (n=153; arm not used in MAIC)	Single arm trial	N/A
Cross over?	Yes	Yes	-
Subsequent therapies?	Dexamethasone, cyclophosphamide, bortezomib and bendamustine	NR in full publication	-

35

Source: company submission pg 117; Morgan. BJH. 2014. Overall survival of relapsed and refractory multiple myeloma patients after adjusting for crossover in the MM-003 trial for pomalidomide plus low-dose dexamethasone

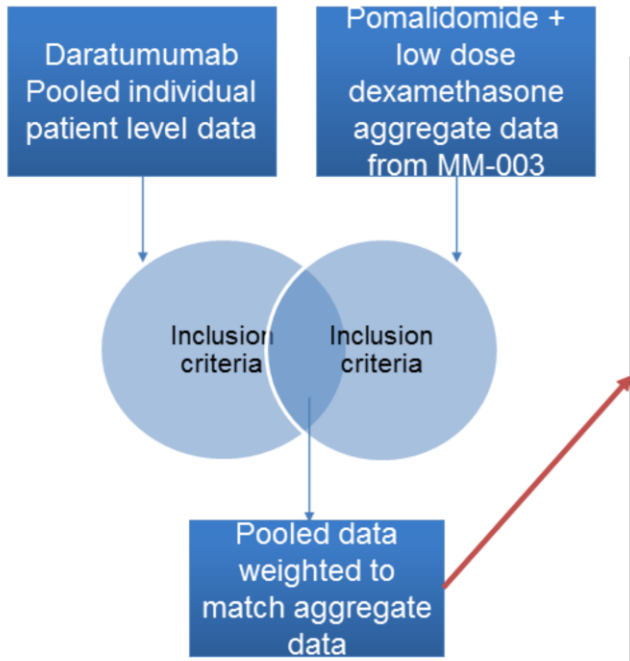
Median number of previous treatments

MM-003	5 (no pomalidomide or carfilzomib)
PANORAMA 2	4
MMY2002	5

Key: IMF international myeloma foundation

MAIC daratumumab *vs* POM+DEX

Most important factors were matched to balance adjustment and reduction in sample size



11 characteristics matched (most important based on clinical expert opinion):

Refractory status:
- Refractory to lenalidomide (%)
- Refractory to bortezomib (%)
- Refractory to both (%)

Number of prior therapies:
- Mean number of prior regimens
- >2 prior regimens (%)

Creatinine clearance:
- Creatinine clearance <30 (%)
- Creatinine clearance 30-60 (%)
- Creatinine clearance ≥60 (%)

Eastern Cooperative Oncology Group (ECOG) score:
- ECOG 0 (%)
- ECOG 1 (%)
- ECOG 2 (%)

36

Baseline characteristics available for matching for daratumumab versus POM+DEX

in order of relevance to effect on OS and order of adjustment

Baseline variable	No. of characteristics to match	MMY2002	GEN501 Part 2	Pooled analysis
Refractory to bortezomib	1	✓	✓	✓
Number of prior regimens	2	✓	✓	✓
ISS stage	3	✓	*x*	*x*
ECOG status	3	✓	✓	✓
Cytogenetics	1	✓	*x*	*x*
Median time since diagnosis	1	✓	✓	✓
Myeloma subtype	3	✓ (only IgA and IgG)	✓	✓
β-microglobulin	1	✓	*x*	*x*
Prior ASCT (%)	1	✓	✓	✓
Age	2	✓	✓	✓
Total	18	17	13	13

37

Source: ERGR pg 104-105 table 17

Key: ASCT, autologous stem-cell transplant; CS, company submission; ECOG, Eastern Cooperative Oncology Group; Ig, immunoglobulin; pg, page; pom+dex, pomalidomide plus dexamethasone.

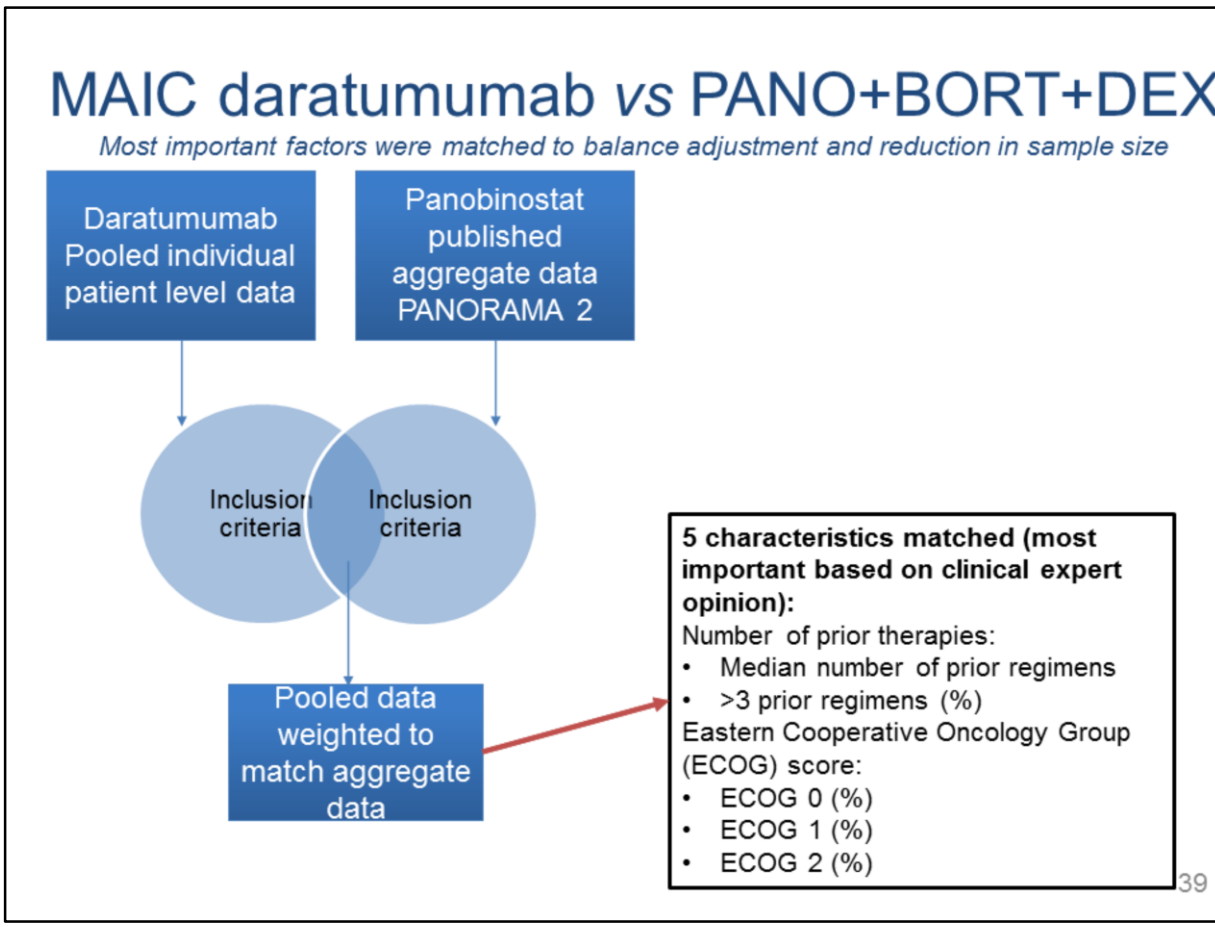
MAIC results daratumumab *vs* POM+DEX

No statistically significant difference between OS and PFS

Number of matched characteristics	N	Net effective sample size[1]	HR (95% CI)	
			PFS	OS
Unadjusted	148		0.88 (0.69, 1.12)	0.61 (0.46, 0.81)
26	136	55	0.72 (0.50, 1.05)	0.56 (0.38, 0.83)
23	136	58	0.75 (0.52, 1.08)	0.57 (0.34, 0.84)
22	136	62	0.81 (0.58, 1.13)	0.59 (0.41, 0.86)
21	137	63	0.81 (0.59, 1.13)	0.59 (0.41, 0.86)
18	148	71	0.78 (0.57, 1.07)	0.55 (0.39, 0.78)
12	148	82	0.78 (0.58, 1.05)	0.55 (0.39, 0.77)
11	148	84	0.81 (0.60, 1.09)	0.57 (0.41, 0.81)
8	148	106	0.83 (0.63, 1.09)	0.56 (0.41, 0.76)
5	148	108	0.85 (0.64, 1.12)	0.60 (0.45, 0.81)
3	148	110	0.84 (0.64, 1.11)	0.61 (0.45, 0.83)

[1]The number of matched patients. The smaller this number is, the poorer the overlap between studies is, and the less stable the estimates are.

38


MAIC daratumumab *vs* PANO+BORT+DEX
Most important factors were matched to balance adjustment and reduction in sample size
Daratumumab Pooled individual patient level data
Panobinostat published aggregate data PANORAMA 2
Inclusion criteria
Inclusion criteria
Pooled data weighted to match aggregate data
5 characteristics matched (most important based on clinical expert opinion):
Number of prior therapies:
• Median number of prior regimens
• >3 prior regimens (%)
Eastern Cooperative Oncology Group (ECOG) score:
• ECOG 0 (%)
• ECOG 1 (%)
• ECOG 2 (%)
39

Baseline characteristics available for matching for daratumumab versus PANO+BORT+DEX

in order of relevance to effect on OS and order of adjustment

Baseline variable	No. of characteristics to match	MMY2002	GEN501 Part 2	Pooled analysis	Pooled analysis pom+dex naïve
Refractory status	3	✓	✓	✓	✓
prior regimens	2	✓	✓	✓	✓
ISS stage	2	✓	*x*	*x*	*x*
Creatinine clearance	3	✓	✓	✓	✓
ECOG status	3	✓	✓	✓	✓
Cytogenetics	1	✓	*x*	*x*	*x*
time since diagnosis	1	✓	✓	✓	✓
Myeloma subtype	6	✓ (excluding IgM)	✓	✓	✓
β-microglobulin	3	✓	*x*	*x*	*x*
Ethnicity	3	✓	*x*	✓	*x*
Bone lesions	1	✓	*x*	✓	*x*
Prior ASCT	1	✓	*x*	✓	*x*
Age	3	*x*	*x*	✓	*x*
Total no.	32	28	18	26	18

40

Source: ERGR pg 107-108 table 18

Key: ASCT, autologous stem-cell transplant; CS, company submission; ECOG, Eastern Cooperative Oncology Group; Ig, immunoglobulin; pg, page; pom+dex, pomalidomide plus dexamethasone.

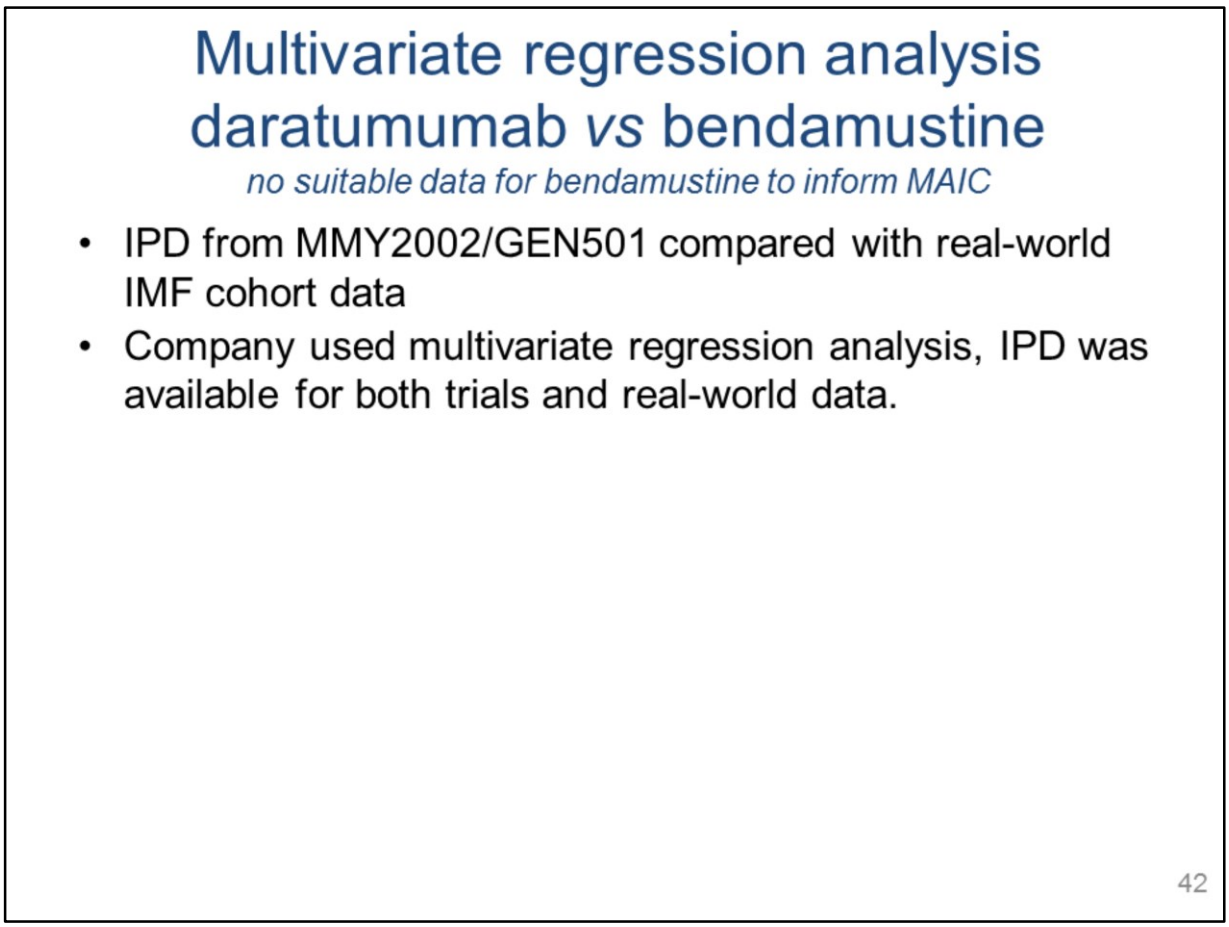
MAIC results daratumumab *vs* PANO+BORT+DEX

no statistically significant difference between OS and PFS

Number of matched characteristics	N	Net effective sample size[1]	HR (95% CI)	
			OS	PFS
Non-BORT refractory included Unadjusted	148	-	0.82 (0.53, 1.26)	1.05 (0.75, 1.47)
Non-BORT refractory excluded Unadjusted	125	-	0.93 (0.60, 1.44)	1.09 (0.77, 1.56)
12	125	46	0.76 (0.44, 1.30)	0.96 (0.60, 1.55)
10	125	52	0.81 (0.48, 1.37)	0.98 (0.63, 1.53)
9	125	67	0.84 (0.51, 1.38)	1.04 (0.69, 1.58)
6	125	79	0.83 (0.51, 1.35)	1.08 (0.73, 1.59)
5	125	80	0.84 (0.52, 1.37)	1.09 (0.74, 1.61)
2	125	91	0.91 (0.57, 1.45)	1.19 (0.83, 1.72)

[1]The number of matched patients. The smaller this number is, the poorer the overlap between studies is, and the less stable the estimates are.

41



Source: company submission pg 118

Multivariate regression analysis of daratumumab monotherapy versus bendamustine-based therapies comparing the IPD from the pooled cohort of MMY2002 and GEN501 (Part 2) and the real-world IMF cohort.

- No appropriate trial data for bendamustine-based therapy to inform MAIC
- Only available on CDF as last line therapy
- Real-world IMF cohort considered most appropriate

ERG comments on MAIC

most adjusted data set considered to be least biased for an unanchored comparison

- ERGs preferred approach is fully adjusted MAIC
  - The Decision Support Unit advises that all prognostic variables and effect modifiers should be included in weighting for MAIC using data from non-randomised trial to minimise variation
- Limitations of unanchored MAIC
  - No within-study randomisation means that differences in prognostic variables are not controlled for
  - Analysis assumes that all effect modifiers and prognostic factors are accounted for
    - ◊ Bias and uncertainty in the accuracy of estimates
  - Assumes that the joint distribution and correlation of covariates is the same as the index study
  - Population modelled based on the comparator trial not the population for which IPD data are available
  - Residual systematic error arising from unobserved prognostic variables and effect modifiers should be quantified

43

Key issues: clinical effectiveness

- Position of daratumumab in treatment pathway
- Is lenalidomide + dexamethasone an appropriate comparator at the place in therapy where daratumumab would be used?
- Generalisability of MMY2002 and GEN501 to the UK: some prior lines and subsequent therapy are not available in the UK
- OS confounded by subsequent therapies received in trials, with no comparator arm to control for this
- Is the pooled analysis of MMY2002 and GEN501 appropriate, and are the methods used valid?
- MAIC results should be interpreted with caution
  - Are the number of matched characteristic in the MAIC company's base case valid?
- Lack of RCT data comparing daratumumab and comparators
  - High risk of bias
  - Time to event data were from single arm studies
  - No clinical effectiveness estimates from head-to-head studies
- A key study was omitted from the report, the ERG cannot conclude whether all relevant evidence was identified

44

Cost effectiveness

Summary of company's cost-effectiveness evidence

- Trial evidence was taken from an pooled analysis of the 2 key trials MMY2002 and GEN501 for the base case
- Single-arm trial data for daratumumab were compared with comparator trial data
- Company tested 5 parametric survival functions, and chose best fitting to the data based on statistical, visual and clinical criteria
- The model assumed proportional hazards
- Company applied adjusted HRs from MAIC
- Company assumed that health-state specific utility and resource use estimates the same for all treatment arms
- Pairwise comparisons to calculate ICERs

46

Summary of ERG comments on the company's cost-effectiveness evidence

- All OS survival estimates should be interpreted with caution as daratumumab and PANO+BORT+DEX data come from single-arm trials
- Company's modelling of survival 'lacks transparency and consistency'
- Some OS curves modelled by ERG differ considerably from those presented in company's submission
- The ERG disagrees with company's assumption of proportional hazards (PH) for OS
- Company used HRs adjusted for the important baseline factors only. More appropriate to adjust for the maximum number of characteristics possible across trials
  - Company's approach overestimates the survival benefit of daratumumab
- Current economic model does not allow for the ERG's preferred assumptions: independently fitted curves + HRs for daratumumab fully adjusted (as far as possible) for baseline characteristics

47

Company's decision problem

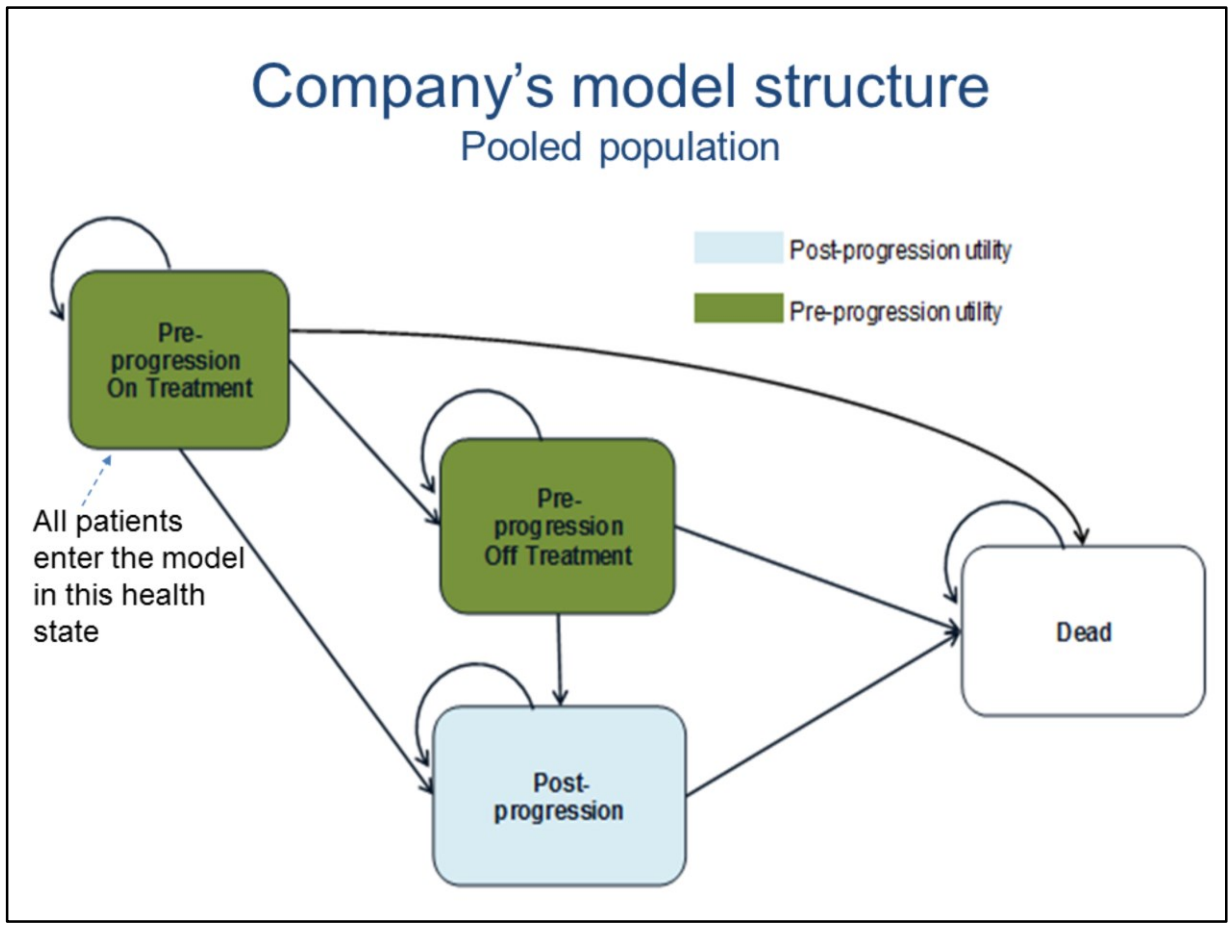
Type	Partitioned survival model, 4 health states
Population	Adults with relapsed or refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent, and who have demonstrated disease progression on the last therapy
Comparators	1. POM + DEX 2. PANO + BORT + DEX 3. Bendamustine
Time horizon	Lifetime, 15 years
Cycle length	1 week, no half cycle correction
Discount rate	3.5% (costs and health effects)
Perspective	NHS and Personal Social Services (PSS)

The ERG did not present a comparison with bendamustide because, as advised by its experts, bendamustine is likely to be used after daratumumab, as the last treatment option.

48

Further detail can be found in the company submission pages 167-169

ERG – pg 181-182 the ERG does not think that the company's submission follows the decision problem in the reference case as the evidence does not disentangle the effect of daratumumab vs daratumumab + subsequent treatments and some of the OS benefit could be from subsequent treatments.

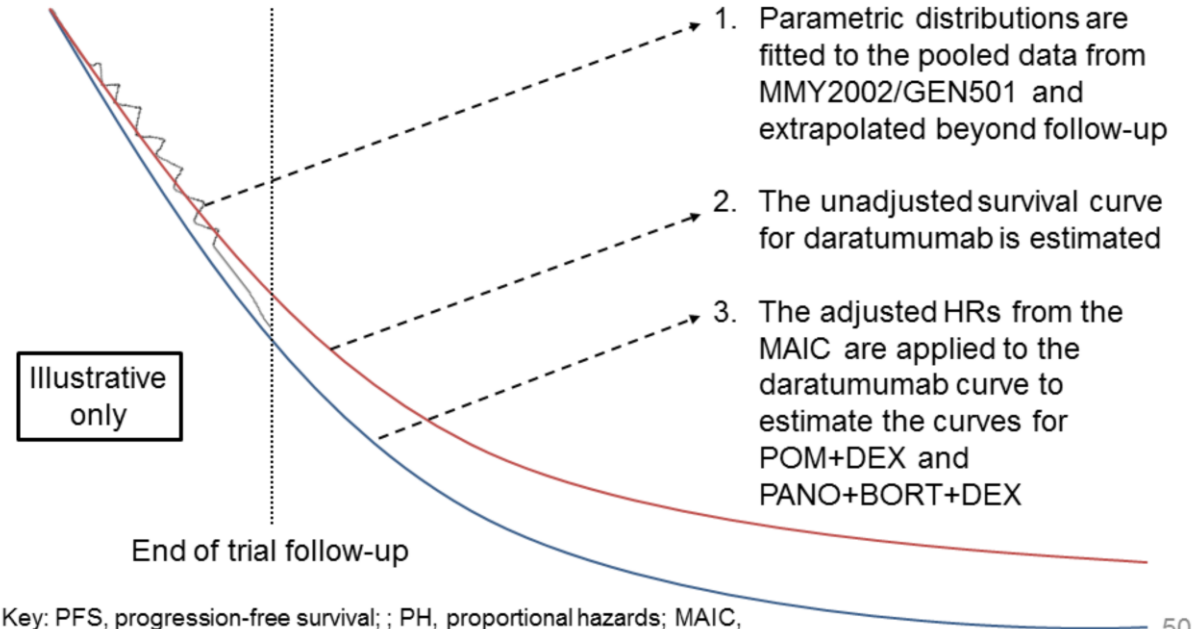


Source: company submission Figure 29 pg 168,

PFS, OS and TTD KM curves from pooled patient–level data from MMY2002 and GEN501 is used to calculate the proportion of people in each health state.

Company's approach to modelling OS, PFS and TTD

Dependently fitted curves (assumes PH)

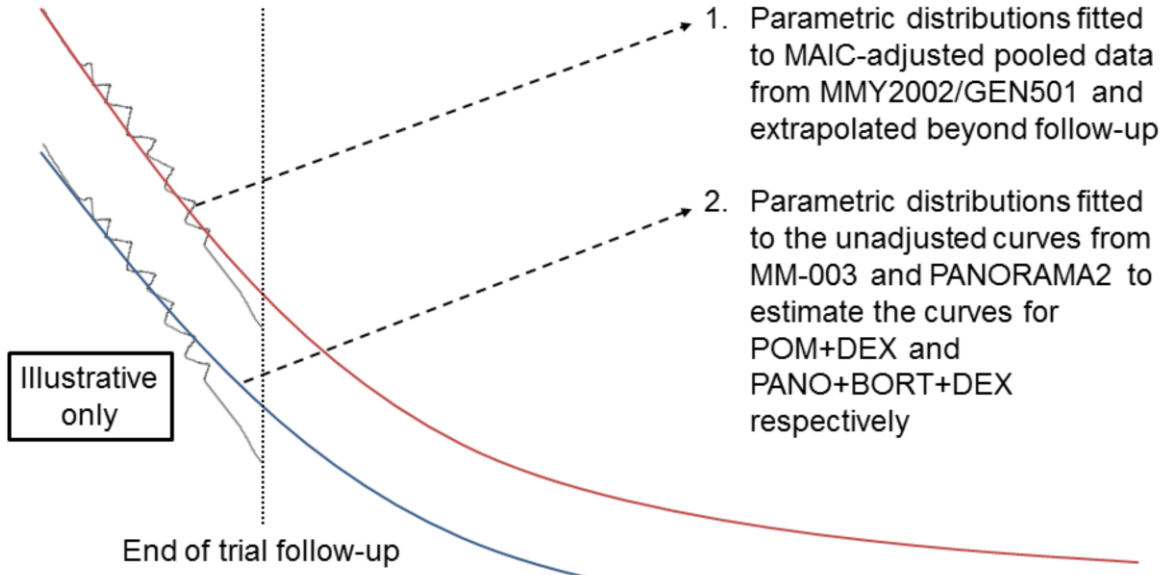


Key: PFS, progression-free survival; ; PH, proportional hazards; MAIC, matching-adjusted indirect comparison; OS, overall survival; TTD, time to treatment discontinuation

50

Alternative approach to modelling OS, PFS and TTD (not used by company)

Independently fitted curves (does not assume PH)

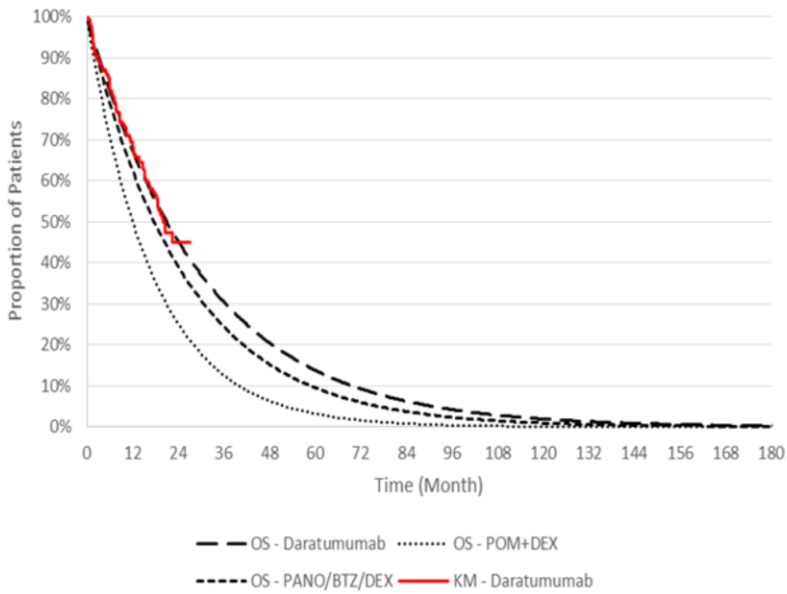


Key: PFS, progression-free survival; PH, proportional hazards; MAIC, matching-adjusted indirect comparison; OS, overall survival; TTD, time to treatment discontinuation

51

Company's modelling of OS

Exponential distribution fitted to data



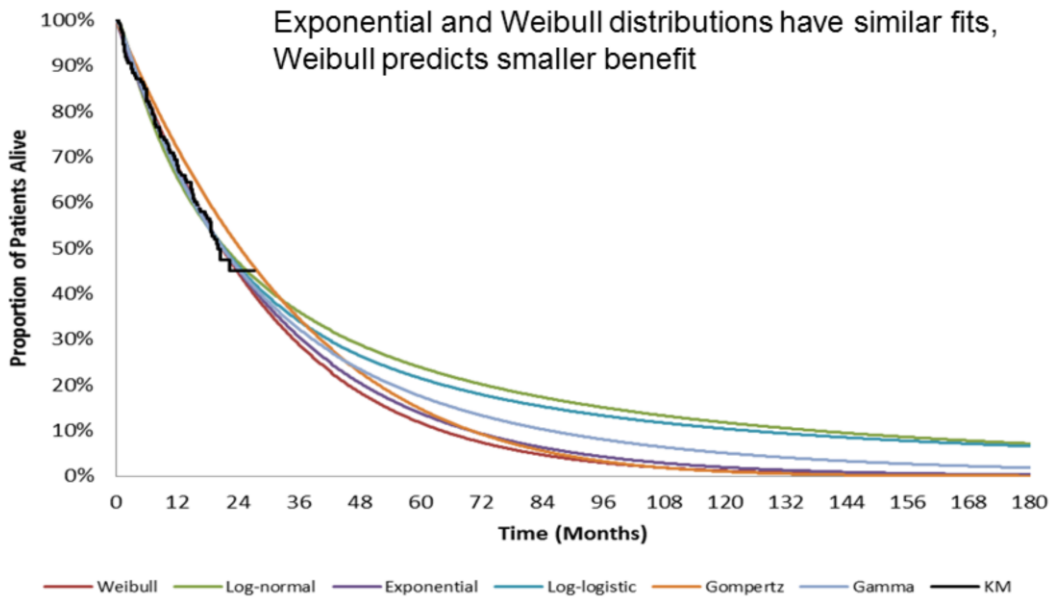
ERG comment

- Methodologically, exponential distribution not appropriate when PH is assumed
- Problem aggravated as exponential distribution (as opposed to any other parametric distribution) assumes that the baseline hazard (i.e. daratumumab) is constant over time
- ERG prefers Weibull distribution

52

Company's modelling of OS

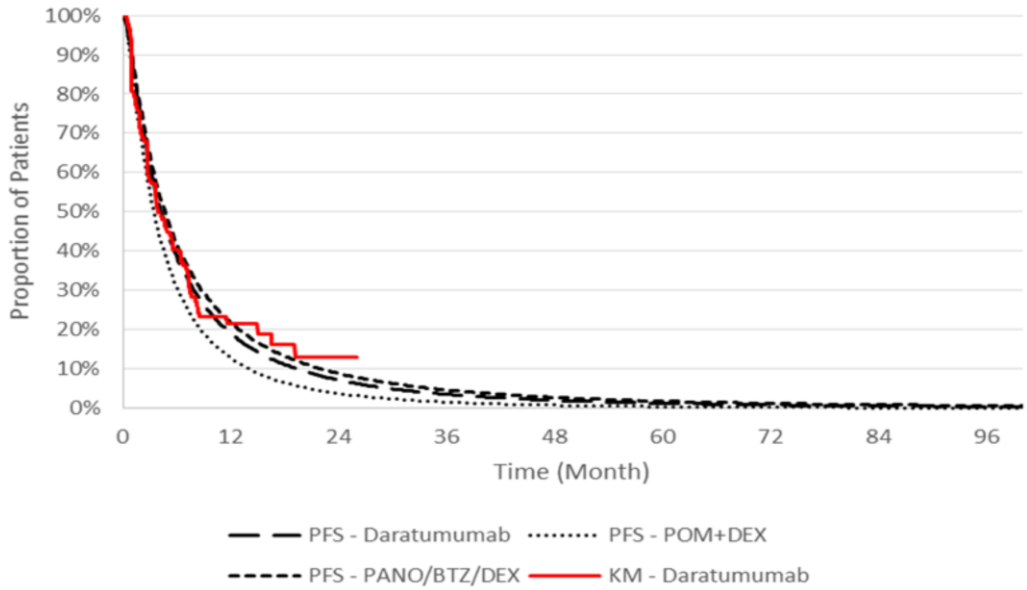
Exponential *vs* Weibull



53

Company's modelling of PFS

Log-normal distribution fitted to data



54

Company's modelling of time to treatment discontinuation (TTD)

Daratumumab	• Estimated based on post hoc analysis of the pooled data from MMY2002 and GEN50
POM+DEX	• Company could obtain only mean and median TTD from the literature • Therefore, it calibrated (adjusted) the TTD curves for daratumumab to match the mean and median TTD observed in MM-003
PANO+BORT+ DEX and bendamustine	• Company could not find TTD data for either treatment • Therefore, it assumed patients are treated until progression, or until the maximum number of treatment cycles has been reached

ERG comments

- The estimation of TTD lacks transparency and clarity, and the company's calibration approach is a 'black box'
- Using these data carries 'potentially high risk'
- PFS could be explored to derive treatment costs i.e. assuming patients stop treatment at disease progression

55

Summary of ERG comments on clinical effectiveness

ERG critique of company's modelling of clinical effectiveness rests on the following points:

1. The confounding of OS caused by subsequent therapies received
2. The assumption of proportional hazards (PH) for OS i.e. the approach to fitting curves (dependent *vs* independent)
3. The use of the MAIC-adjusted HRs

56

1. Effect of subsequent therapies

Company's claims about the effectiveness of daratumumab

- Daratumumab has a favourable safety profile. This allows patients to recover from the cumulative toxicity of previous treatments, which in turn allows a higher proportion of patients to receive subsequent therapy
- The novel mode of action of daratumumab, including immune-mediated mechanisms, increases the likelihood of patients benefiting from subsequent therapy
- The ERG noted that, despite the first claim, the company assumed in the model that a smaller proportion of patients received treatment subsequent to daratumumab (55%) than what was observed in the trial (72%)
- The ERG refutes the second claim based on expert opinion

57

1. Effect of subsequent therapies

ERG: daratumumab effect on OS highly confounded

- POM+DEX data also confounded, but to a much lesser extent because:
  - A smaller proportion of patients had subsequent therapies (44% *vs* 72%)
  - A much smaller proportion of patients had subsequent carfilzomib, lenalidomide and bortezomib (2%, 5% and 18% *vs* 28%, 15% and 24% respectively)
    - ◊ These therapies are not available in the UK, and likely to increase OS considerably
  - None of the patients had subsequent POM+DEX, whereas 31% of patients in daratumumab trials had it
- Large OS benefit of daratumumab compared with small, if any, PFS gain likely due to subsequent therapies, not daratumumab

58

1. Effect of subsequent therapies

Most common anticancer therapies after daratumumab

	MMY2002	GEN501 part 2	Pooled
Dexamethasone	60 (56.6)	26 (61.9)	86 (58.1)
Pomalidomide	34 (32.1)	16 (38.1)	50 (33.8)
Cyclophosphamide	33 (31.1)	14 (33.3)	47 (31.8)
Carfilzomib	31 (29.2)	11 (26.2)	42 (28.4)
Bortezomib	27 (25.5)	9 (21.4)	36 (24.3)
Lenalidomide	8 (7.5)	15 (35.7)	23 (15.5)

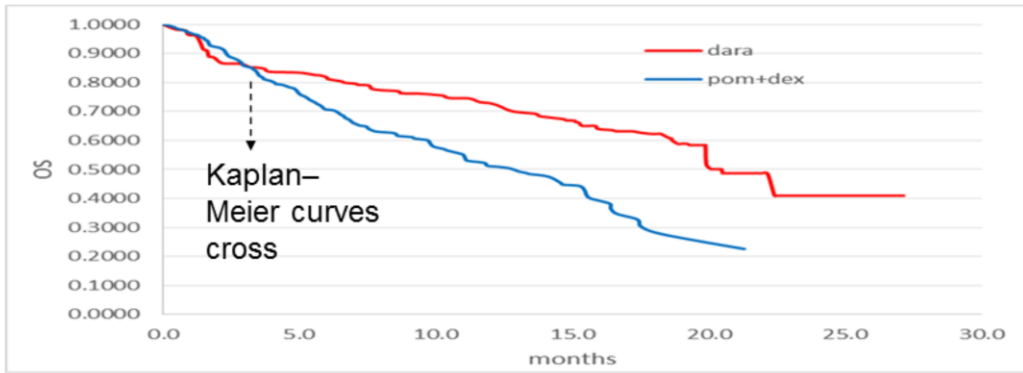
59

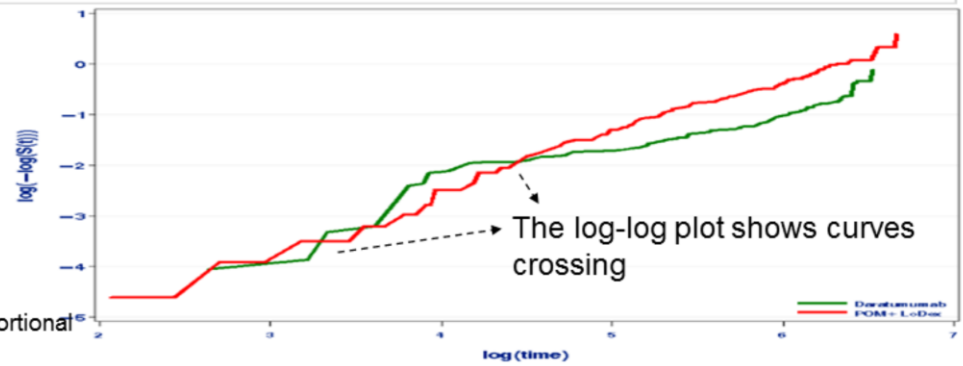
1. Effect of subsequent therapies

60

2. Proportional hazards (PH)

ERG: PH is violated for OS for daratumumab *vs* POM+DEX





Key: PH, proportional hazards

3. MAIC-adjusted HRs

- Based on the recommendation of the NICE Decision Support Unit (DSU), the ERG did not consider that using HRs adjusted for some, but not all possible, characteristics to be appropriate
- The company argued the more characteristics the HRs are adjusted for, the more unstable the estimates will be because the number of matched patients will be reduced
- The ERG agrees that the HRs adjusted for more characteristics reflect poor overlap between study populations and result in highly uncertain estimates
- Nevertheless, it favoured the fully adjusted HRs because even when all observed prognostic/treatment effect modifiers are matched there will unobserved modifiers that confound the analysis

62

3. MAIC-adjusted HRs

All but 1 HR are not statistically significant

	POM+DEX *vs* daratumumab	PANO+BORT+DEX *vs* daratumumab
Company's base case: only important characteristics adjusted		
Population	Pooled	
Number of characteristics adjusted	11	5
Sample size (effective sample size)[1]	148 (84)	125 (80)
PFS HR (95% CI)	1.24 (0.92–1.68)	0.92 (0.62–1.36)
OS HR (95% CI)	1.74 (1.24–2.46)	1.19 (0.73–1.92)
ERG's preferred approach: all possible characteristics adjusted		
Population	MMY2002	
Number of characteristics adjusted	28	16
Sample size (effective sample size)[1]	93 (19)	84 (13)
PFS HR (95% CI)	0.88 (0.49–1.56)	1.18 (0.53–2.56)
OS HR (95% CI)	1.14 (0.57–2.27)	1.64 (0.69–4.00)

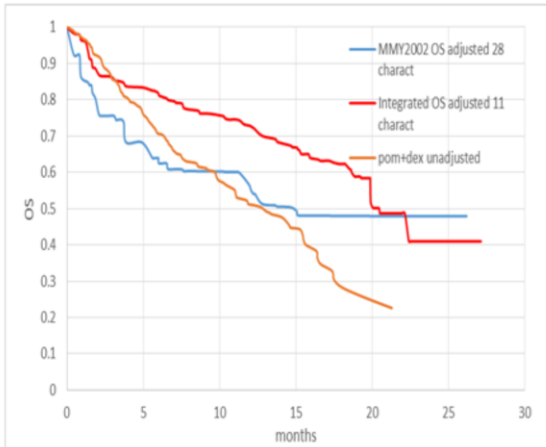
[1]The number of matched patients. The smaller this number is, the poorer the overlap between studies is, and the less stable the estimates are.

63

3. MAIC-adjusted HRs

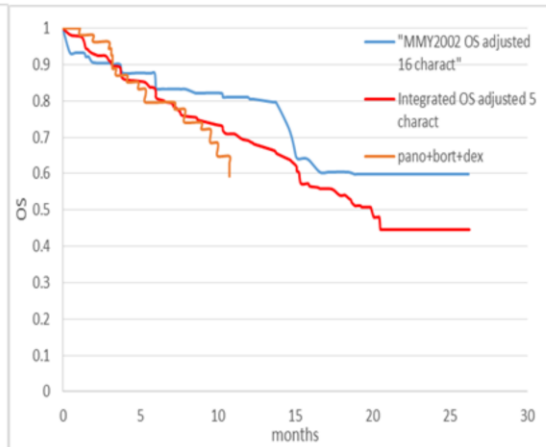
ERG: Number of characteristics adjusted for drastically changes the effect of daratumumab on OS

OS for daratumumab (adjusted) *vs* POM+DEX (unadjusted)



The fully adjusted curve shows <u>much lesser</u> benefit for daratumumab *vs* POM+DEX than the partially adjusted curve

OS for daratumumab (adjusted) *vs* PANO+BORT+DEX (unadjusted)



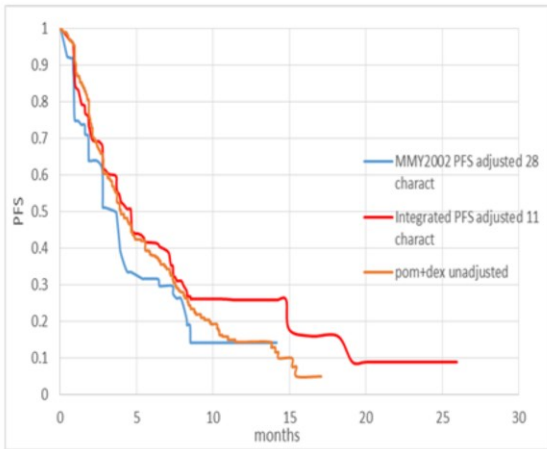
The fully adjusted curve shows <u>more</u> benefit for daratumumab *vs* PANO+BORT+DEX than the partially adjusted curve

64

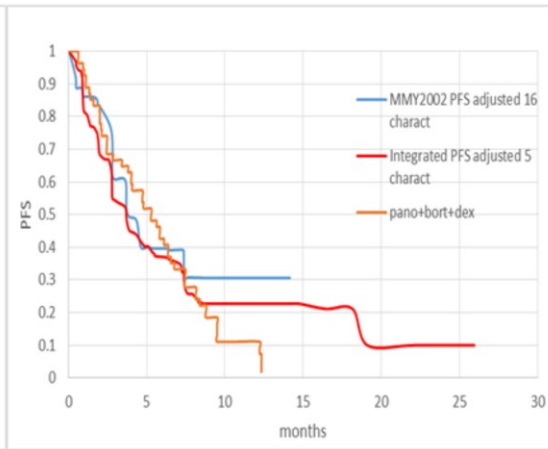
3. MAIC-adjusted HRs

ERG: Number of characteristics adjusted for drastically changes the effect of daratumumab on PFS

PFS for daratumumab (adjusted) *vs* POM+DEX (unadjusted)



PFS for daratumumab (adjusted) *vs* PANO+BORT+DEX (unadjusted)



The number of characteristics adjusted for also changes the relative effect of daratumumab on PFS, although to a lesser extent than that for OS. Yet, the slightest shift in the curves is likely to have an impact on the cost-effectiveness of daratumumab given the sensitivity of the model to PFS.

65

3. MAIC-adjusted HRs

ERG exploratory analyses

- ERG explored the impact of using fully adjusted HRs in the company's base case
- For OS, the ERG also changed the baseline curve used the Weibull distribution instead of the exponential
- The analysis carries the flaws in the company's analysis as it uses dependently fitted curves, but is a 'a step in the right direction'
- The ERG concluded that the model was highly sensitive to adjustment of HRs

Treatment	**ICER (dara'mab *vs* comparator, based on list prices)**			
	PFS		**OS**	
	Company base case	*ERG exploratory analysis*	*Company base case*	*ERG exploratory analysis*
Daratumumab	-	-	-	-
POM+DEX	£55,766	£54,348	£55,766	£154,901
PANO+BORT+DEX	£32,593	£101,040	£32,593	Dara'mab dominates

66

The company supplied unadjusted MAIC data at clarification, however ERG has not used adjusted KM curves in the model (due to time and remit of report).

Utility values

- Quality of life in the model varies on whether or not the disease, and on whether or not the patient experienced adverse reactions to treatment
  - All grade 3 or 4 adverse events occurring in ≥5% of people in the trials were included in the model
- Utility values were based on EQ-5D data collected in MM-003 (Palumbo et al.)
- The data were valued using the UK general population time trade-off values
- The utility decrements of adverse events were based on published estimates, and on expert opinion sought by the company
- Pre-progression state 0.61; progressive disease state 0.57 (same for all treatments)

67

Source: company submission 198-199

MM-003 baseline characteristics are similar to MMY2002

Brown et al: LEN+DEX compared with dexamethasone alone in rrMM

Costs

- Drug costs: acquisition, administration and concomitant medication
- Disease management costs (same for all treatments)
- Adverse events costs
- Cost of treatments received after disease progression
  - Company adjusted the distribution of subsequent therapies received in pivotal trials to reflect available treatments in the UK
- End of life costs

ERG comments

- Not justified in a transparent way and not clinically plausible
- No option to have BSC
- Company assumed 55% of patients receive treatment after daratumumab based on expert opinion instead of 72% in the trials
- Treatments costs do not tally with effectiveness estimates from trials

ERG carried out an explored changing resource use before and after disease progression to reflect feedback from clinical experts

Modelling of subsequent therapies

	Clinical trials		Modelled by company			Modelled by ERG		
	Dara'mab	*POM+ DEX*	*Dara'mab*	*POM+ DEX*	*PANO+ B+DEX*	*Dara'mab*	*POM+ DEX*	*PANO+ B+DEX*
% patients	**72%**	**39%**	**55%**	**39%**	**55%**	**55%**	**39%**	**55%**
DEX	58%	29%	24%	10%	14%	15%	21%	16%
POM+DEX	31%	0%	0%	0%	0%	45%	0%	48%
PANO+B+DEX	-	-	-	-	-	25%	21%	0%
Cyclo'mide	32%	21%	13%	7%	9%	5%	11%	8%
Carfilzomib	28%	2%	0%	0%	0%	-	-	-
Bortezomib	24%	18%	0%	6%	8%	-	-	-
Lenalidomide	15%	5%	-	-	-	-	-	-
Melphalan	16%	8%	9%	0%	0%	-	-	-
Etoposide	10%	3%	6%	0%	0%	-	-	-
Bendamustine	14%	11%	0%	4%	6%	-	-	-
Thalidomide	7%	7%	-	-	-	-	-	-
BSC	-	-	-	-	-	10%	42%	32%

69

Summary of the ERG's comments on clinical effectiveness

	Company's preference	ERG's preferred approach	Rationale for ERG preference
Data source	Pooled data	MMY2002 data	Allows adjusting the HR for more characteristics
Modelling approach	Dependently fitted curves (assumes PH)	Independently fitted curves (does not assumes PH)	The PH assumption does not hold
OS distribution	Exponential	Weibull	To alleviate the assumption of constant hazards characteristic of the exponential distribution
MAIC-adjusted HRs	Adjustment for only the most important characteristics	Adjustment for the maximum number of characteristics possible	Decision Support Unit (DSU) recommendation

70

Results

All the ICERs are presented in the confidential appendix associated with this pre-meeting briefing, as they reflect the patient access scheme discounts for the comparators, which are confidential.

71

ERG general comment on the company's model

The ERG does not consider the company's model to be fit for decision-making because:

- The modelling approach is flawed i.e. curve fitting, the exponential distribution used to extrapolate OS, and the adjusted HRs
- The OS estimates are highly confounded due to subsequent therapies received in the daratumumab trials
- The clear lack of a robust internal quality assurance process on the company's model and data making the economic analysis unsuitable to estimate a reasonably robust ICER.

In the ERG's opinion, the company's model and data analysis need further internal consistency checks and a thorough quality check.

72

ERG exploratory analyses

All use the MMY2002 population

	Scenario	Rationale
1	Using fully adjusted HRs for PFS	DSU recommendation
2	Deriving treatment costs from PFS curves i.e. assuming treatment stops at disease progression	TTD lacks transparency and clarity
3	Using fully adjusted HRs for OS, and a baseline Weibull distribution for daratumumab	DSU recommendation, alleviate constant hazards assumption
4	Changing resource use in health states	Feedback from experts
5	Modelling subsequent therapies received in daratumumab and POM+DEX trials (as far as possible)	Align treatments costs with effectiveness estimates from trials
6	Modelling subsequent therapies based on expert opinion	Reflect clinical practice
7	Assuming no effect for daratumumab on PFS and OS (i.e. HR=1)	None of the HRs is statistically significant
8	Removing the utility decrements for adverse events	Remove double-counting of the impact of AEs

73

Innovation

- Treatment options for heavily pre-treated and refractory population are limited.
- Daratumumab is a first-in-class drug
- Manageable safety profile

74

Equality and diversity

- Multiple myeloma is more common in men than in women and the incidence is also reported to be higher in people of African family origin

75

End of life considerations (1)

NICE criterion	Company assessment	ERG assessment
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median life expectancy: less than 24 months, and is in fact closer to 12 months.	The corrected model for the company's analysis of the MMY2002 population shows the following undiscounted total life-years for each treatment: Daratumumab: 26 months Pom+dex: 17 months Pano+bort+dex: 24 months Bendamustine: 11 months The ERG's exploratory analysis using the fully adjusted HRs shows the following undiscounted total life-years for each treatment: Daratumumab: 25 months Pom+dex: 22 months Pano+bort+dex: 16 months Bendamustine: 11 months

76

Source: ERGR Table 95 pg 282-283

End of life considerations (2)

NICE criterion	Company assessment	ERG assessment
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Mean OS estimates: Daratumumab monotherapy: 2.54 life years (30.4 months) Pano+bort+dex: 2.14 life years (25.7 months) Pom+dex: 1.46 life years (17.5 months) Bendamustine: 1.10 life years (13.2 months) Source: MMY2002/GEN501, PANORAMA 2, MM-003, IMF cohort	The corrected model for the company's analysis of the MMY2002 population shows the following undiscounted total life-years for each treatment: Daratumumab: 26 months Pom+dex: 17 months Pano+bort+dex: 24 months Bendamustine: 11 months The ERG's exploratory analysis using the fully adjusted HRs shows the following undiscounted total life-years for each treatment: Daratumumab: 25 months Pom+dex: 22 months Pano+bort+dex: 16 months Bendamustine: 11 months

77

Source: ERGR Table 95 pg 282-283

Issues

- Overall suitability of the company's model for decision-making
- The lack of RCT data
- The source of data for daratumumab: pooled data *vs* data from MMY2002
- The confounding effect of subsequent therapies
- Subgroups
  - Pomalidomide-naïve
  - Subgroups receiving specific subsequent therapies or no therapies
- The modelling approach: dependently *vs* independently fitted curves (i.e. PH *vs* no PH)
- MAIC-adjusted HRs: some characteristics matched *vs* maximum number of characteristics
- Estimating treatment costs: TTD *vs* PFS
- Estimating treatment costs for subsequent therapies

78

Authors

- **Jessica Maloney**
  Technical Lead
- **Ahmed Elsada**
  Technical Adviser
- with input from the Lead Team Sumeet Gupta and John Cairns

79

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of daratumumab within its marketing authorisation for treating relapsed and refractory multiple myeloma.

Background

Multiple myeloma is a form of cancer that arises from plasma cells (a type of white blood cell) in the bone marrow. Myeloma cells produce large quantities of an abnormal antibody, known as paraprotein. Unlike normal antibodies, paraprotein has no useful function and lacks the capacity to fight infection. Myeloma cells supress the development of normal blood cells that are responsible for fighting infection (white blood cells), carrying oxygen around the body (red blood cells) and blood clotting (platelets). The term multiple myeloma refers to the presence of more than one site of affected bone at the time of diagnosis. People with multiple myeloma can experience bone pain, bone fractures, tiredness (due to anaemia), infections, hypercalcaemia (too much calcium in the blood) and kidney problems.

In 2013, 4,703 people were diagnosed with multiple myeloma in England[i]. Forty-three percent of people diagnosed are aged 75 years and over[i]. Multiple myeloma is more common in men than in women and the incidence is also reported to be higher in people of African family origin[i]. The 5-year survival rate for adults with multiple myeloma in England is estimated to be 47%[ii].

The main aims of therapy are to prolong survival and maintain a good quality of life by controlling the disease and relieving symptoms. Following initial treatment, subsequent therapy is influenced by previous treatment and response to it, duration of remission, comorbidities and patient preference. NICE technology appraisal guidance 129 recommends bortezomib monotherapy as an option for treating progressive multiple myeloma in people who are at first relapse having received 1 prior therapy and who have undergone, or are unsuitable for bone marrow transplantation. NICE technology appraisal guidance 171 recommends lenalidomide in combination with dexamethasone as a treatment option for people with multiple myeloma who have received at least 2 prior therapies. NICE technology appraisal guidance 380 recommends panobinostat in combination with bortezomib and dexamethasone as an option for treating multiple myeloma in adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent. For people who have had at least 3 prior therapies, treatment options include

bendamustine (available through the Cancer Drugs Fund) or combination chemotherapy regimens (for example, alkylating agents such as melphalan and cyclophosphamide). Other subsequent treatment options may include repeating high-dose chemotherapy or chemotherapy with alkylating agents and anthracyclines, thalidomide and corticosteroids. NICE technology appraisal guidance 338 does not recommend pomalidomide in combination with dexamethasone for treating relapsed or refractory multiple myeloma in adults who have had at least 2 previous treatments, including lenalidomide and bortezomib. NICE has decided to review technology appraisal 338 because new clinical evidence is available and the company is proposing a patient access scheme for pomalidomide.

The technology

Daratumumab (Darzalex, Janssen) is a humanised monoclonal antibody that kills multiple myeloma cells, targeting the CD38 protein. It is administered intravenously.

Daratumumab has a marketing authorisation in the UK for treating adults with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

Intervention(s)	Daratumumab
Population(s)	People with relapsed and refractory multiple myeloma that has previously been treated with a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy
Comparators	• Panobinostat with bortezomib and dexamethasone • Lenalidomide with dexamethasone • Pomalidomide with dexamethasone (subject to ongoing NICE appraisal) • Bendamustine (not appraised by NICE but funded via the Cancer Drugs Fund; does not currently have a marketing authorisation in the UK for this indication)

Outcomes	The outcome measures to be considered include: • progression-free survival • overall survival • response rates • time to next treatment • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Bortezomib monotherapy for relapsed multiple myeloma' (2007). NICE technology appraisal 129. Moved to static list, November 2012. 'Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy' (2009). NICE technology appraisal 171. Moved to static list, November 2012. 'Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib' (2015). NICE technology appraisal 338. Update in progress. 'Panobinostat for treating multiple myeloma after at least 2 previous treatments' (2016). NICE technology

	appraisal 380. Review date March 2018. Appraisals in development 'Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib' NICE technology appraisals guidance ID985. Publication expected April 2017. 'Elotuzumab for previously treated multiple myeloma'. NICE technology appraisals guidance [ID855]. Publication date to be confirmed. 'Carfilzomib in combination with dexamethasone for previously treated multiple myeloma'. NICE technology appraisals guidance [ID934]. Publication expected April 2017. 'Lenalidomide for the treatment of multiple myeloma following treatment with bortezomib' (part review of Technology Appraisal guidance 171). NICE technology appraisal [ID667]. Publication date to be confirmed. 'Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma'. NICE technology appraisal [ID807]. Publication expected January 2017. Related Guidelines: 'Myeloma: diagnosis and management of myeloma'. NICE guideline 35. Review date to be confirmed. NICE pathway: Blood and bone marrow cancers, Pathway created: December 2013
Related National Policy	NHS England (2014) 'Manual for prescribed specialised services 2013/14'. Chapter 29. Department of Health (2014) 'NHS Outcomes Framework 2015-16'. Domains 1 to 5.

References

[i] Cancer Research UK (2013). Multiple myeloma incidence statistics. Accessed February 2016.
[ii] Cancer Research UK (2011). Multiple myeloma survival statistics. Accessed February 2016.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933]

Final matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Janssen (daratumumab) Patient/carer group • Black Health Agency • Bloodwise • Cancer Black Care • Cancer Equality • Cancer52 • Delete Blood Cancer • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Leukaemia Cancer Society • Leukaemia CARE • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • Myeloma UK • Rarer Cancers Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care Professional groups • Association of Cancer Physicians • British Committee for Standards in Haematology • British Geriatrics Society • British Psychosocial Oncology Society • British Society for Haematology • Cancer Research UK • Royal College of General Practitioners	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Possible comparator companies • Aspen (dexamethasone) • Celgene (lenalidomide, pomalidomide) • Focus Pharmaceuticals (dexamethasone) • Hameln Pharmaceuticals (dexamethasone) • Hospira (dexamethasone) • Janssen (bortezomib) • Merck, Sharp and Dohme (dexamethasone) • Novartis (panobinostat) • Rosemont Pharmaceuticals (dexamethasone) Relevant research groups

Consultees	**Commentators (no right to submit or appeal)**
• Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • UK Health Forum • UK Myeloma Forum • UK Clinical Pharmacy Association • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS England • NHS Kingston CCG • NHS Lancashire North CCG • Welsh Government	• Cochrane Haematological Malignancies Group • Institute of Cancer Research • Leuka • Leukaemia Busters • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do share it. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies;
Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Daratumumab for treating relapsed and refractory multiple myeloma [ID933]

Company evidence submission

[November 2016]

File name	Version	Contains confidential information	Date
[ID933]_Janssen_Daratumumab_submission_25112016 [ACIC]	**4.0**	**Yes**	**25th November 2016**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

Tables

Figures

Abbreviations

Abbreviation	Definition
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse event
AIC	Akaike information criterion
ALKY	Alkylating agents
ASCT	Autologous stem cell transplant
BIC	Bayesian information criterion
BORT	Bortezomib
BSA	Body surface area
BSC	Best supportive care
CARF	Carfilzomib
CC	Complications and comorbidity
CDC	Complement-dependent cytotoxicity
CDF	Cancer Drugs Fund
CE	Cost Effectiveness
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CR	Complete response
CTD	Cyclophosphamide, thalidomide, dexamethasone
DARA	Daratumumab
DC	Discontinuation
DCEP	Dexamethasone, cyclophosphamide, etoposide + cisplatin
DEX	Dexamethasone
DoR	Duration of response
DRMM	Double relapsed and refractory multiple myeloma
DT-PACE	Dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide
EAP	Early access programme
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMC	Electronic medicines compendium
eMIT	Electronic market information
EMR	Electronic medical record
EORTC	European Organization for Research and Treatment of Cancer

Abbreviation	Definition
EPAR	European public assessment report
ERG	Evidence review group
ESMO	European Society for Medical Oncology
FDA	US Food and Drug Administration
GCSF	Granulocyte colony-stimulating factor
GP	General practitioner
HiDex	High-dose dexamethasone
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IgA/D/G/M	Immunoglobulin A/D/G/M
IMF	International Myeloma Foundation
IMiD	Immunomodulatory
IMWG	International Myeloma Working Group
INV	Investigator
IPD	Individual patient-level data
IRC	Independent review committee
IRR	Infusion-related reactions
ISS	International Staging System
ISSG	Information Specialists' Sub-Group
ITC	Indirect treatment comparison
IV	Intravenous
KM	Kaplan-Meier
LEN	Lenalidomide
LoDEX	Low-dose dexamethasone
LOT	Lines of treatment
LY	Life-year
MAIC	Matching-adjusted indirect comparison
mEBMT	Modified European Group for Blood and Marrow Transplant
MIMS	Monthly Index of Medical Specialities
MM	Multiple myeloma
MoA	Mechanism of action
MPB	Melphalan, prednisone, bortezomib
MPL	Melphalan, prednisone, lenalidomide
MPT	Melphalan, prednisone, thalidomide

Abbreviation	Definition
MR	Minimal response
MRI	Magnetic resonance imaging
MRU	Medical resource utilisation
MTA	Multiple technology appraisal
MTD	Maximum tolerated dose
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NR	Not reported
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analyses
PACE	Patient and Clinician Engagement
PAD	Adriamycin, bortezomib, dexamethasone
PANO	Panobinostat
PD	Progressive disease
PFD	Progression-free disease
PFS	Progression-free survival
PH	Proportional hazard
PI	Proteasome inhibitor
POM	Pomalidomide
PPS	Post-progression survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life-year
QoL	Quality of life
RBC	Red blood cell
RCT	Randomised controlled trial
rrMM	Relapsed and refractory multiple myeloma
RU	Resource use
RWE	Real world evidence
SA	Sensitivity analysis
ScHARR	School of Health and Related Research

Abbreviation	Definition
sCR	Stringent complete response
SCT	Stem cell transplant
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SmPC	Summary of product characteristics
SQ	Subcutaneous
STA	Single technology appraisal
TAD	6-thioguianine, cytarabine, daunorubicin
TEAE	Treatment-emergent adverse events
TFI	Treatment-free interval
THAL	Thalidomide
TSD	Technical support document
TTD	Time to treatment discontinuation
TTR	Time to response
VAD	Vincristine, doxorubicin, dexamethasone
VBA	Visual Basic for Applications
VCD	Bortezomib, cyclophosphamide, dexamethasone
VGPR	Very good partial response
VMP	Bortezomib, melphalan, prednisone
VMPT-VT	Bortezomib, melphalan, prednisone, thalidomide- bortezomib, thalidomide
VRD	Bortezomib, lenalidomide, dexamethasone
VTD	Bortezomib, dexamethasone, thalidomide, cisplatin
ZOL	Zoledronic acid

1 Executive summary

Daratumumab (Darzalex®) is a first-in-class, fully human $IgG1_K$ monoclonal antibody that induces myeloma cell death through a multitude of mechanisms by targeting CD38. The licensed indication for daratumumab monotherapy is *"for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy."* This indication is based on Phase II and earlier Phase I/II data that support a positioning of daratumumab in the fourth-line setting. Marketing authorisation was granted by the European Medicines Agency (EMA) after accelerated assessment in light of the unmet medical need and primary efficacy demonstrated in early phase trials. Daratumumab was also granted breakthrough designation by the US Food and Drug Administration (FDA) for encouraging activity as a single agent in relapsed and refractory multiple myeloma (rrMM).

CD38 is a distinct and novel target from those of other approved agents for multiple myeloma (MM) and is universally expressed; meaning daratumumab is effective, irrespective of clonal heterogeneity. This is crucial in the relapsed and refractory setting where clonal heterogeneity contributes to the progression of MM and the development of drug resistance. In the absence of a cure, all patients with MM eventually relapse and with each successive relapse, the chance of durable response decreases, with patients becoming refractory to treatment over time. Each relapse is therefore associated with a marked reduction in prognosis and health-related quality of life (HRQL). Patients' health status is also impaired at each relapse through the cumulative toxicity of multiple treatment regimens. The European Medicines Agency (EMA) acknowledge that median survival is only between eight to nine months in this patient population. Real world evidence (RWE) also confirms that patients who have progressive disease following prior therapy with a proteasome inhibitor (PI) and immunomodulatory agent (IMiD) have short life expectancy.

In the pivotal Phase II trial, MMY2002 (SIRIUS), and earlier Phase I/II trial, GEN501, daratumumab monotherapy was associated with a deep and durable clinical response and high levels of disease stabilisation; both desirable and clinically meaningful outcomes in the fourth-line setting. Despite the poor prognosis of patients

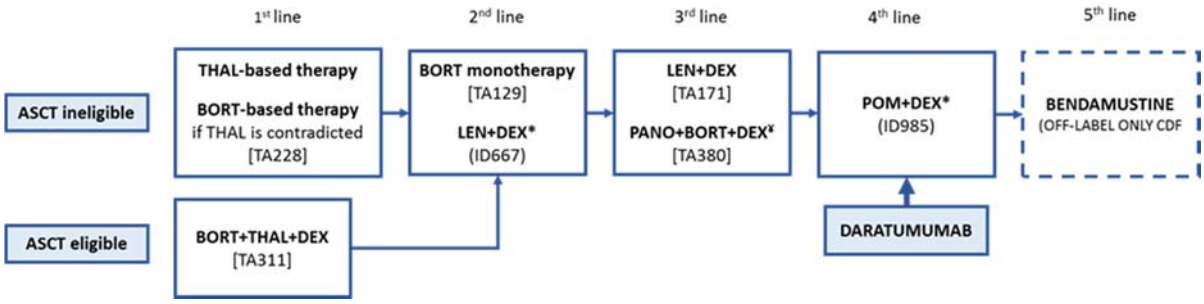
enrolled in MMY2002 and GEN501, who were heavily pre-treated (median of five prior therapies) and highly refractory (86.5% of patients double refractory to a PI and an IMiD), daratumumab monotherapy provided an unprecedented survival benefit, resulting in a median overall survival (OS) of 20.1 months.

As the first treatment to demonstrate single agent efficacy in rrMM, daratumumab represents a step-change in the management of this condition. Research is ongoing as to the exact biological processes involved in the unprecedented clinical efficacy observed, but it is almost certainly attributable to the novel and unique multifactorial MoA of daratumumab which appears to change the natural course of disease, such that the disease is effectively reset. Daratumumab is an innovative treatment that enables patients to be able to regain somewhat normal living, previously thought unattainable. Furthermore, the psychological impact and hope that a life-extending medicine such as daratumumab monotherapy offers a patient and their family should be acknowledged, as well as wider emotional benefits that are not intrinsically captured in the QALY

Importantly, daratumumab was well tolerated with clinically manageable side effects, as evidenced by the fact that no patients died or discontinued due to study drug toxicity. Daratumumab's favourable safety profile, coupled with the apparent disease reset, culminates in an improved health status of patients. This allows patients, upon inevitable progression (given rrMM is incurable), to receive and benefit from further active treatment to which they were previously refractory.

Due to the heterogeneity of MM, it is not possible to define a sequential treatment pathway that is applicable to all patients; however, pomalidomide in combination with dexamethasone (POM+DEX) is the most likely alternative treatment to be used in the fourth-line setting in National Health Service (NHS) England. While POM+DEX is currently under NICE appraisal, it has been widely used on the Cancer Drugs Fund (CDF) in previous years, thus making it the most appropriate comparator for consideration (Figure 1).

Figure 1. Treatment pathway in rrMM



Key: ASCT, autologous stem-cell transplant; BORT, bortezomib; BORT+THAL+DEX, bortezomib plus thalidomide plus dexamethasone; CDF, Cancer Drugs Fund; LEN+DEX, lenalidomide plus dexamethasone; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; POM+DEX, pomalidomide plus dexamethasone.

Other treatments listed in the NICE scope include lenalidomide in combination with dexamethasone (LEN+DEX), panobinostat in combination with bortezomib plus dexamethasone (PANO+BORT+DEX) and bendamustine.

In current practice, LEN+DEX is used earlier in the treatment pathway (i.e. third-line). Trial data for daratumumab monotherapy are derived from a heavily pre-treated patient group, of whom 98% had received prior lenalidomide and 84% were refractory to lenalidomide. As such a fair comparison to LEN+DEX is impossible given the available evidence. For these reasons, LEN+DEX is not considered further in this submission.

PANO+BORT+DEX is recommended by NICE as a third-line treatment option, based on the PANORAMA 1 trial. However, as a consequence of toxicity concerns, uptake has been low and generally at fourth-line rather than third-line. Evidence for the effectiveness of PANO+BORT+DEX at fourth-line is limited to the PANORAMA 2 trial (n=55) and as such it is difficult to determine comparative effectiveness in this patient population.

Only when a patient has “relapsed disease where all other treatments are contraindicated or inappropriate” could off-label bendamustine be considered for use through the CDF. The restricted terms for use of bendamustine means it would only ever be used after, and not instead of, daratumumab monotherapy. Therefore, bendamustine is not a relevant comparator.

POM+DEX, PANO+BORT+DEX and bendamustine are all associated with several limitations, including considerable toxicity concerns and limited proven clinical

benefit. As a result, many rrMM patients are not receiving effective, tolerable therapy in clinical practice, optimal for their care, hence emphasising the unmet need in this setting.

In the absence of head-to-head data, indirect estimates of comparative efficacy have been synthesised from the wider evidence base. Results of these analyses suggest daratumumab monotherapy offers a superior survival benefit compared with alternative fourth-line treatments used in the NHS. Based on matching-adjusted indirect comparisons (MAICs), daratumumab monotherapy demonstrated a statistically significant reduced risk of death compared with POM+DEX and a clinically meaningful OS benefit against PANO+BORT+DEX. Based on multivariate regression analysis, daratumumab monotherapy demonstrated a statistically significant reduced risk of death compared with bendamustine-based therapy. While being mindful of cross-trial naïve comparisons, qualitative synthesis of safety data suggests that daratumumab monotherapy also offers an improved safety profile compared with these alternative treatment options.

Daratumumab has beeng granted orphan designation from the Committee for Orphan Medicinal Products (COMP) and meets the NICE end-of-life criteria. Clinical expert opinion strongly supports the end-of-life criteria for effective treatments in the fourth-line setting of rrMM and this aligns with previous NICE conclusions that end-of-life criteria applied for POM+DEX.

To analyse the cost-effectiveness of daratumumab monotherapy, an economic model was constructed using health states to capture disease progression and treatment status. The analysis demonstrates that daratumumab is an effective and life-extending treatment for patients with rrMM at fourth-line. Incremental cost-effectiveness ratios (ICERs), using list-prices for all interventions, are close to NICE's willingness to pay (WTP) threshold for end-of-life, orphan treatments.

At list price, daratumumab monotherapy is estimated to provide an incremental benefit of 0.54 quality-adjusted life years (QALYs) versus POM+DEX, 0.19 QALYs versus PANO+BORT+DEX, and 0.74 QALYs versus bendamustine-based therapy. These health gains contribute to offseting the incremental cost of daratumumab monotherapy resulting in cost per QALY estimates of £53,804, £24,109, and £55,161, respectively.

As with all economic evaluations, estimates of cost-effectiveness are not without uncertainty. Sensitivity analyses revealed that the key driver of uncertainty is comparative effectiveness, particularly versus PANO+BORT+DEX and also versus bendamustine-based therapy. This is because of the paucity of effectiveness data for PANO+BORT+DEX or bendamustine in heavily pre-treated and highly refractory MM patients. Given the nature and type of uncertaintly, engaging in the new CDF would not alleviate the uncertainty inherent in this appraisal, as it is highly unlikely that enough patients would be treated with PANO+BORT+DEX or bendamustine in clinical practice to inform robust estimates of comparative effectiveness. Furthermore, should daratumumab monotherapy be available in clinical practice, it is unlikely that patients receiving daratumumab would be comparable to patients receiving PANO+BORT+DEX or bendamustine-based therapy. Consultation with clinical experts confirmed that PANO+BORT+DEX is most likely to be reserved for patients where retreatment with bortezomib is sought and bendamustine-based therapy will be reserved for when all other active treatment options have been exhausted.

In conclusion, daratumumab represents a step-change in the treatment of rrMM. The novel MoA, durable clinical response, and a manageable safety profile of daratumumab results in long-term survival benefit and improved quality of life. As recognised by the COMP and the EMA, daratumumab monotherapy has great potential to fulfil the unmet medical need in rrMM. Daratumumab monotherapy offers a cost-effective use of NHS resources in this small group of end-of-life patients.

1.1 Statement of decision problem

The decision problem addressed in this submission, compared with that defined in the final scope issued by NICE, is summarised in Table 1.

Of note, daratumumab monotherapy is positioned for use in the fourth-line setting, in line with available trial data. Since the final scope was informed by the license indication for daratumumab monotherapy, which technically allows it to be used earlier in the treatment pathway, the comparators included in the submission differ slightly from those outline in the final scope.

The trial data for daratumumab is derived from a heavily pre-treated patient group, of whom 98% had received prior lenalidomide and 84% refractory to lenalidomide, therefore a fair comparison to LEN+DEX is not possible.

It should be noted that the restricted terms for use of bendamustine means it would only ever be used after, and not instead of, daratumumab monotherapy. Bendamustine is therefore not a relevant comparator.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with relapsed and refractory multiple myeloma that has previously been treated with a proteasome inhibitor and an immunomodulatory agent, and who have demonstrated disease progression on the last therapy.	People with relapsed and refractory multiple myeloma that has previously been treated with a proteasome inhibitor and an immunomodulatory agent, and who have demonstrated disease progression on the last therapy. The typical position of daratumumab monotherapy is anticipated to be as an alternative treatment for people who have received three or more prior therapies.	The anticipated positioning is based on the available trial data for daratumumab monotherapy.
Intervention	Daratumumab	Daratumumab monotherapy	-
Comparator (s)	▪ Panobinostat with bortezomib and dexamethasone ▪ Lenalidomide with dexamethasone ▪ Pomalidomide with dexamethasone (subject to ongoing NICE appraisal) ▪ Bendamustine (not appraised by NICE but funded via the Cancer Drugs Fund; does not currently have a marketing authorisation in the UK for this indication)	▪ Panobinostat with bortezomib and dexamethasone ▪ Pomalidomide with dexamethasone (subject to ongoing NICE appraisal) ▪ Bendamustine (not appraised by NICE but funded via the Cancer Drugs Fund; does not currently have a marketing authorisation in the UK for this indication)	Due to the anticipated positioning for daratumumab monotherapy, and the preclusion of fair comparison due to lenalidomide pre-treatment in the daratumumab trial patients; LEN+DEX is not considered
Outcomes	The outcome measures to be considered include: ▪ Progression-free survival ▪ Overall survival ▪ Response rates ▪ Time to next treatment	The outcome measures to be considered include: ▪ Progression-free survival ▪ Overall survival ▪ Response rates ▪ Time to next treatment	-

	▪ Adverse effects of treatment ▪ Health-related quality of life	▪ Adverse effects of treatment ▪ Health-related quality of life ▪ Time to treatment discontinuation	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.	A cost-effectiveness analysis expressed in terms of incremental cost per quality-adjusted life year is presented. A lifetime time horizon of 15 years is used in the base-case analysis. Costs are considered from a National Health Service and Personal Social Services perspective. List prices are used within the submission document as requested by NICE.	-
Subgroups to be considered	None identified.	-	-
Special considerations including issues related to equity or equality	None identified.	-	-
Key: LEN+DEX, lenalidomide plus dexamethasone.			

1.2 Description of the technology being appraised

Details of the technology being appraised in this submission are summarised in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Daratumumab (Darzalex®)
Marketing authorisation status	Marketing authorisation was granted by the EMA on 20 May 2016
Indications and any restriction(s) as described in the summary of product characteristics	The licensed indication for daratumumab monotherapy is: *"For the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy."*
Method of administration and dosage	Daratumumab 16mg/kg is administered through intravenous infusion. Daratumumab is administered every week for weeks 1-8, every 2 weeks for weeks 9 to 24 and every four weeks from week 25 onwards.
Key: EMA, European Medicines Agency.	

1.3 Summary of the clinical effectiveness analysis

The clinical trial programme supporting the use of daratumumab monotherapy for the treatment of patients with rrMM whose prior therapy included a PI and an IMiD, and who have demonstrated disease progression on the last therapy, consists of one Phase II trial, MMY2002 and one earlier Phase I/II trial, GEN501. Integrated analyses of patients treated with daratumumab 16mg/kg monotherapy across the MMY2002 and GEN501 trials are summarised below:

- In total, 148 patients were treated with daratumumab 16mg/kg monotherapy; these patients were heavily pre-treated (median of five prior therapies) and highly refractory (86.5% of patients double refractory to a PI and an IMiD).

- In primary endpoint analysis, the overall response rate (ORR) assessed by independent review committee (IRC) using International Myeloma Working Group (IMWG) criteria was 31%.
  - The median time to response (TTR) was 1.0 month and the median duration of response (DoR) was 8.0 months with 22% of patients remaining progression-free at two years.
  - Further to clinical response, the clinical benefit rate (at least minimal response [MR]) was 37%, and 83% of patients achieved at least disease stabilisation.
- In secondary endpoint analysis, the median OS was 20.1 months (95% CI: 16.6, not reached) and the 2-year OS rate was 45% (median follow-up 20.7 months).
  - Median OS was not reached in responding patients, with 76% alive at 2 years.
  - Median survival in patients who experienced at least stabilisation of disease was 18.5 months (95% CI: 15.1, 22.4), with 35% alive at 2 years.
- In safety analysis, there were low rates of discontinuation or death due to treatment-emergent adverse events (TEAE) (4% and 2%, respectively) and no patient discontinued treatment or died due to a study-drug related TEAE.

In the absence of head-to-head trials between daratumumab monotherapy, POM+DEX, PANO+BORT+DEX and bendamustine-based therapy, indirect treatment comparison (ITC) is required to synthesise the relative differences in OS and progression-free survival (PFS) between treatments. The most robust sources of efficacy in the patient population of interest to this appraisal for POM+DEX and for PANO+BORT+DEX were identified through systematic literature review (SLR) as the MM-003 trial (n=302) and the PANORAMA 2 trial (n=55), respectively. Given the lack of a common comparator between trials, a standard ITC could not be undertaken. An unadjusted comparison would derive biased estimates of relative efficacy due to variation across trial populations, particularly in prior treatment exposure with the daratumumab-treated patients representing a more heavily pre-treated population.

Therefore, a more sophisticated approach was used in the form of MAIC, for which there is precedent in previous NICE health technology appraisals (HTAs). No robust sources of efficacy in the patient population of interest to this appraisal were identified for bendamustine-based therapy through SLR. Therefore, individual patient-level data (IPD) from a retrospective chart review of the International Myeloma Foundation (IMF) were used in multivariate regression analyses; a method recognised by NICE as a robust way of using observational data to inform estimates of treatment effectiveness.

Using MAIC, daratumumab monotherapy demonstrated a reduced risk of death compared with POM+DEX and PANO+BORT+DEX, irrespective of the number of characteristics matched.

The comparison of daratumumab with POM+DEX resulted in a statistically significant hazard ratio (HR) for death of 0.57 (95% CI: 0.41, 0.81); improving to 0.42 (95% CI: 0.30, 0.60) in sensitivity analysis which focussed on POM+DEX naïve patients. The comparison of daratumumab with PANO+BORT+DEX resulted in a HR for death of 0.84 (95% CI: 0.52, 1.37). As a consequence of the paucity of effectiveness data for PANO+BORT+DEX in the fourth-line patient population, this result is not statistically significant; however, this result represents a clinically meaningful OS benefit to patients.

In multivariate regression analysis, daratumumab monotherapy was associated with a statistically significant reduction in the risk of death versus bendamustine-based therapy, with a HR of 0.43 (95% CI: 0.30, 0.63); $p<0.001$.

While being mindful of cross-trial naïve comparisons, qualitative synthesis of safety data suggests that daratumumab monotherapy also offers an improved safety profile compared with alternative treatment options with markedly reduced rates of serious TEAEs, discontinuations due to TEAEs, dose modifications for AE management, and deaths due to TEAEs. This is particularly important for these end-of-life patients who have been exposed to multiple prior regimens. Indeed, this favourable safety profile and novel MoA contributes to an improved health status, meaning patients survive to benefit from subsequent active treatment.

1.4 Summary of the cost-effectiveness analysis

To appraise the cost-effectiveness of daratumumab in rrMM patients, a de novo economic model was developed. A semi-Markov partitioned-survival cohort model approach was designed to be consistent with previously accepted economic models in rrMM, and to capture the key clinical outcomes of time to treatment discontinuation, PFS and OS. Parametric extrapolation of clinical data from the integrated MMY2002/GEN501 dataset were used to inform effectiveness estimates for daratumumab monotherapy; the best available approaches were used to compare these single-arm effectiveness data to POM+DEX, PANO+BORT+DEX and bendamustine-based therapy, with robust and extensive testing of the assumptions and uncertainty around these comparisons. Since the EMA granted early license based on Phase II data, in which no HRQL was collected, HRQL assumptions are based on EQ-5D data from POM+DEX trial patients. HRQL and resource use assumptions were designed to be both conservative and consistent with key recent NICE appraisals (TA338 and TA380).

Daratumumab monotherapy is estimated to provide an incremental benefit of 0.54 quality-adjusted life years (QALYs) versus POM+DEX, 0.19 QALYs versus PANO+BORT+DEX, and 0.74 QALYs versus bendamustine-based therapy. These health gains contribute to offseting the incremental cost of daratumumab monotherapy resulting in cost per QALY estimates (at list price) of £53,804, £24,109, and £55,161, respectively.

Notwithstanding limitations in the available data, comprehensive sensitivity analyses demonstrate that the results are generally robust; particularly with respect to the key comparator of interest POM+DEX. The probability of daratumumab being cost-effective at a WTP threshold of £50,000/QALY is 43%, 63% and 39% versus POM+DEX, PANO+BORT+DEX and bendamustine-based therapy, respectively. Moreover, there are numerous plausible scenarios in which daratumumab is estimated to be more cost-effective than shown in the base-case reflecting the conservative nature of the overall economic evaluation.

Cancer Drugs Fund Considerations

Under new NICE processes, additional data may be collected over a funded period of up to two years with the aim of reducing the uncertainty inherent to an appraisal. While further data collection through the CDF was considered by Janssen, it was concluded that additional data gathered through the CDF would not be sufficient to reduce uncertainty within the current decision problem, for the following reasons:

- Given that MM is an orphan condition, it is unlikely that the number of rrMM patients treated with daratumumab, PANO+BORT+DEX and bendamustine in clinical practice would facilitate robust estimates of comparative effectiveness.
- The comparability of patients treated with daratumumab monotherapy and alternative treatments available in clinical practice is likely to be low. This is because daratumumab is likely to be the treatment of choice given the limitations associated with alternative therapies.

Moreover, with the anticipated approval of POM+DEX as well as a number of pipeline therapies coming through in MM, the time horizon of the decision problem is likely to be less than two years. The time horizon of the decision problem is defined in the NICE decision support unit [DSU] report on managed entry agreements as the number of years which the decision maker considers the decision between the treatment options to be relevant. That is to say, in two years' time the comparative effectiveness of daratumumab monotherapy versus PANO+BORT+DEX and versus bendamustine-based therapies is unlikely to be relevant.

2 The technology

2.1 Description of the technology

Brand Name: Darzalex®

UK approved name: Daratumumab

Therapeutic class: immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody (mAb)

Brief overview of the mechanism of action:

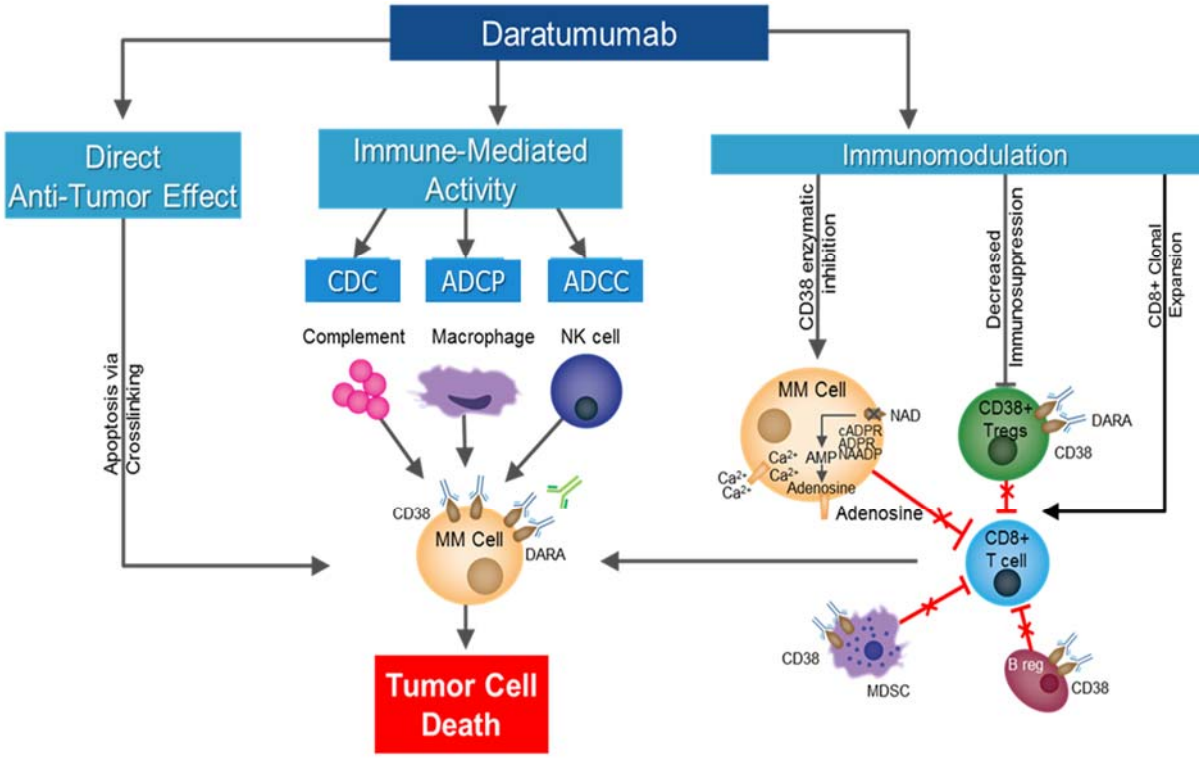
Daratumumab is a first-in-class, fully human IgG1κ mAb with a serum half-life of 21 days.[1] Daratumumab binds to CD38, a transmembrane glycoprotein that is highly and ubiquitously expressed on the surface of many immune cells, including plasma cells and myeloma cells.[2, 3] CD38 has several functions in cell adhesion, signal transduction and calcium signalling, such that CD38-positive cell populations are associated with decreased immune function and disease progression in multiple myeloma (MM).[1, 4] CD38 is a distinct and novel target from those of other approved agents for MM due to its universal expression in plasma and myeloma cells. This universal expression not only allows daratumumab to induce myeloma cell death through the multifactorial mechanisms described below, but also means daratumumab is effective, irrespective of clonal heterogeneity, which is crucial in the relapsed and refractory setting where clonal heterogeneity is commonly observed (see Section 3.1).

As depicted in Figure 2, daratumumab binding to CD38 induces a number of parallel processes that contribute to myeloma cell death. These processes include immune-mediated mechanisms of action (complement-dependent cytotoxicity [CDC], antibody-dependent cell-mediated cytotoxicity [ADCC] and antibody-dependent cellular phagocytosis [ADCP]) as well as induction of myeloma cell apoptosis (via Fc receptor-mediated crosslinking) and various immunomodulatory mechanisms.[4-8] The extent of the immunomodulatory effects of daratumumab is still under investigation, but to date, its immunomodulatory mechanisms described include:

- Reduction of CD38-positive immunosuppressive cell populations including T regulatory cells, myeloid derived suppressor cells and B regulatory cells[8]
- Modulation of the enzymatic activity of CD38 that may lead to a reduction in immunosuppressive adenosine levels[8]
- Induction of helper and cytotoxic T-cell expansion and production of interferon-gamma in response to viral peptides[8]
- Increased T-cell receptor (CD38) clonality[8]

These immunomodulatory mechanisms serve to decrease immunosuppression and increase adaptive immune responses that may contribute to deeper clinical responses and enhanced survival.

Figure 2: Mechanism of action of daratumumab



Key: ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; MM, multiple myeloma; NK, natural killer.
Source: adapted from Usmani et al. 2015.[9]

2.2 Marketing authorisation/CE marking and health technology assessment

The licensed indication for daratumumab monotherapy is:

"For the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy."

This indication is based upon the results of MMY2002, a Phase II, randomised, two-part study evaluating daratumumab monotherapy in patients with relapsed and refractory multiple myeloma (rrMM) previously treated with at least three prior therapies (including proteasome inhibitors [PI] and immunomodulatory [IMiD] agents) or who are refractory to both a PI and IMiD (see Section 4). Supportive evidence came from GEN501, a Phase I/II study evaluating daratumumab monotherapy in MM patients whose disease was relapsed and refractory to two prior lines of therapies and without further established treatment options (see Section 4).

Marketing authorisation was granted by the European Medicines Agency (EMA) on 20 May 2016 after accelerated assessment in light of the unmet medical need and promising efficacy demonstrated in early phase trials. A positive opinion from the Committee for Medicinal Products for Human Use (CHMP) was granted in April 2016. Daratumumab is also approved for use in this indication by the US Food and Drug Administration (FDA), who granted breakthrough designation in November 2015 for encouraging activity as a single agent in rrMM.

The summary of product characteristics (SmPC) and the European public assessment report (EPAR) are provided in Appendix 1.

While the absence of a control arm and the small number of patients treated with daratumumab in MMY2002 and GEN501 (see Section 4) was identified by the EMA to impact on the interpretation of efficacy and safety data, they recognised that "an ORR of 29%-36% is quite high for monotherapy in this clinical setting and a clinical benefit for daratumumab, can be considered established" and that "the overall safety profile of daratumumab 16 mg/kg dosing regimen is considered acceptable…. the adverse events appeared manageable". The EMA noted that comparative

confirmatory Phase III studies are required in order to better quantify the magnitude of effect and further establish the safety profile, and thus, the final clinical study reports (CSRs) for Phase III studies of daratumumab combination therapy at an earlier line of treatment for rrMM are to be submitted to the EMA once available.

Daratumumab has also been submitted to the Scottish Medicines Consortium (SMC) for rrMM. Daratumumab has been accepted as an orphan, end-of-life product in Scotland and appraisal will include a Patient and Clinician Engagement (PACE) meeting, with a decision anticipated by the end of 2016.

2.3 Administration and costs of the technology

Administration and costs of daratumumab are summarised in Table 3.

Table 3: Costs of the technology being appraised

	Cost/detail	**Source**
Pharmaceutical formulation	Concentrate for solution for infusion	SmPC
Acquisition cost (excluding VAT) *	£360.00 for 100mg vial £1,440.00 for 400mg vial	MIMS
Method of administration	Intravenous infusion	SmPC
Doses	16mg/kg	SmPC
Dosing frequency	Weekly for weeks 1-8, every 2 weeks for weeks 9 to 24 and every four weeks from week 25 onwards	SmPC
Average length of a course of treatment	Treatment should be continued until disease progression Median duration of treatment was 3.4 months in an integrated analysis	SmPC Trial data
Average cost of a course of treatment (at list price)	£68,862 excluding administration costs; £74,531 including administration costs.	Economic model Section 5.7
Anticipated average interval between courses of treatments	Retreatment not anticipated	-
Anticipated number of repeat courses of treatments	Retreatment not anticipated	-

	Cost/detail	Source
Dose adjustments	No dose adjustments are recommended. Incremental escalation of the infusion rate should be considered if the previous infusion was well-tolerated; infusion should be interrupted for IRRs of any severity.	SmPC
Anticipated care setting	Hospital	SmPC
Key: IRR, infusion-related reactions; MIMS, Monthly Index of Medical Specialities; SmPC, Summary of Product Characteristics.		

2.4 Changes in service provision and management

In accordance with the SmPC, daratumumab should be administered by a healthcare professional in an environment where resuscitation facilities are available. Established haematology units already have the staffing and infrastructure needed for the administration of cancer treatments, and it is anticipated that the administration of daratumumab would utilise this existing infrastructure.

There is an additional resource requirement associated with the administration of daratumumab monotherapy compared with some existing treatment options because daratumumab is provided as a concentrate for solution for intravenous (IV) infusion, whereas some alternative agents are oral in nature (see Section 3.2). Daratumumab is also infused over a longer period than alternative IV agents (see Section 3.2).

Patients treated with daratumumab should also be regularly monitored for signs or symptoms of infusion-related reactions (IRRs), as early identification of IRRs, and intervention to resolve them are an important part of the safe use of daratumumab. As such, and as stated in the SmPC, both pre- and post-infusion medications should be administered to all patients to minimise the risk of IRRs. Prior to every daratumumab infusion, patients should be administered IV corticosteroids, oral antipyretics and oral or IV antihistamine medication. Following the second infusion, the dose of corticosteroids can be reduced at the discretion of the physician. Oral corticosteroids should also be administered to patients the first and second day after all infusions for the prevention of delayed IRRs.

While the initial infusion may not necessitate an inpatient stay, due to the time required (median duration of approximately 7 hours), it is a possibility, especially in the event of IRRs. However, both the length of infusion and risk of IRRs markedly decrease with subsequent infusions, which are therefore expected to be administered as part of an outpatient appointment.

Staff and administration costs, as well as costs for monitoring and AE management, are all fully accounted for in the economic modelling (see Section 5) and it is important to consider this additional resource requirement alongside the substantial clinical and safety advantages of daratumumab (see Section 4).

2.5 Innovation

While significant advancements in the treatment of MM have been made in the last 15 years (notably the introduction of PIs and IMiDs), treatment options for heavily pre-treated and highly refractory patients remain limited such that there remains a significant unmet need for novel treatment options that can extend life expectancy in rrMM. This unmet need is recognised by the EMA, which state that:

"All patients eventually relapse. With each successive relapse, the chance of response and duration of response typically decreases. After relapse from PIs and IMiDs, patients are often retreated with drugs that have the same mechanism of action. Ultimately, the disease becomes refractory. Patients who are heavily pretreated and/or refractory to both a PI and IMiD have a dismal prognosis, are difficult to get back into a durable remission, and median survival is only between 8 to 9 months".[10]

Daratumumab is a first-in-class, CD38-targeting mAb with a novel mechanism of action (see Section 2.1) and broad therapeutic potential.[1] As demonstrated in Phase I/II trials, daratumumab offers heavily pre-treated and highly refractory rrMM patients the opportunity for deep and durable response and substantial extension of life with a manageable safety profile (see Section 4). The significance of this is reflected in the fact that daratumumab was approved by the EMA under the accelerated assessment procedure which concluded that:

"Daratumumab fulfils an unmet medical need for patients with poor long-term prognosis and limited treatment alternatives" and that *"Daratumumab has a new mechanism of action, a manageable safety profile, and treatment with daratumumab was associated with durable response, which provides a major therapeutic advantage."* [10]

These conclusions were based on a review by the Committee for Orphan Medicinal Products (COMP) which recommended maintenance of the orphan designation of daratumumab, stating that:

"for most authorised products - including all authorised PIs and IMiDs - the MMY2002 and GEN501 studies confirm a clinically relevant advantage of improved efficacy, as these studies showed responses in patients who were considered refractory to those products." and that *"an indirect comparison of clinical data supports that daratumumab monotherapy is more efficacious and less toxic than the authorised product panobinostat"*[11]

While we would anticipate most of the health-related benefits to patients will be captured in the quality-adjusted life year (QALY) calculation, health-related quality of life (HRQL) data were not directly captured in the pivotal trial programme and thus inferred utilities are likely to be conservative. This is because utilities from TA338 were used to derive expected health gain. However, unlike TA338, utility data were not disaggregated by response; rather average utility values were used. The use of average utility will be likely to underestimate the quality of life associated with the deep and durable response observed with daratumumab (see Section 5.4). Furthermore, the granularity of EuroQol-5 Dimension (EQ-5D) data may not fully capture patient benefits such as improvement in fatigue.[12]

As the first treatment to demonstrate single agent efficacy in rrMM, daratumumab represents a step-change in the management of this condition, as acknowledged by the FDA who granted daratumumab breakthrough designation for encouraging activity as a single agent in rrMM. Research is ongoing as to the exact biological processes involved in the unprecedented clinical efficacy observed, but it is almost certainly attributable to the novel and unique multifactorial MoA of daratumumab that appears to change the natural course of disease in rrMM. Daratumumab is an

innovative treatment that enables patients to be able to regain somewhat normal living, previously thought unattainable. Furthermore, the psychological impact and hope that a life-extending medicine such as daratumumab monotherapy offers a patient and their family should be acknowledged, as well as wider emotional benefits that are not intrinsically captured in the QALY.

3 Health condition and position of the technology in the treatment pathway

3.1 Disease overview

Disease background

MM is a rare haematological cancer characterised by clonal proliferation of malignant plasma cells in the bone marrow and production of excess monoclonal (M) protein (an abnormal immunoglobulin).[13] The median age of patients at diagnosis is 65-70 years with people under 40 years of age rarely affected; MM is twice as common in black populations as it is in white and Asian populations, and more common in men than in women.[14-16] While the exact mechanism that triggers the malignant transformation of plasma cells is yet to be identified, the development of MM is preceded by a pre-malignant, asymptomatic state (monoclonal gammopathy of undetermined significance [MGUS]) that develops from a primary oncogenic event in the form of either a hyperdiploidy (having more than 46 chromosomes) or a chromosomal translocation (switching of genetic material between two different chromosomes).[17, 18]

MM itself is a genetically complex disease that develops from the continued accumulation of genetic abnormalities over time.[19] This results in subclones of plasma cells with considerable genetic heterogeneity that contribute to the progression of MM and the development of drug resistance.[19, 20] As a result of this heterogeneity, MM can take a variable clinical course[15, 16], although typically, the disease is characterised by multiple relapses with patients becoming refractory to treatment over time, with marked reduction in prognosis.[21-25]

In the relapsed and refractory setting, MM represents a serious and life-threatening disease. Patients whose disease follows an aggressive clinical course, despite receiving active therapy, have a particularly poor prognosis; survival estimates for patients with rrMM whose prior therapy included a PI and an IMiD does not exceed 12 months in real world evidence (RWE) studies.[26-31] Such data emphasises the severity of this condition and supports daratumumab monotherapy as a life-extending, end-of-life treatment.

3.2 Effect of disease or condition on patients, carers and society

Patients with MM experience a variety of complications and disease-related symptoms, all of which affect normal living. The clinical and HRQL burden substantially increases as the disease progresses.

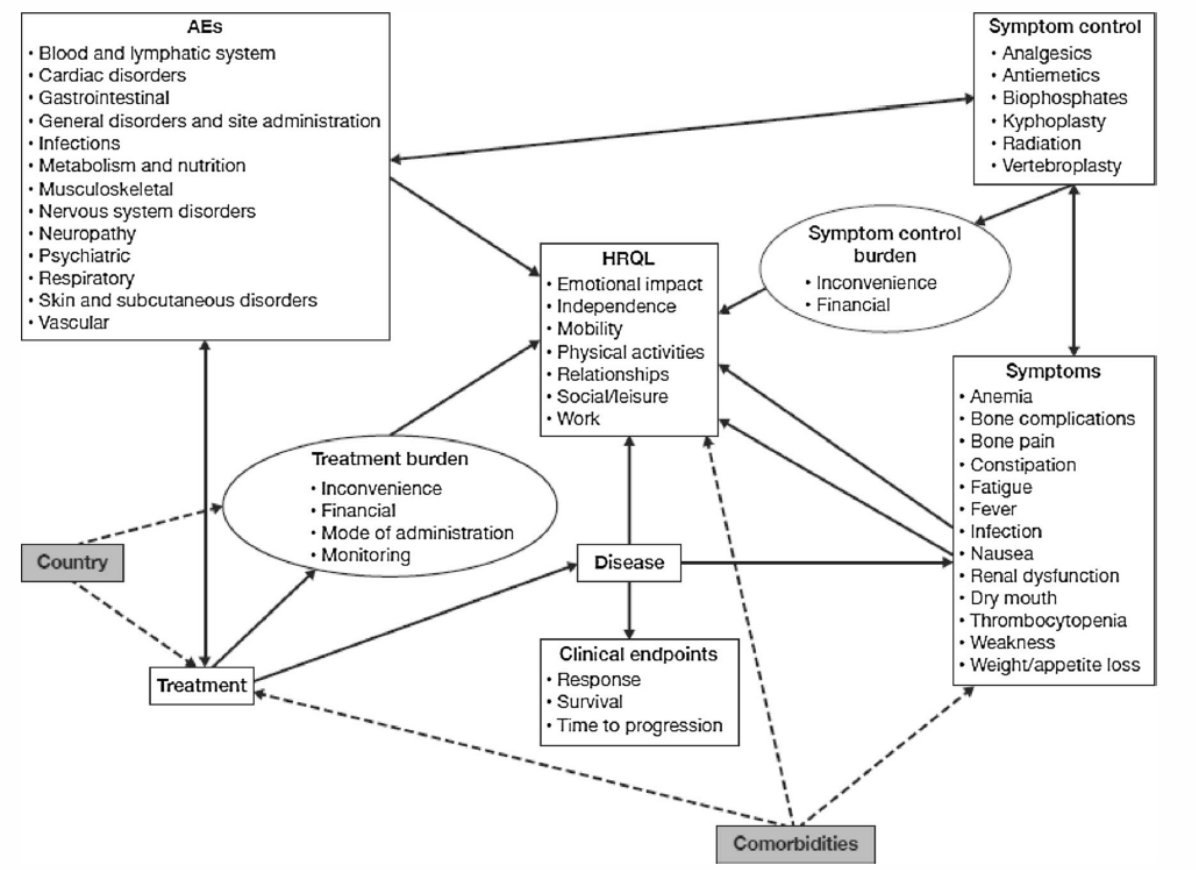
The high number of plasma cell clones interferes with haematopoiesis in the bone marrow; this not only puts patients at increased risk of infection but can also result in the destruction of skeletal structures and associated neurological impairment.[13, 17, 32] In addition, the M protein produced by plasma cell clones can cause hyperviscosity and damage organs, specifically the kidney.[13, 17, 32] The acronym “CRAB” is often used to describe the following symptoms commonly associated with organ and bone damage caused by MM: hyperCalcaemia, Renal impairment, Anaemia and Bone disease. CRAB symptoms require urgent treatment to minimise the development of additional complications and long-term organ damage.[13, 17, 21]

This clinical burden results in a detrimental impact on HRQL and MM patients score significantly lower on the European Organization for Research and Treatment of Cancer 30-item Quality of Life Questionnaire (EORTC-QLQ-C30) in the physical, role, emotional, cognitive and social functional domains compared with the normative population ($p<0.0001$ for all domains).[33] Similarly, MM patients report significantly higher symptom scores for fatigue, nausea and vomiting, pain, dyspnoea, sleeping problems, appetite loss, constipation, diarrhoea, and financial problems, indicating worsened symptomology compared with the normative population.[33] There is also

evidence that patients with myeloma report worse symptoms and problems than those with other haematological cancers, including lymphoma or leukaemia.[34]

As the disease progresses and the severity of MM symptoms increases, HRQL worsens with respect to global health status, quality of life, physical and social functioning and future perspective.[35] Treatment-emergent adverse events (TEAEs) can further reduce patient HRQL, as summarised in the conceptual model presented in Figure 3.[36]

Figure 3: Conceptual model of factors affecting HRQL in MM



Key: AEs, adverse events; HRQL, health-related quality of life; MM, multiple myeloma.
Notes: Arrows indicate the direction of influence; double-headed arrows indicate that the influence can go in both directions; concepts are shown in square boxes; oval boxes represent mediators of impact, whereas shaded square boxes with dotted arrows represent moderators of impact; country is included in the model as available treatments vary by geographical location.
Source: Baz et al. 2015.[36]

There is paucity of data on caregiver burden specifically related to MM[37], but it is reasonable to assume that informal provision of supportive care also negatively

impacts the HRQL of family and friends of patients with rrMM. As is observed in other types of cancer[38], increasing caregiver burden can be expected with functional deterioration that can be associated with both disease progression and cumulative toxicity of multiple treatment lines for patients with rrMM.

MM is also associated with a substantial economic burden that increases as the disease progresses and worsens.[37] Although direct care requirements are normally identified as key cost drivers in economic studies, management of treatment-related AEs also contribute to costs and resource use[37]. This further demonstrates the need for tolerable treatment options in clinical practice, particularly for patients at later stages of relapse who have already received multiple toxic agents.

3.3 Clinical pathway of care

The NICE pathway for the management of myeloma recommends induction treatment with bortezomib in combination with dexamethasone ± thalidomide for transplant-eligible patients [TA311], and first-line treatment with thalidomide in combination with an alkylating agent and a corticosteroid for transplant-ineligible patients [TA228]. Bortezomib in combination with an alkylating agent and a corticosteroid can be used at first-line for transplant-ineligible patients unable to tolerate or with contraindications to thalidomide [TA228].

Patients who relapse should be offered a second autologous stem cell transplantation (ASCT) if suitable or bortezomib monotherapy if ASCT is unsuitable [TA129]. For patients who further relapse, lenalidomide plus dexamethasone (LEN+DEX) is currently recommended for patients who have received at least two prior regimens [TA171] and is being assessed for treating MM after one prior treatment with bortezomib (ID667). More recently, panobinostat in combination with bortezomib plus dexamethasone (PANO+BORT+DEX) has also been recommended as a treatment option for rrMM patients who have received at least two prior therapies including bortezomib and an IMiD agent [TA380]. Of note, the recommendation was based on a subgroup from the PANORAMA 1 trial which allows PANO+BORT+DEX to be used at third-line. However, due to toxicity concerns, clinicians confirm that it is unlikely to replace LEN+DEX, which is an

established regimen in the third-line setting. As such, it will normally be reserved for patients who are unsuitable for LEN+DEX or have progressed following LEN+DEX. Market research reports that six months after its recommendation, PANO+BORT+DEX had a [redacted] share of all third-line treatment use in the UK whereas LEN+DEX had a [redacted] share. Uptake of PANO+BORT+DEX was not much higher in the fourth-line setting with a [redacted] market share reported. Clinical consultation and patient experience suggests this is due to concerns over the considerably debilitating toxicity associated with this regimen, particularly gastrointestinal (GI) events (see Sections 3.6 and 4.12).

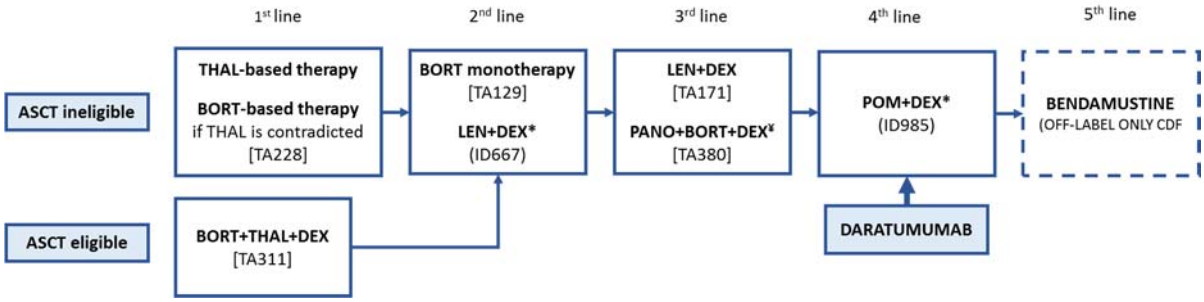
At present, there are no NICE-approved treatment options at subsequent stages of relapse however it should be acknowledged that the treatment landscape in this setting is on the cusp of change. Pomalidomide plus dexamethasone (POM+DEX), is the subject of an ongoing appraisal for rrMM (ID985) and, like daratumumab monotherapy, is positioned as a fourth-line treatment option. POM+DEX is already approved for use in NHS Scotland and NHS Wales[39, 40], and has been widely used on the CDF in previous years. Thus, upon approval it is anticipated that POM+DEX will be the predominant fourth-line treatment and therefore the most appropriate comparator within this decision problem. Bendamustine is currently available through the CDF and is used off-label for rrMM where all other treatments are contraindicated or inappropriate. Clinical consultation[41, 42] and RWE of bendamustine use (see Section 4.10) confirms that bendamustine is normally administered in combination with thalidomide ± corticosteroids. RWE also indicates there is significant geographical variation in the use of bendamustine and, in line with CDF terms, it is indeed reserved for patients with no other treatment option. In addition, it is anticipated that daratumumab monotherapy will be used ahead of, rather than instead of, bendamustine-based therapy.

Due to the heterogeneity of MM (see Section 3.1), it is not possible to define a sequential treatment pathway that is applicable to all patients. The clinical pathway of care in line with NICE recommendations is depicted in Figure 4. As a consequence of the data available for daratumumab (see Sections 4.7 and 4.9), the

typical position of daratumumab monotherapy is anticipated to be as an alternative treatment for people who have received three or more prior therapies.

According to clinical consultation, there is no established standard of care in this fourth-line setting. Although LEN+DEX is named as a comparator in the decision problem, this treatment is used earlier in the treatment pathway and is therefore not considered relevant to this appraisal. Licensed treatment options that could be used in the fourth-line setting are associated with various limitations and toxicities (see Section 3.6) and there is little evidence to support the clinical effectiveness of the off-label use of bendamustine (see Section 4).

Figure 4: Typical treatment pathway for MM in England



Key: ASCT, autologous stem-cell transplant; BORT, bortezomib; BORT+THAL+DEX, bortezomib plus thalidomide plus dexamethasone; CDF, Cancer Drugs Fund; LEN+DEX, lenalidomide plus dexamethasone; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; POM+DEX, pomalidomide plus dexamethasone.

3.4 Life expectancy and patient population

The life expectancy for patients with rrMM who have progressive disease despite prior treatment with a PI and an IMiD does not exceed 12 months, based on RWE.[26-31] For patients who are refractory to both a PI and an IMiD, life expectancy is further reduced to 8-9 months, and for patients who are refractory to three or four of the common PIs and IMiDs, life expectancy decreases to only 3-5 months.[31] This patient population clearly meets the end-of-life criteria.

When reviewing prospective clinical trials of the currently available treatment options that have enrolled patients who have received at least two prior regimens that

include a PI and an IMiD, PANO+BORT+DEX has demonstrated the longest median overall survival (OS) at 17.5 months.[43] However, it is important to note that the patient population of the PANORAMA 2 trial (from which these data are taken) were not as heavily pre-treated as the population intended for daratumumab monotherapy.

PANO+BORT+DEX is recommended by NICE based on subgroup data from PANORAMA 1 for use as a third-line treatment. However, according to clinical experts, PANO+BORT+DEX has yet to demonstrate a significant impact on the life expectancy of patients with rrMM in clinical practice. This is likely related to concerns over the considerably debilitating toxicity associated with PANO+BORT+DEX (see Sections 3.6 and 4.12) restricting its general use in clinical practice. According to market research, six months after it was recommended for use in NHS England, PANO+BORT+DEX only had a [redacted] market share across the third- and fourth-line settings.

In 2013, 4,703 people were diagnosed with MM in England[44] and an estimated 15% of patients with rrMM receive four or more lines of therapy in clinical practice.[45] Applying these percentages to the incidence of MM in England, an estimated 705 patients would be eligible for daratumumab monotherapy in the fourth-line setting in the NHS in England per year. This meets the orphan status definition of a population size of <5 per 10,000, as recognised with the COMP maintaining the orphan designation of daratumumab.

Daratumumab monotherapy is not licensed for use outside of its rrMM indication. Therefore, no other patients would be treated with daratumumab monotherapy if approved for use.

3.5 Relevant NICE guidance and clinical guidelines

NICE guidance and clinical guidelines of relevance to this appraisal are summarised in Table 4.

Table 4: Relevant NICE guidance and clinical guidelines

Organisation	Title	Date	Summary
NICE guidance			
NICE STA No. 129[46]	Bortezomib monotherapy for relapsed multiple myeloma	2007	Bortezomib monotherapy is recommended as a possible treatment for progressive multiple myeloma for people: • Whose multiple myeloma has relapsed for the first time after having one treatment, and • Who have had a bone marrow transplant, unless it is not suitable for them • After not more than four cycles of treatment, a blood or urine test should be done to check how well the cancer has responded to bortezomib Treatment should be continued only if there has been at least a partial response to the drug
NICE STA No. 171[47]	Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy	2009	Lenalidomide in combination with dexamethasone is recommended as a possible treatment for patients with multiple myeloma who have previously received at least two other treatments
NICE MTA No. 228[48]	Bortezomib and thalidomide for the first-line treatment of multiple myeloma	2011	Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with SCT is considered inappropriate. Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if high-dose chemotherapy with SCT is considered inappropriate and the person is unable to tolerate or has contraindications to thalidomide.
NICE STA No. 311[49]	Bortezomib for induction therapy in multiple myeloma	2014	Bortezomib in combination with dexamethasone ± thalidomide is recommended as a possible treatment for adults with multiple myeloma before having chemotherapy and

Organisation	Title	Date	Summary
	before high-dose chemotherapy and ASCT		stem cell transplantation, if their multiple myeloma has not been treated before
NICE STA No. 338[50]	Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib	2015	Pomalidomide in combination with dexamethasone is not recommended for treating rrMM in patients who have previously received lenalidomide and bortezomib
NICE STA No. 380[51]	Panobinostat for treating multiple myeloma after at least 2 previous treatments	2016	Panobinostat in combination with bortezomib and dexamethasone is recommended for the treatment of adult patients with rrMM who have received at least two prior regimens including bortezomib and an immunomodulatory agent

Organisation	Title	Date	Summary
Clinical guidelines			
ESMO[16]	Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	2013	Immediate treatment is not recommended for patients with indolent myeloma. Treatment should be initiated in all patients with symptomatic lymphoma. In elderly patients (in the non-transplant setting) oral combinations of melphalan and prednisone plus novel agents are considered as standards of care in Europe; MPT and VMP are approved in this setting by the EMA. Bendamustine + prednisone is approved in patients who have clinical neuropathy. Lenalidomide + dexamethasone is not approved in Europe. In patients <65 years or fit patients in good clinical condition, induction followed by high-dose therapy with ASCT is standard treatment. Bortezomib + dexamethasone ± thalidomide/doxorubicin/lenalidomide or cyclophosphamide is the standard induction therapy. In rrMM, lenalidomide + dexamethasone and bortezomib ± pegylated doxorubicin are recommended although bortezomib is usually used in combination with dexamethasone. Younger patients should be offered a second ASCT, and where possible, patients should be offered participation in clinical trials
BCSH/UKMF[21, 52]	Guidelines for the diagnosis and management of multiple myeloma	2014	For induction therapy prior to high-dose therapy: induction regimens should contain at least 1 novel agent; e.g. CTD, TAD, bortezomib + dexamethasone or PAD. In older and/or less fit patients where high-dose therapy is not planned, induction therapy should consist of a thalidomide-containing regimen + an alkylating agent and steroid or bortezomib + melphalan + prednisolone. High-dose therapy with ASCT should be part of primary treatment in newly diagnosed patients up to 65 years and >65 years with good performance status. A second ASCT should be strongly considered in patients with >12-18 months response to the first ASCT. Thalidomide-, bortezomib- and lenalidomide-based regimens are recommended at first and subsequent relapse; treatment with thalidomide, bortezomib or lenalidomide should be delivered with dexamethasone ± chemotherapy to increase the response rate. A

Organisation	Title	Date	Summary
			second ASCT may be considered in patients who had good response to the initial transplant All patients should be considered for entry into a clinical trial.
	United Kingdom Myeloma Forum (UKMF) position statement on the use of bendamustine in myeloma	2013	For induction therapy, CTD is favoured over VAD and for patients not eligible for HDT-ASCT, attenuated CTD or MPT are most widely used. Maintenance treatment options include thalidomide, bortezomib or lenalidomide. In the relapse setting, treatment currently incorporates various combinations of bortezomib (usually at first relapse) or lenalidomide (usually at second relapse) with steroids and/or alkylating agents.
IMWG[53]	International Myeloma Working Group Consensus Statement for the Management, Treatment, and Supportive Care of Patients with Myeloma Not Eligible for Standard Autologous Stem-Cell Transplantation	2014	Reduced dose-intensity ASCT with melphalan should be considered in very fit patients 65-70 years or younger patients with comorbidities. Patients aged 65-70 years in good clinical condition should be treated with full-dose conventional chemotherapy. MPT is preferred for its oral administration in fit patients however VMP, VMPT-VT or VCD and VRD may be preferred in patients who need rapid, profound cytoreduction. Unfit patients should receive reduced-dose MPT or VMP. In relapsed disease, repeating the same treatment should be considered after long-lasting remission (20-24 months); an alternative regimen is suggested for patients with shorter remission duration. Bortezomib + dexamethasone, bortezomib + pegylated liposomal doxorubicin and lenalidomide + dexamethasone are treatments of choice.
NICE guideline 35[54]	Myeloma: diagnosis and management of myeloma	2016	Recommended first-line treatments include bortezomib in combination with dexamethasone ± thalidomide, thalidomide in combination with an alkylating agent and a corticosteroid or bortezomib in combination with an alkylating agent and a corticosteroid Treatment with bortezomib- and dexamethasone-based combination regimen should be considered for people with myeloma-induced acute renal disease. To prevent bone disease, patients should be offered zoledronic acid, disodium pamidronate if zoledronic acid or sodium clodonate if both zoledronic acid and disodium pamidronate are not

Organisation	Title	Date	Summary
			tolerated. To prevent infections patients should be offered the seasonal influenza vaccine and the pneumococcal vaccination should be considered for patients who are under 65. IV immunoglobulin replacement therapy should be considered for patients with hypogammaglobulinaemia and recurrent infections. Aciclovir or equivalent antiviral prophylaxis should be considered after treatment with bortezomib and for people who are taking both IMiDs and high-dose steroids. Neuropathic pain should be managed by reducing the dose of drugs or stopping treatment for a period of time. At first relapse, bortezomib monotherapy is recommended for patients who have received one prior therapy and have undergone, or are unsuitable form bone marrow transplantation. A second ASCT should be offered to patients with relapsed myeloma who have completed re-induction therapy without disease progression and had a response over 12 months after first ASCT. For subsequent therapy, lenalidomide in combination with dexamethasone is recommended in patients who have received two or more prior therapies. Pomalidomide in combination with dexamethasone is not recommended.
NICE pathways[55]	NICE pathway: Myeloma	2016	Induction treatment for transplant eligible patients should consist of bortezomib in combination with dexamethasone ± thalidomide followed by a stem cell transplant. For transplant ineligible patients, thalidomide in combination with an alkylating agent and a corticosteroid is recommended. Patients with smouldering myeloma should be monitored every 3 months for the first 5 years and then as needed depending on the long-term stability of the disease. At first relapse, bortezomib monotherapy is recommended for patients who have received one prior therapy. A second ASCT should be offered to patients with relapsed myeloma who have completed re-induction therapy without disease progression and had a response over 12 months after first ASCT. At subsequent relapse, lenalidomide in combination with dexamethasone is recommended in patients who have received two or more prior therapies. Panobinostat

Organisation	Title	Date	Summary
			in combination with bortezomib and dexamethasone is also recommended as a treatment option for adult patients with rrMM who have received at least two prior regimens including bortezomib and an IMiD.
NCCN[56]	Multiple myeloma, Version 3	2016	Recommendations for primary therapy for transplant candidates: bortezomib + dexamethasone; bortezomib + cyclophosphamide + dexamethasone; bortezomib + doxorubicin + dexamethasone; bortezomib + lenalidomide + dexamethasone; bortezomib + thalidomide + dexamethasone; lenalidomide + dexamethasone; carfilzomib + lenalidomide + dexamethasone; dexamethasone; ixazomib + lenalidomide + dexamethasone; liposomal doxorubicin + vincristine + dexamethasone; thalidomide + dexamethasone Recommendations for primary therapy for non-transplant candidates: bortezomib + dexamethasone; bortezomib + cyclophosphamide + dexamethasone; bortezomib + lenalidomide + dexamethasone; lenalidomide + low-dose dexamethasone; MPB; MPL; MPT For all patients in primary therapy, herpes zoster prophylaxis is recommended for patients treated with proteasome inhibitors. Subcutaneous bortezomib should be considered for patients with pre-existing or high-risk peripheral neuropathy. Prophylactic anticoagulation is recommended for patients receiving immunomodulator-based therapy. For previously treated MM, primary induction therapy should be repeated is relapse was at >6 months. Recommendations for previously treated multiple myeloma: bortezomib ± dexamethasone; bortezomib + cyclophosphamide + dexamethasone; bortezomib + lenalidomide + dexamethasone; bortezomib + liposomal doxorubicin; bortezomib + thalidomide + dexamethasone; carfilzomib ± dexamethasone; carfilzomib + lenalidomide + dexamethasone; cyclophosphamide + lenalidomide + dexamethasone; daratumumab; DCEP; DT-PACE ± bortezomib (VTD-PACE); elotuzumab + lenalidomide + dexamethasone; ixazomib ± dexamethasone; ixazomib + lenalidomide + dexamethasone; high-dose cyclophosphamide; lenalidomide + dexamethasone; panobinostat + bortezomib + dexamethasone; pomalidomide + dexamethasone;

Organisation	Title	Date	Summary
			thalidomide + dexamethasone; bendamustine; bortezomib + vorinostat; lenalidomide + bendamustine + dexamethasone; panobinostat + carfilzomib

Key: ASCT, autologous stem cell transplant; BCSH, British Committee for Standards in Hematology; CTD, cyclophosphamide, thalidomide, dexamethasone; DCEP, dexamethasone, cyclophosphamide + etoposide + cisplatin; DT-PACE, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology;IMiD, Immunomodulatory; IMWG, International Myeloma Working Group; IV, Intravenous; MPB, melphalan, prednisone, bortezomib; MPL, melphalan, prednisone, lenalidomide; MPT, melphalan, prednisone, thalidomide; MTA, multiple technology appraisal; NCCN, National Comprehensive Cancer Network; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PAD, adriamycin, bortezomib, dexamethasone; rrMM, relapsed refractory multiple myeloma; SCT, Stem Cell Transplant; STA, Single Technology Appraisal; TAD; 6-thioguianine, cytarabine, daunorubicin; UKMF, United Kingdom Myeloma Foundation; VAD, bortezomib, Adriamycin, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VMP, bortezomib, melphalan, prednisone; VMPT-VT, bortezomib, melphalan, prednisone, thalidomide, bortezomib, thalidomide; VRD, bortezomib, lenalidomide, dexamethasone; VTD-PACE, bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide.

3.6 Issues relating to clinical practice

As noted in Section 3.3, due to the heterogeneity of MM, it is not possible to define a sequential treatment pathway that is applicable to all patients. Thus, there is no established standard of care for patients with rrMM who have previously received a PI and an IMiD and shown disease progression on the last therapy.

Daratumumab monotherapy is to be positioned at fourth-line and alternative treatments that could be used in this end-of-life setting in clinical practice are associated with a number of limitations, as summarised in Table 5.

Table 5: Issues with end-of-life treatment options for rrMM

Treatment	Summary of key issues
Pomalidomide plus dexamethasone	▪ High rate of death due to TEAEs (48%) reported in key clinical trial[57] ▪ High rate of serious TEAEs (61%) reported in key clinical trial[57] ▪ Black box warning against embryo-foetal toxicity and venous and arterial thromboembolism ▪ High rate of dose reductions/interruptions (67%) ▪ Not recommended for use by NICE
Panobinostat plus bortezomib plus dexamethasone	▪ Multi-agent regimen including bortezomib, to which many patients are already refractory ▪ High rates of serious TEAEs reported in key clinical trials (60-67%)[58, 59] ▪ Black box warning against fatal and serious toxicities of severe diarrhoea and cardiac events ▪ High rates of discontinuation due to TEAEs (18-36%)[58, 60] and dose reductions / interruptions (51-64%)[58, 59] ▪ Limited clinical effectiveness data at fourth-line

Treatment	Summary of key issues
Bendamustine	▪ Not licensed for the treatment of rrMM ▪ Not available through routine commissioning; only available through the CDF where all other treatments are contraindicated or inappropriate ▪ Typically used as part of a multi-agent regimen including thalidomide, to which many patients are already refractory ▪ No proven effectiveness and low quality evidence supporting its use ▪ No proven tolerability and low quality evidence supporting its use
Key: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACT GOG, Functional Assessment of Cancer Therapy Gynecologic Oncology Group; HRQL, health-related quality of life; OS, overall survival; PFS, progression0free survival; TESAE, treatment-emergent serious adverse event	

Taking these key issues into account, in addition to the heterogeneity of the disease, there are still a number of patients with rrMM who are not receiving effective, tolerable therapy in clinical practice, optimal for their care. This further confirms the significant unmet medical need recognised by the EMA for patients with MM who are heavily pre-treated and highly refractory. Daratumumab has great potential to fulfil this currently unmet need.

3.7 Equality

No equality issues related to the use of daratumumab have been identified or are foreseen.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

Search strategy

A systematic literature review (SLR) designed to identify studies of daratumumab and potential comparator therapies for the treatment of patients with rrMM who have received at least two prior treatment regimens was initiated in January 2016.

Information retrieval methods were based upon the research question "What is the clinical efficacy and tolerability of daratumumab and potential comparator therapies for the treatment of relapsed and refractory multiple myeloma?"

Searches were performed in the following electronic databases:

- MEDLINE and MEDLINE-In-Process
- EMBASE
- The Cochrane Library, including the following:
  - Cochrane Central Register of Controlled Trials
  - The Cochrane Database of Systematic Reviews
  - Database of Abstracts of Reviews of Effectiveness

In addition, 2014 and 2015 proceedings of the following conferences were hand searched in order to identify any relevant, on-going research:

- The American Society of Hematology (ASH)
- The European Hematology Association (EHA)
- The American Society of Clinical Oncology (ASCO)
- The European Society for Medical Oncology (ESMO)
- The British Journal of Haematology (BSH)

Reference lists of existing SLRs/meta-analyses, clinical guidelines and previous HTAs identified through systematic searches were also hand-searched to identify any further relevant studies.

The search strategies used for clinical effectiveness searches are provided in Appendix 2.

Disease terms were developed based on systematic searches in this disease area, including Cochrane reviews[61-63] and evaluation of search strategy critiques of those previously submitted to NICE.[46-48, 50] Intervention terms were developed based on targeted searching for common synonyms and further evaluation of search strategy critiques of those previously submitted to NICE. A number of potential comparator therapies were included in the systematic searches; these therapies were identified through review of clinical guidelines, UK HTA recommendations, National Cancer Drugs Fund list v6.0 (UK), ongoing Phase II+ studies (clinicaltrials.gov) and RWE studies[16, 21, 25, 27, 64-67], and the list was refined (based on market research) to include only those currently used in routine clinical practice or those that were anticipated to potentially be used in clinical practice by the time of daratumumab licensing. Terms for principal interventions were included in the systematic searches with terms for interventions only used in combination with principal interventions not required. Terms for publication types in clinical efficacy searches were adapted from published SIGN filters. SIGN was chosen as a validated source of search strategy filters with high sensitivity[68], recognised and recommended by HTA agencies (including NICE via the Information Specialists' Sub-Group [ISSG] search filter resource).

Prior to running, systematic search strategies were critiqued and refined by a team of information specialists at the School of Health and Related Research (ScHARR).

Study selection

The full eligibility criteria applied to the identified evidence base is presented in Table 6. Of note, this review was conducted from a global perspective and therefore a number of comparators were included that are not relevant to a UK setting (and not named in the decision problem).

Scoping exercises suggested a paucity of evidence in the specific target population of adult patients with rrMM, whose prior therapy included a PI and an IMiD agent. Therefore, the eligibility criterion regarding previous treatment was broadened to studies that enrolled adult patients with rrMM that have received at least two prior regimens. Studies that enrolled a mixed patient population in regard to treatment history were excluded unless they reported outcome data for patients who had received at least two prior regimens. In this instance, all citations associated with the study were included in the final evidence base. The more specific population covered in the marketing authorisation for daratumumab monotherapy, as well as the populations enrolled in key clinical trials (MMY2002 and GEN501) were named as specific subgroups of interest.

As a reflection of its accelerated review, only Phase II (non-controlled) trial data are currently available for daratumumab monotherapy. Scoping exercises also suggested a lack of randomised controlled trial (RCT) evidence for a number of potential comparators. Non-RCT evidence encompassing controlled clinical trials (non-randomised), non-controlled clinical trials (single-arm) and prospective or retrospective observational studies were therefore also included in the final evidence base. RWE studies that included patients treated with a variety of interventions were not routinely included if they did not report clinical outcomes for independent interventions of interest. However, since there is no established standard of care for the target population of daratumumab monotherapy, RWE studies that were explicitly designed to investigate a named subgroup of interest (Table 6) were included, regardless of whether clinical outcomes were reported per intervention or across interventions with treatment described as “available care”.

Table 6: Eligibility criteria used in the search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adult patients with rrMM Received ≥2 prior regimens	Non rrMM population Paediatric patients Treatment naïve population Patients who have received <2 prior therapies
Comparators	Any active therapy Best supportive care Placebo No treatment	-
Outcomes	Clinical response (including response rates, time to response, duration of response) HRQL Overall survival Progression free survival Safety/tolerability Time to progression Time to next treatment	-
Study design	RCTs Non-RCTs Prospective observational studies Retrospective observational studies Safety studies	Case studies/series Case reports In vitro studies Animal studies Letter Commentary Editorial
Subgroups of interest	Received ≥3 prior regimens including a PI and an IMiD Received ≥2 prior regimens including a PI and an IMiD Double relapsed and/or refractory to a PI and an IMiD	-
Language restrictions	None Papers not available in English assessed on English abstract	-

Key: HRQL, health-related quality of life; IMiD, immunomodulatory agent; PI, proteasome inhibitor; RCT, randomised controlled trial; RCT, randomised controlled trial; rrMM, relapsed refractory multiple myeloma.
Notes: [a], included for reference review only.

Two reviewers independently inspected each reference (title and abstract) identified by the literature searches and applied basic study selection criteria based on the eligibility criteria presented in Table 6 (primary screening). Citations meeting basic study selection criteria (or in cases of disagreement between the two reviewers) were obtained in full and independently assessed against the full eligibility criteria presented in Table 6 (secondary screening). In the event of disagreement between the two reviewers, a third reviewer independently assessed the paper and applicability of selection criteria attained by consensus.

If study duplication within publications was suspected, author names, location and setting, specific intervention details, participant numbers, baseline data and date and duration of study were assessed. If uncertainties remained, the authors would have been contacted, but this situation did not occur. Where multiple publications were identified for the same clinical trial, all were included in the final list of articles meeting the eligibility criteria but clearly identified as primary and secondary sources for the same trial.

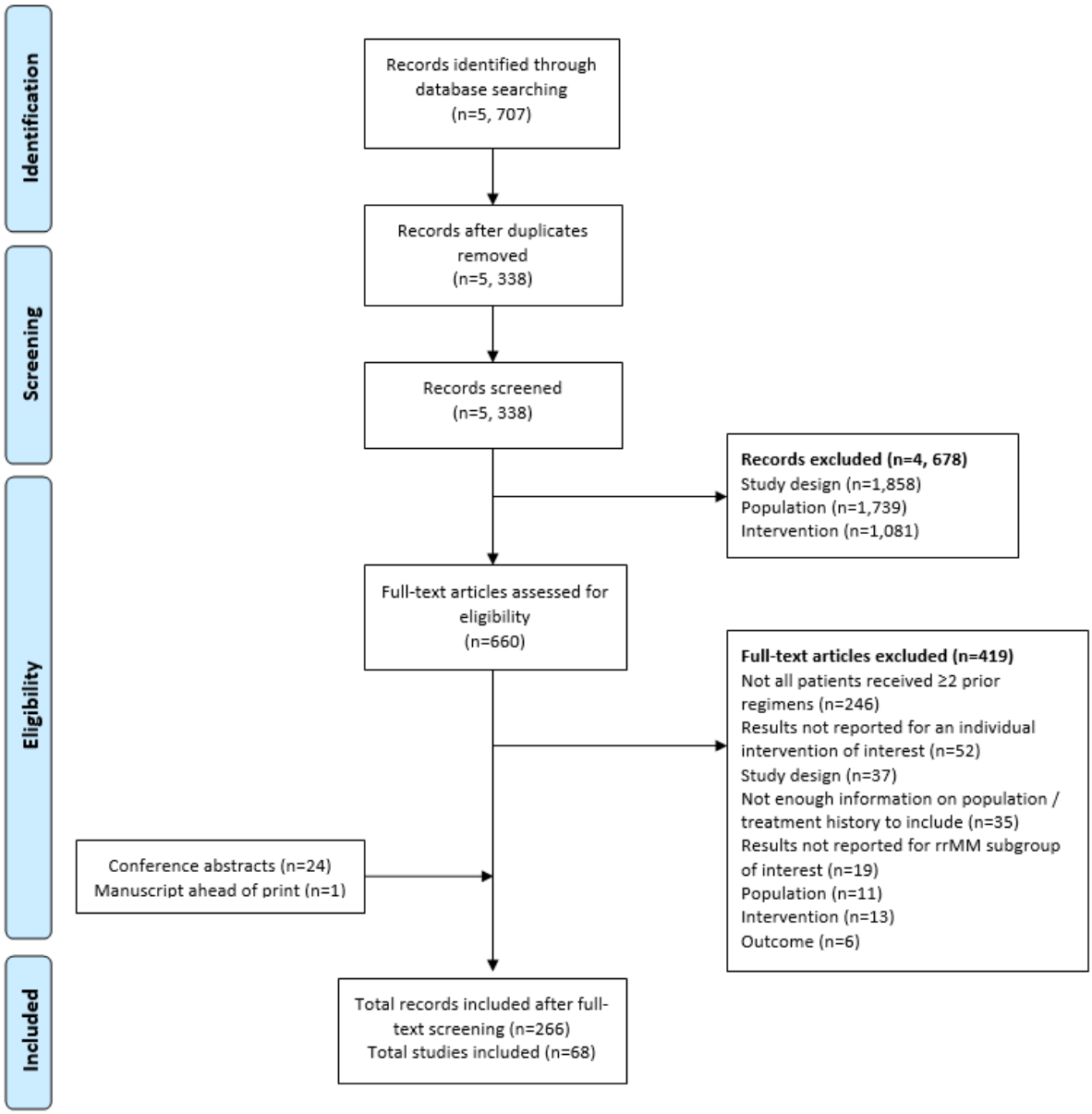
Original search results

Original systematic searches were conducted in January 2016.

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the number of studies included and excluded at each stage of the review is presented in Figure 5.

Electronic database searches identified 5,338 unique citations in total. During primary screening, a total of 4,678 citations were excluded as they were clearly not of relevance to the research question. A total of 660 citations were accessed in full for further evaluation. Of these citations, 63 were primary publications of trials meeting the eligibility criteria of the review, and a further 178 were secondary publications providing additional data sources. Conference proceeding searches identified 4 primary publications of trials meeting the eligibility criteria of the review and a further 20 secondary publications providing additional data sources. A further manuscript ahead of print was also included from Janssen files (primary publication).

Figure 5: PRISMA flow diagram of the clinical effectiveness literature search process (January 2016)



Key: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Updated search results

An update to the SLR of clinical evidence was initiated in July 2016, 6 months after the original SLR, to ensure the most up to date evidence was available for this appraisal.

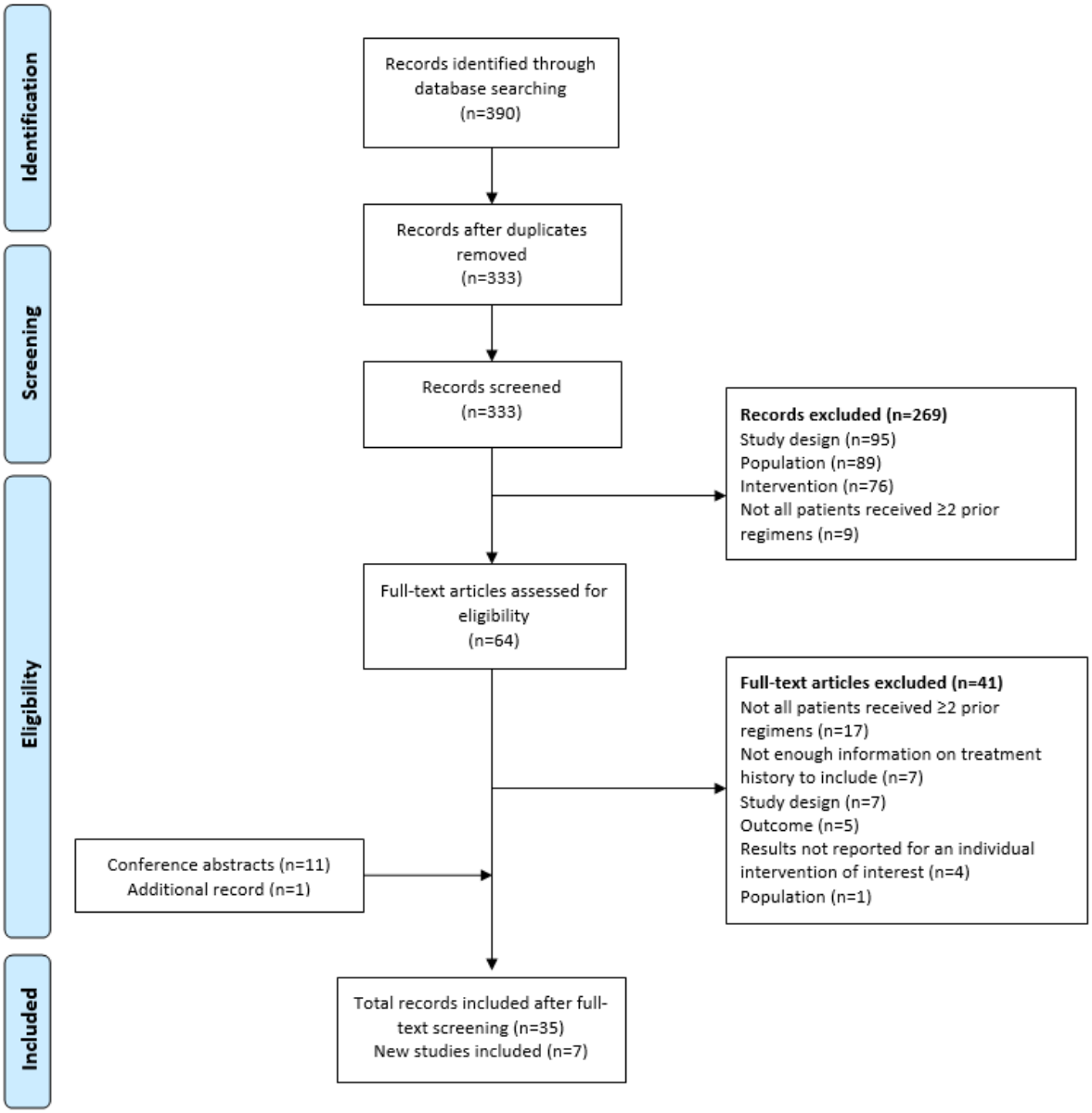
The methods adopted in this SLR update were as previously reported, with the exception that a date limit of 2016 was applied to the electronic database searches (in order to identify only new evidence published since the time of the original searches), and conferences hand searched in order to identify any relevant, on-going research were:

- The European Hematology Association (EHA) 2016
- The American Society of Clinical Oncology (ASCO) 2016

A PRISMA flow diagram showing the number of studies included and excluded at each stage of the review update is presented in Figure 6.

Electronic database searches identified 333 unique citations in total. During primary screening, a total of 269 citations were excluded as they were clearly not of relevance to the research question. A total of 64 citations were accessed in full for further evaluation. Of these citations, five were primary publications of new trials meeting the eligibility criteria of the review, and one was a secondary publication providing an additional data source for one of these new trials; a further 17 citations provided additional data sources for trials identified in the original review. Conference proceeding searches identified two primary publications of new trials meeting the eligibility criteria of the review and one secondary publication providing an additional data source for a new trial identified through electronic database updates. A further eight citations providing additional data sources for trials identified in the original review were also identified in conference proceeding searches. One final citation was included as an additional data source for a trial identified through conference proceeding searches in the original review; this citation is a manuscript that was published shortly after the systematic search updates were conducted.

Figure 6: PRISMA flow diagram of the clinical effectiveness literature search process (July 2016)



Key: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Of the 75 studies identified through SLR, 27 investigated interventions of interest to this appraisal, that is, POM+DEX, PANO+BORT+DEX and bendamustine. Primary data sources for these studies are listed in Table 7; secondary data sources are presented in Appendix 3. In addition, seven RWE studies were identified that were explicitly designed to investigate a named subgroup of interest. Primary data sources for these studies are summarised in Table 7, and secondary data sources are presented in Appendix 3.

Table 7: Primary data sources for trials identified through clinical effectiveness searches that investigated interventions of interest

Intervention	Trial name	Treatment arm(s)	Primary data source
Daratumumab	GEN501	Daratumumab 16mg/kg Daratumumab 8mg/kg	Lokhorst et al. 2015[69]
	MMY2002	Daratumumab 16mg/kg Daratumumab 8mg/kg	Lonial et al. 2016[70]
	MMY2002/GEN501 Integrated	Daratumumab 16mg/kg Daratumumab 8mg/kg	Usmani et al. 2016[71]
Pomalidomide	Alliance A061202	Pomalidomide 2mg-4mg + ixazomib 3mg-4mg + dexamethasone 40mg Pomalidomide 2mg-4mg + dexamethasone 40mg	Vorhees et al. 2015[72]
	IFM 2009-02	Pomalidomide 4mg + dexamethasone 40mg	Leleu et al. 2013[73]
	MM-002	Pomalidomide 4mg + dexamethasone 40mg Pomalidomide 4mg	Richardson et al. 2014[74]
	MM-003	Pomalidomide 4mg + low-dose dexamethasone 40mg Pomalidomide 4mg + high-dose dexamethasone 40mg	San Miguel et al. 2013[57]
	MM-004	Pomalidomide 2mg + dexamethasone 40mg	Matsue et al. 2015[75]
	MM-011	Pomalidomide 4mg + dexamethasone 40mg	Ichinohe et al. 2016
	MM-013	Pomalidomide 4mg + low-dose dexamethasone 40mg	Sonneveld et al. 2014[76]

Intervention	Trial name	Treatment arm(s)	Primary data source
	MM-014	Pomalidomide 4mg + low-dose dexamethasone 40mg	DiCapua et al. 2014[77]
	NCT00558896	Pomalidomide 2mg + dexamethasone 40mg Pomalidomide 4mg + dexamethasone 40mg	Lacy et al. 2011[78]
	NCT02654132	Pomalidomide 4mg + dexamethasone 40mg Pomalidomide 4mg + dexamethasone 40mg + elotuzumab 20mg	San Miguel et al. 2016[79]
	NCT01432600	Pomalidomide 4mg + dexamethasone 40mg Pomalidomide 4mg + dexamethasone 40mg + cyclophosphamide 400mg	Baz et al. 2014[80]
	POSEIDON	Pomalidomide (dose NR) + low-dose dexamethasone	Dechow et al. 2016[81]
	STRATUS	Pomalidomide 4mg + dexamethasone 40mg	Dimoopoulos et al. 2014[82]
	MM-002, MM-003, STRATUS	Pomalidomide 4mg + dexamethasone 40mg	Siegel et al. 2015
	Miles 2015	Pomalidomide + dexamethasone, as per licence Pomalidomide + dexamethasone, as per licence + cyclophosphamide	Miles et al. 2015[83]
	Montes-Gaisan 2015	Pomalidomide 2mg + dexamethasone 40mg Pomalidomide 4mg + dexamethasone 40mg	Montes-Gaisan et al. 2015[84]
	Sriskandarajah 2015	Pomalidomide[b]	Sriskandarajah et al.[85] 2015
Panobinostat	PANORAMA 1	Panobinostat 20mg + bortezomib 1.3mg/m^2 + dexamethasone 20mg Placebo + bortezomib 1.3mg/m^2 +	San Miguel et al. 2014[59]

Intervention	Trial name	Treatment arm(s)	Primary data source
		dexamethasone 20mg	
	PANORAMA 2	Panobinostat 20mg + bortezomib 1.3mg/m^2 + dexamethasone 20mg	Richardson et al. 2013[58]
Bendamustine	BHS MM	Bendamustine	Caers et al. 2014[86]
	KKM125	Bendamustine 100mg + prednisone	Kim et al. 2013[87]
	Grey-Davies 2012	Bendamustine 60mg/m^2 + thalidomide 50-200mg + dexamethasone 20mg	Grey-Davies et al. 2012[88]
	Lau 2015	Bendamustine 200mg + thalidomide 50-150mg + dexamethasone 160mg per cycle	Lau et al. 2015[89]
	Mian 2014	Bendamustine 60mg/m^2 + thalidomide 100mg + dexamethasone 20mg	Mian et al. 2014[90]
	Musto 2015	Bendamustine ± steroids	Musto et al. 2015[91]
	Stohr 2015	Bendamustine 120mg/m^2 Bendamustine 120mg/m^2 steroids 40mg[a]	Stohr et al. 2015[92]
Notes: [a], proportion of whole population; [b], presumed to be POM+DEX as UK practice with pomalidomide access through the CDF			

Table 8: Primary data sources for RWE studies identified through clinical effectiveness searches

Study ID	Population	Setting	Primary data source
Gooding 2015	Double relapsed/refractory MM defined as relapsed and/or refractory to bortezomib and lenalidomide (N=39)	UK Thames Valley Cancer Network	Gooding et al. 2015[26]
Jagannath 2016	MM patients with relapsed/refractory disease who had received ≥3 lines of prior therapy (N=391)	US International Oncology Network EMR database	Jagannath et al. 2016[93]
Kistler 2012	MM patients previously	US	Kistler et al.

Study ID	Population	Setting	Primary data source
	treated with ≥3 regimens including bortezomib and an IMiD (N=1,723)	Marketscan and Medicare data	2012[94]
Kumar 2012	MM patients refractory to bortezomib and relapsed/refractory, intolerant or ineligible for/to an IMiD (N=286; Treated=213)	US, Europe, Asia International Myeloma Working Group	Kumar et al. 2012[27]
Streetly 2014	Double relapsed/refractory MM defined as relapsed and/or refractory to bortezomib and lenalidomide (N=29)	UK Guys and St Thomas' NHS Trust; King's Health Partners; King's College Hospital NHS Trust	Streetly et al. 2014[29]
Tarrant 2013	MM patients sequentially exposed to thalidomide, bortezomib and lenalidomide (N=55)	UK Single centre	Tarrant et al. 2013[28]
Usmani 2016	MM patients previously treated with ≥3 regimens including a PI and an IMiD, or double-refractory to a PI and an IMiD (N=662)	US IMS LifeLink: IMS Oncology EMR database	Usmani et al. 2016[31]
Wang 2014	Dual refractory/intolerant MM defined as refractory or intolerant to both bortezomib and lenalidomide (N=65)	US Siteman Cancer Center/Washington University	Wang et al. 2014[30]

Key: EMR, electronic medical record; IMiD, immunomodulatory agent; MM, multiple myeloma; NHS, National Health Service; PI, proteasome inhibitor.

Evidence providing data for daratumumab monotherapy are presented in Sections 4.3 to 4.9 and Appendix 16. Evidence providing data for comparator therapies are only utilised in indirect treatment comparison (ITC) and comparative safety analysis and are therefore presented in Sections 4.10 and 4.12.1.

4.2 List of relevant randomised controlled trials

No RCTs are available for daratumumab monotherapy. Non-RCT data on which marketing authorisation was granted are therefore presented in the following sections.

4.3 Summary of methodology of the relevant non-randomised and non-controlled trials

A summary of the methodology of the MMY2002 and GEN501 studies is presented below, and further details are reported in Appendix 4.

Of note, MMY2002 and GEN501 are the pivitol trials for daratumumab monotherapy, and all results are hereafter presented for both trials. However, the key evidence used in the submission is taken from meta-analysis of these trials (i.e., the integrated MMY2002/GEN501 data), detailed in Section 4.9.

4.3.1 MMY2002

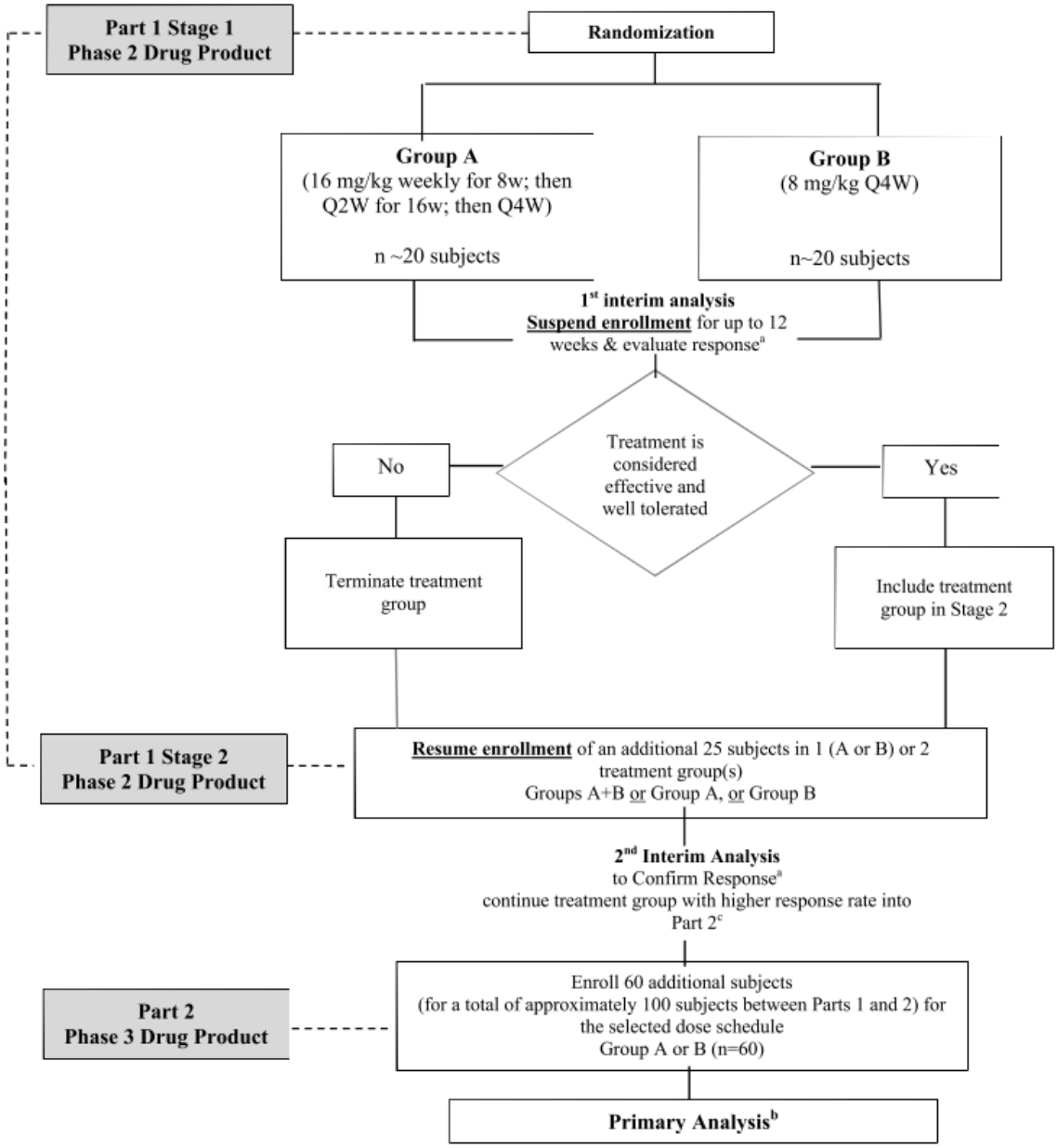
MMY2002 was a Phase II, randomised, multicentre, open-label, two-part study evaluating the safety and efficacy of daratumumab monotherapy in MM patients previously treated with at least three lines of therapy (including proteasome inhibitors [PIs] and IMiDs) or who are refractory to both a PI and IMiD. The study was initiated in September 2013 at 26 sites across the United States, Canada, and Spain and is comprised of two sequential parts. The purpose of Part 1 was to select the optimal dose and schedule for daratumumab monotherapy with higher ORR, and the purpose of Part 2 was to evaluate the selected dosing regimen from Part 1 in an expanded population.

The trial profile for MMY2002 is presented in Figure 7. Any daratumumab dose considered ineffective and/or poorly tolerated could be discontinued on the basis of

results from the first interim analysis, conducted after at least eight weeks of treatment for patients in Stage 1, Part 1. After the first interim analysis, patients treated with an ineffective/poorly tolerated dose could cross over to the more effective dose if it was in their best interest in the opinion of the treating investigator (Stage 2). A second interim analysis was conducted after another 25 patients were treated for at least 8 weeks in Stage 2, Part 1. Part 2 of the study was an expansion cohort with patients treated at the selected daratumumab dose of 16mg/kg to determine safety and efficacy. Dose reductions were not permitted in Part 2, and patients were treated until disease progression or unacceptable toxicity; long-term follow-up began after treatment discontinuation (ongoing).

Primary data presented in this appraisal are from both Part 1 and Part 2 of the study and include the primary endpoint of ORR and secondary endpoints of DoR, PFS, OS, clinical benefit rate (MR plus ORR), and safety. Data are based on the latest cut-off of 31 December 2015 where available; the median follow-up at this time was 20.7 months (range: 0.5-26.3) in the daratumumab 16mg/kg group. Not all endpoints were assessed at this time; therefore, some data are based on the primary data cut-off of 9 January 2015 when the median follow-up was 9.3 months (range: 0.5-14.4); a summary of data available at each data cut is presented in Table 9. The primary efficacy dataset consisted of all patients who received at least one dose of daratumumab and had at least one post treatment evaluation for response.

Figure 7: Schematic overview of study MMY2002



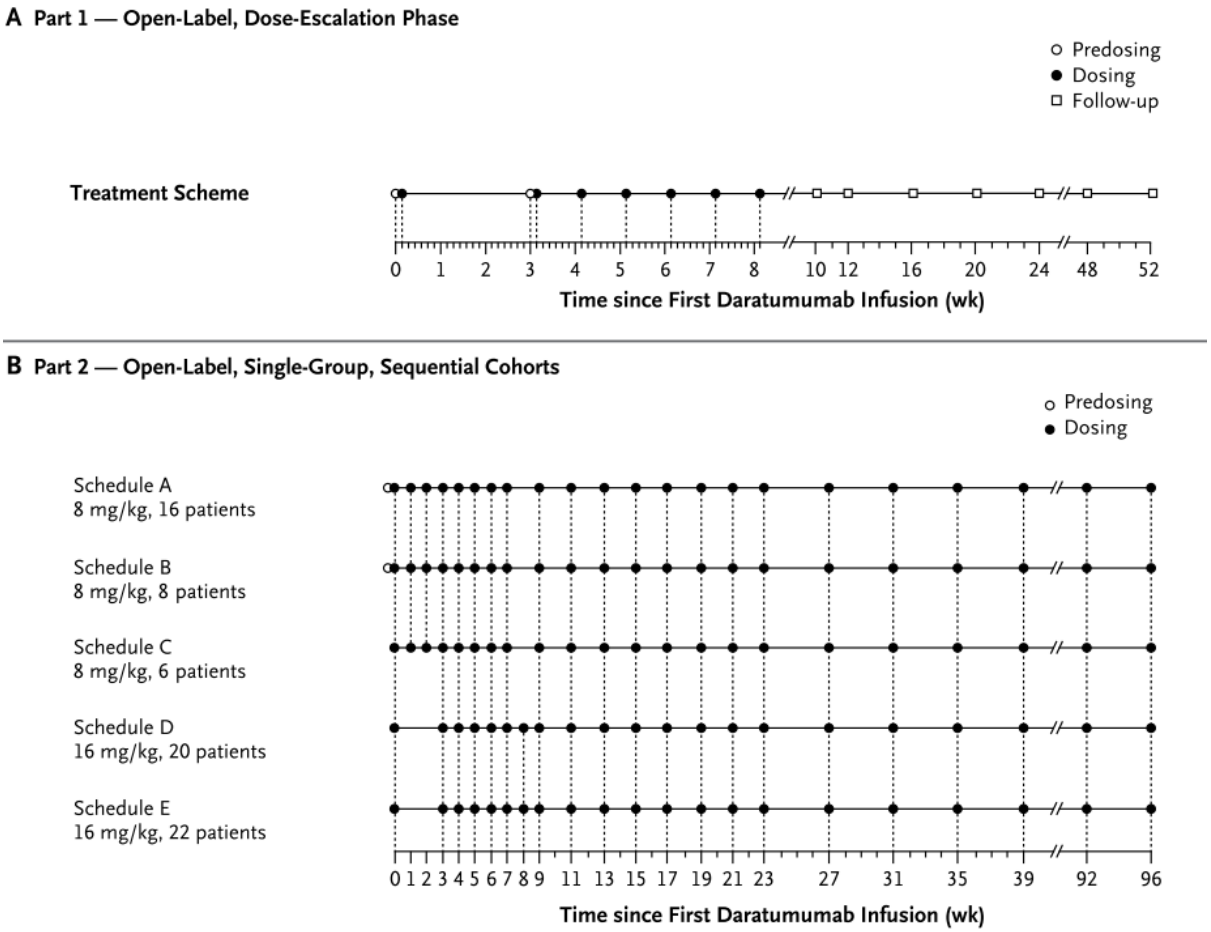
Notes: [a], response will be assessed by the sponsor based on available data (e.g. pharmacodynamics, efficacy, safety, biomarkers); [b], confirmation of response by the IRC is required; [c], if only 1 treatment group proceeded to Part 1 Stage 2, this will be the dose that is used in Part 2 of the study.
Source: Janssen et al. 2015.[95]

4.3.2 GEN501

Study GEN501 was a Phase I/II, multicentre, open-label, two-part study evaluating the safety and efficacy of daratumumab monotherapy in MM patients whose disease was relapsed and refractory to two prior lines of therapies and without further established treatment options. The study was initiated in March 2008 at 10 sites across the United States, Denmark, Sweden and the Netherlands and comprises two sequential parts. The purpose of Part 1 was to determine the maximum tolerated dose (MTD) for daratumumab monotherapy, and the purpose of Part 2 was to evaluate selected dosing regimens from Part 1 in multiple cohorts.

The trial profile for GEN501 is presented in Figure 8. Part 1 of the study was a dose-escalation design, with 10 dose levels of daratumumab ranging from 0.005 to 24mg/kg, sequentially evaluated. Part 2 of the study was a single-arm design with multiple cohorts; as the MTD was not reached in Part 1, an independent data monitoring committee (IDMC) recommended that the study move forward with daratumumab doses ≥8mg/kg.

Figure 8: Schematic overview of study GEN501



Source: Lokhorst et al. 2015.[69]

Primary data presented in this appraisal are from Part 2 of the study and include the primary endpoint of safety and secondary endpoints of ORR, DoR, PFS, and OS. Data are based on the latest cut-off of 31 December 2015 where available; the median follow-up at this time was 20.5 months (range: 1.2-27.1) in the daratumumab 16mg/kg group. Not all endpoints were assessed at this time; therefore, some data are based on the primary data cut-off of 9 January 2015 when the median follow-up was 10.2 months (range: 1.2-16.0) in the daratumumab 16mg/kg group; a summary of data available at each data cut is presented in Table 9. The primary efficacy dataset consisted of all patients who received at least one dose of daratumumab.

Table 9: Overview of outcomes assessed at different trial data cuts

Trial ID	Data cut	Median (range) duration of follow-up	Outcomes assessed
MMY2002	Primary analysis: January 9, 2015	9.3 months (0.5-14.4)	ORR, DoR, PFS, OS, clinical benefit rate (MR plus ORR), TTR and safety.
	6-month interim analysis: June 30, 2015	14.7 months (0.5-20.0)	OS
	18-month analysis: December 31, 2015	20.7 months (0.5-26.3)	DoR, OS
GEN501	Primary analysis: January 9, 2015	10.2 months (1.2-16.0)	Safety, ORR, DoR, PFS, and OS.
	6-month interim analysis: June 30, 2015	15.2 months (1.2-21.4)	OS
	18-month analysis: December 31, 2015	20.5 (1.2-27.1)	ORR, DoR, PFS, OS
Key: DoR, duration of response; MR, minimal response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTR, time to response.			

4.4 Statistical analysis and definition of study groups in the relevant non-randomised and non-controlled trials

The hypothesis and statistical analysis methods adopted in MMY2002 and GEN501 are summarised below with further details provided in Appendix 4.

In both studies, the all-treated analysis set was the primary population used for all efficacy and safety analyses; this included all patients who received at least one dose of daratumumab.

For the primary efficacy endpoint of ORR, the number and percentage of patients in response categories were tabulated and two-sided 95% exact CI presented by treatment group. Time-to-event endpoints including OS were analysed with the use of the Kaplan–Meier (KM) method with median values and corresponding 95% CIs provided.

Standard censoring methods were used to take account of missing data in time to event analyses; no data imputation was conducted for ORR analysis with patients who did not have at least one post-treatment evaluation classed as not evaluable.

4.5 Participant flow in the relevant non-randomised and non-controlled trials

Participant flow in studies MMY2002 and GEN501 is presented in Table 10.

A total of 124 patients were treated in MMY2002, 106 of whom received daratumumab 16mg/kg (41 in Part 1 and 65 in Part 2).

A total of 72 patients were treated in GEN501 Part 2, 42 of whom received daratumumab 16mg/kg (Cohorts D and E). Treatment discontinuation was mainly due to progressive disease across both trials.

Table 10: Patient disposition, MMY2002 and GEN501 Part 2 (various data cut-offs)

	MMY2002		**GEN501 Part 2**	
	Dara 8mg/kg	**Dara 16mg/kg**	**Dara 8mg/kg**	**Dara 16mg/kg**
Analysis set, n	18	106	30	42
Discontinued from treatment, n (%)	16 (88.9)	100 (94.3)	30 (100)	36 (85.7)
Progressive disease	16 (88.9)	92 (86.8)	30 (100)	31 (73.8)
Physician decision	-	-	0	4 (9.5)
Adverse event	0	5 (4.7)	0	1 (2.4)
Withdrawal of consent	0	3 (2.8)	-	-
Death	0	0	-	-

Key: Dara, daratumumab.
Notes: 16mg/kg data based on 31 December 2015 data cut-off for both studies; 8mg/kg data based on 9 January 2015 data cut-off for both studies.
Source: Janssen et al. 2015[95]; Janssen et al. 2015.[96]

Duration of exposure and releative dose intensity at the latest data cut-off (31 December 2015; median follow-up of 20.7 months in MMY2002 and 20.5 months in GEN501 Part 2) are presented in Table 11.

Table 11: Duration of exposure and relative dose intensity, MMY2002 and GEN501 Part 2 (various data cut-offs)

	MMY2002		GEN501 Part 2	
	Dara 8mg/kg (n=18)	**Dara 16mg/kg (n=106)**	**Dara 8mg/kg (n=30)**	**Dara 16mg/kg (n=42)**
Duration of treatment, median months (range):	1.87 (0.03- 13.90)	2.83 (0.03-25.5)	2.86 (0.1-14.8)	5.36 (0.03- 26.0)
Total dose received, mean mg/kg (SD)	51.96 (65.06)	217.0 (132.4)	86.64 (46.83)	240.9 (161.3)
Total number of daratumumab infusions, median (range)	3.0 (1.0-26.0)	11.0 (1.0-40.0)	10.5 (1.0- 26.0)	14.5 (1.0- 37.0)
Relative dose intensity, mean % (SD)	97.48 (10.0)	99.1 (8.7)	100	95.4 (10.0)
Duration of infusions, mean hours (SD):				
First infusion	8.16 (3.96)	7.34 (1.60)	6.77 (1.37)	7.81 (1.35)
Second infusion	4.95 (1.85)	4.86 (1.31)	4.40 (0.75)	6.66 (0.41)
All subsequent infusions	3.69 (0.53)	3.49 (0.39)	3.42 (0.21)	3.49 (0.55)

Key: Dara, daratumumab; SD, standard deviation.
Notes: 16mg/kg data based on 31 December 2015 data cut-off for both studies with the exception of duration of infusion data that is based on 9 January 2015 data cut-off; 8mg/kg data based on 9 January 2015 data cut-off for both studies.
Source: Janssen et al. 2015[95]; Janssen et al. 2015[96]; 18-month integrated analysis.[97]

Baseline demographics and disease characteristics of the patients enrolled in MMY2002 and GEN501 Part 2 are presented in Table 12.

Overall, the two study populations were well balanced, and minor differences were attributable to differences in the eligibility criteria of the individual trials and the trial initiation dates. The median lines of prior therapy was lower in the GEN501 study and patient exposure to carfilzomib and pomalidomide was higher in the MMY2002 study, which is indicative of the broader availability of these agents at the time of trial initiation.

Table 12: Baseline demographics and disease characteristics of patients, MMY2002 and GEN501 Part 2

	MMY2002		GEN501 Part 2	
	Dara 8mg/kg (n=18)	**Dara 16mg/kg (n=106)**	**Dara 8mg/kg (n=18)**	**Dara 16mg/kg (n=106)**
Age, median (range)	65.5 (49-76)	63.5 (31-84)	58.5 (38-76)	64.0 (44-76)
Male, n (%)	12 (66.7)	52 (49)	21 (70)	27 (64)
ECOG score, n (%)	0: 7 (38.9) 1: 9 (50.0) 2: 2 (11.1)	0: 29 (27) 1: 69 (65) 2: 8 (8)	0: 6 (20) 1: 23 (76.7) 2: 1 (3.3)	0: 12 (29) 1: 28 (67) 2: 2 (5)
ISS staging, n (%)	I: 2 (11.1) II: 8 (44.4) III: 8 (44.4)	I: 26 (25) II: 40 (38) III: 40 (38)	Not assessed	Not assessed
Extramedullary plasmacytomas, n (%)	0: 16 (88.9) ≥1: 2 (11.1)	0: 92 (87) ≥1: 14 (13)	0: 26 (86.7) ≥1: 4 (13.3)	0: 38 (90) ≥1: 4(10)
Cytogenetic profile, n (%)	N=17 t(4;14): 2 (1.8) del17p: 6 (35.3) del13q: 4 (23.5) amp1q21: 3 (17.6) other: 5 (29.4)	N=95 t(4;14): 9 (9.5) del17p: 16 (16.8) del13q: 30 (31.6) amp1q21: 23 (24.2) other: 43 (45.3)	Not assessed	Not assessed
Time since initial diagnosis, median years (range)	4.21 (1.2-9.1)	4.8 (1.1-23.8)	5.52 (2.15-15.3)	5.8 (0.8-23.7)
Number of lines of prior therapy, median (range)	5 (2-11)	5 (2-14)	4 (3-10)	4 (2-12)
>3 prior lines of therapy, n (%)	12 (66.7)	87 (82)	24 (80)	26 (62)

	MMY2002		GEN501 Part 2	
	Dara 8mg/kg (n=18)	**Dara 16mg/kg (n=106)**	**Dara 8mg/kg (n=18)**	**Dara 16mg/kg (n=106)**
Prior PI, n (%):	18 (100)	106 (100)	30 (100)	42 (100)
Bortezomib	18 (100)	105 (99)	30 (100)	42 (100)
Carfilzomib	6 (33.3)	53 (50)	2 (6.7)	8 (19)
Prior IMiD, n (%)	18 (100)	106 (100)	29 (96.7)	40 (95)
Lenalidomide	18 (100)	105 (99)	29 (96.7)	40 (95)
Pomalidomide	9 (50)	67 (63)	2 (6.7)	15 (36)
Thalidomide	6 (33.3)	47 (44)	20 (66.7)	19 (45)
Refractory to last line of therapy, n (%)	15 (83.3)	103 (97)	25 (83)	32 (76)
Refractory to PI/IMiD, n (%)	15 (83.3)	101 (95)	19 (63.3)	27 (64)
PI only	1 (5.6)	3 (3)	2 (6.7)	3 (7)
IMiD only	0	1 (1)	6 (20)	4 (10)
Refractory to PI + IMiD + alkylating agent, n (%)	13 (72.2)	79 (75)	18 (60)	21 (50)

	MMY2002		GEN501 Part 2	
	Dara 8mg/kg (n=18)	**Dara 16mg/kg (n=106)**	**Dara 8mg/kg (n=18)**	**Dara 16mg/kg (n=106)**
Refractory to, n (%):				
Bortezomib	16 (88.9)	95 (90)	21 (70)	30 (71)
Carfilzomib	6 (33.3)	51 (48)	2 (6.7)	7 (17)
Lenalidomide	16 (88.9)	93 (88)	26 (86.7)	31 (74)
Pomalidomide	9 (50.0)	67 (63)	2 (6.7)	15 (36)
Thalidomide	4 (22.2)	29 (27)	10 (33.3)	12 (29)
Alkylating agent	13 (72.2)	82 (77)	21 (70.0)	25 (60)

Key: Dara, daratumumab; ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory agent; ISS, International Staging System; PI, proteasome inhibitor.
Source: Lonial et al. 2016;[70] Janssen et al. 2015[95]; Lokhorst et al. 2015[69]; Janssen et al. 2015.[96]

4.6 Quality assessment of the relevant non-randomised and non-controlled trials

A detailed quality assessment for the MMY2002 and GEN501 studies are provided in Appendix 4, and outcomes of this assessment are summarised below.

Studies MMY2002 and GEN501 were conducted in accordance with good clinical practice (GCP) guidelines by qualified investigators using a single protocol to promote consistency across sites, and with measures taken to minimise bias.

In study MMY2002, disease evaluations were reviewed by an IRC blinded to treatment allocation; in GEN501, disease evaluations were conducted through a computerised algorithm, and an IDMC reviewed unblinded data on a routine basis and provided recommendations on the continuation, modification, or termination of the study. Randomisation to daratumumab dose in MMY2002 was carried out centrally with stratification for key prognostic factors, and patient allocation in GEN501 was carried out sequentially to avoid selection bias.

Disease evaluation and safety evaluation methods are consistent with other studies of rrMM therapy, and outcome assessments were all conducted in accordance with trial-validated methodologies. Disease evaluations were conducted every 28 days to adequately detect on-treatment effects, and survival follow-up was conducted every 12 weeks, in line with standard trial practice. Analyses were conducted on all treated patients, with missing data handled through standard censoring, although the most common reason for study withdrawal in both studies was disease progression, which is accounted for within the efficacy assessments.

Both studies are thought to adequately reflect routine clinical practice in England with respect to population, treatment administration and outcomes assessed; however, patients represent a heavily pre-treated and highly refractory cohort within the licensed population. Any bias caused by this would be against daratumumab monotherapy.

4.7 Clinical effectiveness results of the relevant non-randomised and non-controlled trials

MMY2002 and GEN501 provide compelling trial data to support the use of daratumumab 16mg/kg monotherapy for use at fourth-line in patients with rrMM who have previously received a PI and an IMiD and shown disease progression on the last therapy.

4.7.1 Response analysis

In both daratumumab monotherapy trials, ORR was assessed by independent review committee (IRC) using International Myeloma Working Group (IMWG) criteria.

The ORR of patients treated with daratumumab 16mg/kg in MMY2002 and GEN501 was 29% and 36%, respectively with >40% of all responders experiencing at least a very good partial response (VGPR), as summarised in Table 13. Stabilisation of disease or better was achieved in the vast majority of patients in both trials.

Table 13: Summary of overall response, MMY2002 and GEN501 Part 2 (IRC assessed; various data cut-offs)

	MMY2002		GEN501 Part 2	
	Dara 8mg/kg (n=18)	**Dara 16mg/kg (n=106)**	**Dara 8mg/kg (n=30)**	**Dara 16mg/kg (n=42)**
Data cut-off	January 2015		Jan 2015	Dec 2015
ORR, n (%)	2 (11.1)	31 (29.2)	3 (10)	15 (35.7)
Clinical benefit rate, n (%)	4 (22.2)	36 (34.0)	9 (30)	19 (45.2)
BOR, n (%):				
sCR	0	3 (2.8)	0	0
CR	0	0	0	4 (9.5)
VGPR	1 (5.6)	10 (9.4)	0	3 (7.1)
PR	1 (5.6)	18 (17.0)	3 (10)	8 (19.0)
MR	2 (11.1)	5 (4.7)	6 (20)	4 (9.5)
SD	10 (55.6)	46 (43.4)	14 (46.7)	22 (52.4)
PD	1 (5.6)	18 (17.0)	6 (20)	0
NE	3 (16.7)	6 (5.7)	1 (3.3)	1 (2.4)

	MMY2002	GEN501 Part 2
Key: CR, complete response; Dara, daratumumab; Dec, December; Jan, January; MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response. **Notes:** Analysis based on 9 January 2015 data cut-off for MMY2002 and the 8mg/kg arm of GEN501 Part 2, 31 December 2015 data cut-off for the 16mg/kg arm of GEN501 Part 2. **Source:** Lonial et al. 2015[70]; Janssen et al. 2015[96]; Lokhorst et al. 2015.[69]		

Response to treatment with daratumumab 16mg/kg was rapid as most patients were seen to respond at the time of the first disease assessment (approximately one month after treatment initiation), and most achieved their best response by the time of second disease assessment (approximately two months after treatment initiation), as summarised in Table 14.

Table 14: Time to response, MMY2002 and GEN501 Part 2 (IRC assessed; 9 January 2015 data cut-off)

	MMY2002		GEN501 Part 2	
	Dara 8mg/kg (n=2)	**Dara 16mg/kg (n=31)**	**Dara 8mg/kg (n=3)**	**Dara 16mg/kg (n=15)**
Time to first response, median months (range)	0.99 (1.0-1.0)	0.99 (0.9-5.6)	1.41 (0.6-2.1)	0.92 (0.5-3.2)
Time to best response, median months (range)	5.59 (1.0-10.2)	1.87 (0.9- 7.4)	1.41 (0.6-2.1)	1.84 (0.5- 9.0)
Time to VGPR or better, median months (range)	10.22 (10.2-10.2)	1.84 (0.9- 7.40	Not applicable	0.49 (0.5-0.5)
Key: CI, confidence interval; Dara, daratumumab; IRC, independent review committee; SD, standard deviation; VGPR, very good partial response. **Source:** Lokhorst et al. 2015[69]; Lonial et al. 2015[70]; Janssen et al. 2015[95]; Janssen et al. 2015.[96]				

Duration of response (DoR) at the latest data cut-off (31 December 2015; median follow-up of 20.7 months in MMY2002 and 20.5 months in GEN501 Part 2) is presented in in Table 15. The difference in DoR observed between the trials is attributed to the fact that patients in GEN501 were less heavily pre-treated and less

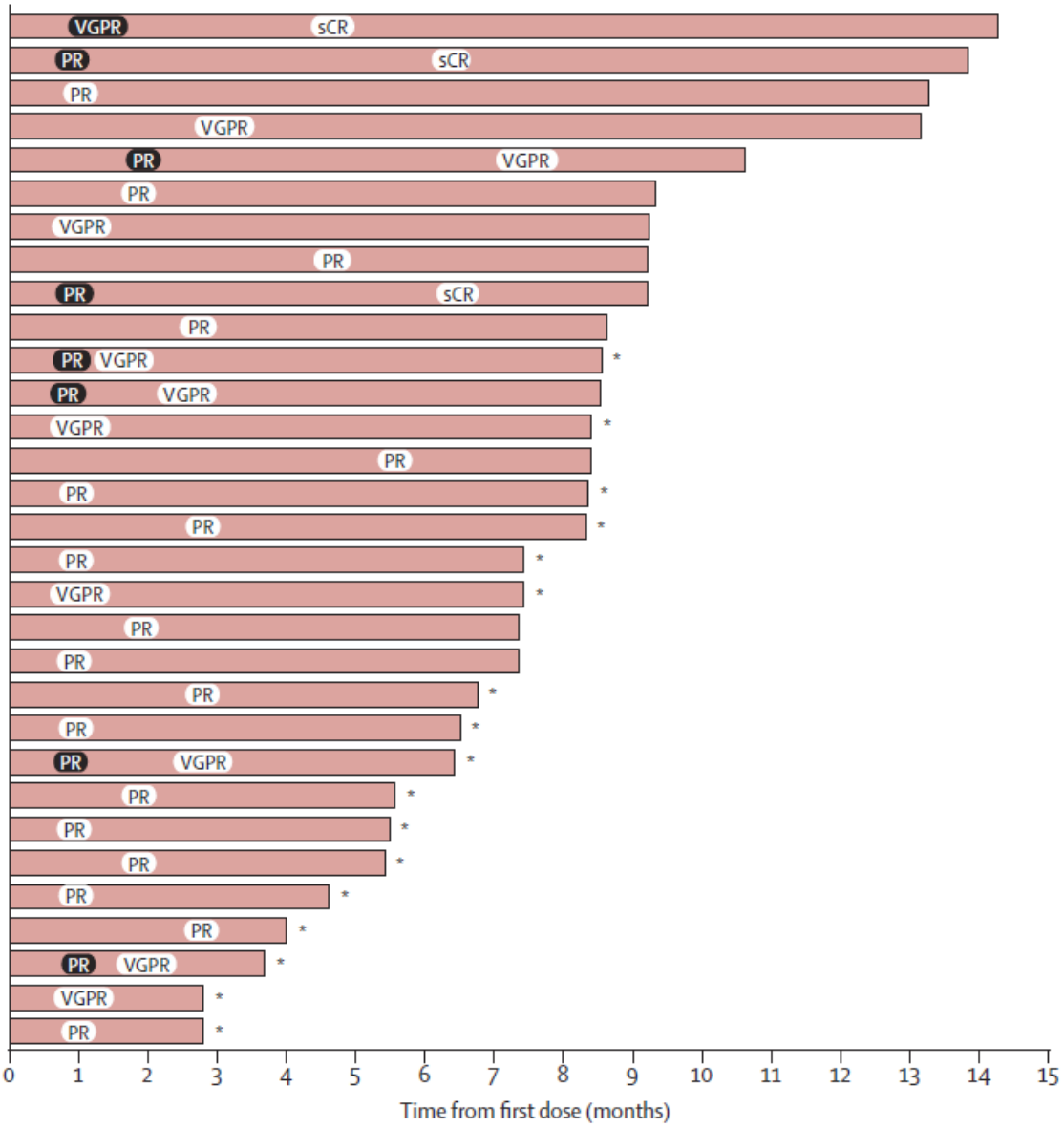
refractory compared with MMY2002. Results show responses to daratumumab 16mg/kg to be deep and durable.

Table 15: Duration of response, all patients treated with daratumumab 16mg/kg (IRC assessed; 31 December 2015 data cut-off)

	MMY2002	GEN501 Part 2
	Dara 16mg/kg (n=31)	**Dara 16mg/kg (n=15)**
Median DoR, months (95% CI)	6.82 (5.55, 11.07)	18.66 (5.55, not reached)
3 month progression-free rate, % (95% CI)	86.7 (68.3, 94.8)	86.2 (55.0, 96.4)
6 month progression-free rate, % (95% CI)	63.3 (43.6, 77.8)	79.0 (47.9, 92.7)
12 month progression-free rate, % (95% CI)	26.7 (12.6, 43.0)	71.8 (41.1, 88.4)
18 month progression-free rate, % (95% CI)	20.0 (8.1, 35.6)	54.7 (25.0, 76.9)
24 month progression-free rate, % (95% CI)	13.3 (3.2, 30.6)	43.8 (15.7, 69.1)
Key: CI, confidence interval; Dara, DoR, duration of response; IRC, independent review committee. **Source:** 18-month integrated efficacy analysis.[97]		

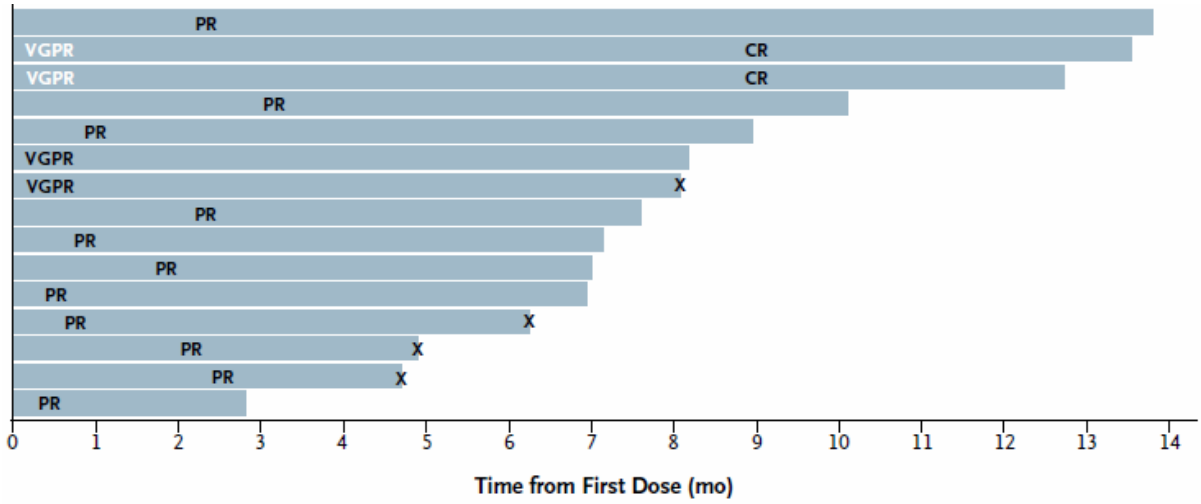
Responses deepened with continued exposure to daratumumab in eight patients in MMY2002 and two patients in GEN501, as depicted in the swimmer plots presented as Figure 9 and Figure 10, respectively.

Figure 9: Depth and duration of response, MMY2002 (IRC assessed; 9 January data 2015 cut-off)



Key: IRC, independent review committee; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
Notes: Black oval indicates first response; white oval indicates best response; * indicates disease progression.
Source: Lonial et al. 2016.[70]

Figure 10: Depth and duration of response, GEN501 Part 2 (IRC assessed; 9 January 2015 data cut-off)



Key: CR, complete response; IRC, independent review committee; PR, partial response; VGPR, very good partial response.
Notes: White text indicates first response; black text indicates best response; X indicates disease progression.
Source: Lokhorst et al. 2015.[69]

4.7.2 Survival analysis

At the latest data cut-off (31 December 2015; median follow-up of 20.7 months in MMY2002 and 20.5 months in GEN501 Part 2), patients treated with daratumumab 16mg/kg demonstrated a median OS of 18.6 months in the MMY2002 study, with a 2-year OS rate of 41% (Table 16). Median OS is yet to be reached in the daratumumab 16mg/kg arm of GEN501 Part 2, despite a median follow-up of 20.5 months, with a 2-year OS rate of 57% (Table 16).

Table 16: Summary of OS, MMY2002 and GEN501 Part 2 (various data cut-offs)

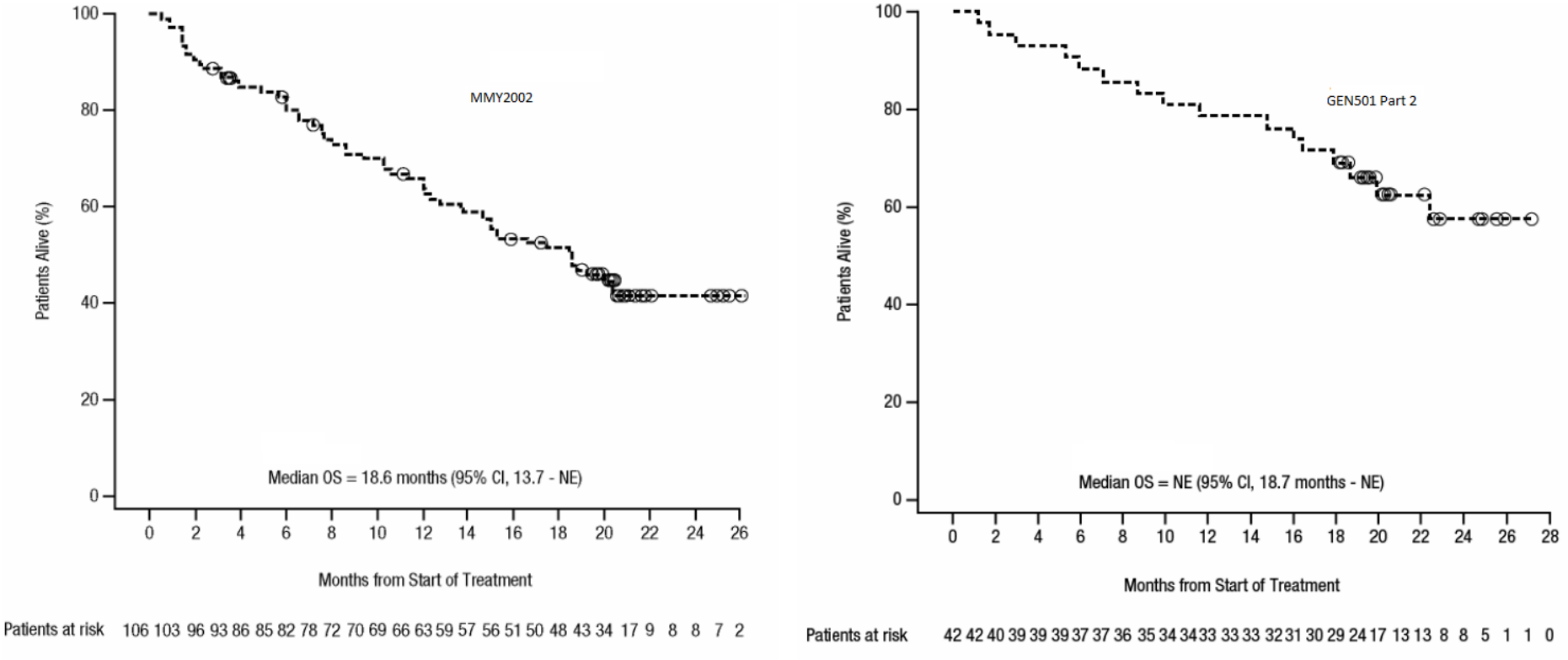
	MMY2002		GEN501 Part 2	
	Dara 8mg/kg (n=18)	**Dara 16mg/kg (n=106)**	**Dara 8mg/kg (n=30)**	**Dara 16mg/kg (n=42)**
Median OS, months (95% CI)	Not reached (7.72, not reached)	18.6 (13.7, not reached)	18.2 (7.5, 23.4)	Not reached, (18.7, not reached)
Number of events, n (%)	8 (44.4)	57 (53.8)	22 (73.3)	16 (38.1)

	MMY2002		GEN501 Part 2	
	Dara 8mg/kg (n=18)	**Dara 16mg/kg (n=106)**	**Dara 8mg/kg (n=30)**	**Dara 16mg/kg (n=42)**
6 month OS rate, % (95% CI)	87.5 (58.6, 96.7)	81.8 (73.0, 88.0)	76.7 (57.2, 88.1)	88.1 (73.7, 94.9)
12 month OS rate, % (95% CI)	62.5 (24.9, 81.1)	64.7 (54.5, 73.1)	56.3 (36.8, 71.8)	78.6 (62.9, 88.2)
18 month OS rate, % (95% CI)	-	51.3 (41.1, 60.6)	-	69.0 (52.7, 80.7)
24 month OS rate, % (95% CI)	-	41.3 (31.0, 51.2)	-	57.4 (38.7, 72.3)

Key: CI, confidence interval; Dara, daratumumab; Dec, December; IRC, independent review committee; OS, overall survival.
Notes: Analysis based on 9 January 2015 data cut-off for 8mg/kg arms, 31 December 2015 data cut-off for 16mg/kg arms.
Source: Janssen et al. 2015[98]; Janssen et al. 2015[99]; Usmani et al. 2016.[71]

The KM plots for OS in the daratumumab 16mg/kg arms of MMY2002 and GEN501 Part 2 are presented in Figure 11.

Figure 11: KM plot for OS, daratumumab 16mg/kg arms of MMY2002 and GEN501 Part 2 (31 December 2015 data cut-off)



Key: CI, confidence interval; NE, not evaluable; OS, overall survival.
Notes: Circles represent censoring.
Source: Usmani et al. 2016.[71]

Median PFS across MMY2002 and GEN501 Part 2 ranged from 3.7 to 6.2 months in the daratumumab 16mg/kg arm with 1-year PFS rates of 18% to 31%, as summarised in Table 17. On face value, this may appear relatively short considering the median OS of ≥18.6 months. There is however some precedence for extended OS relative to observed PFS with immunomodulatory therapy in rrMM.[50] This is further discussed in Section 4.13.

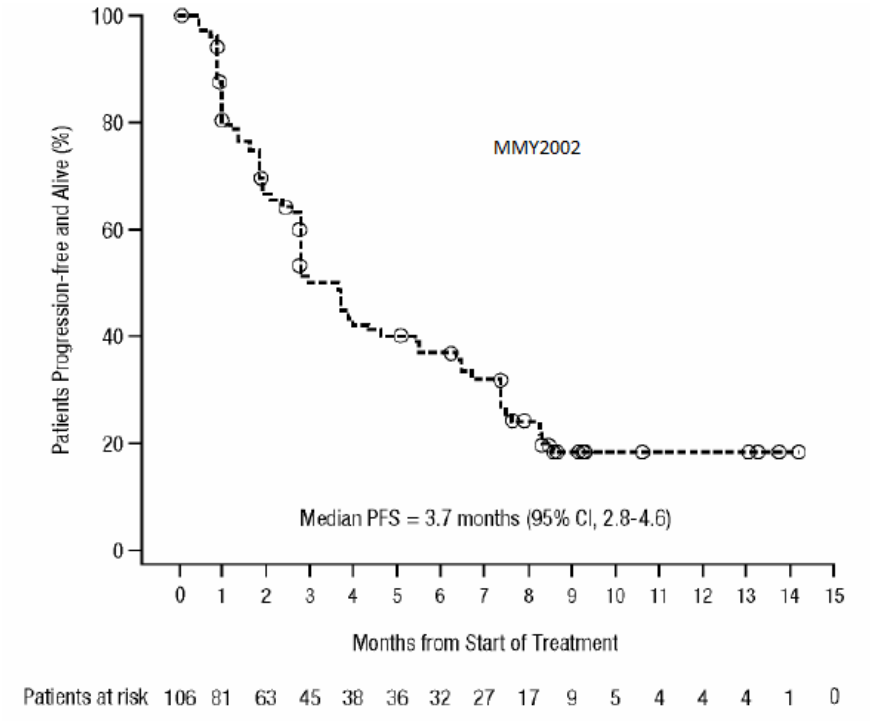
Table 17: Summary of PFS, MMY2002 and GEN501 Part 2 (IRC assessed; various data cut-offs)

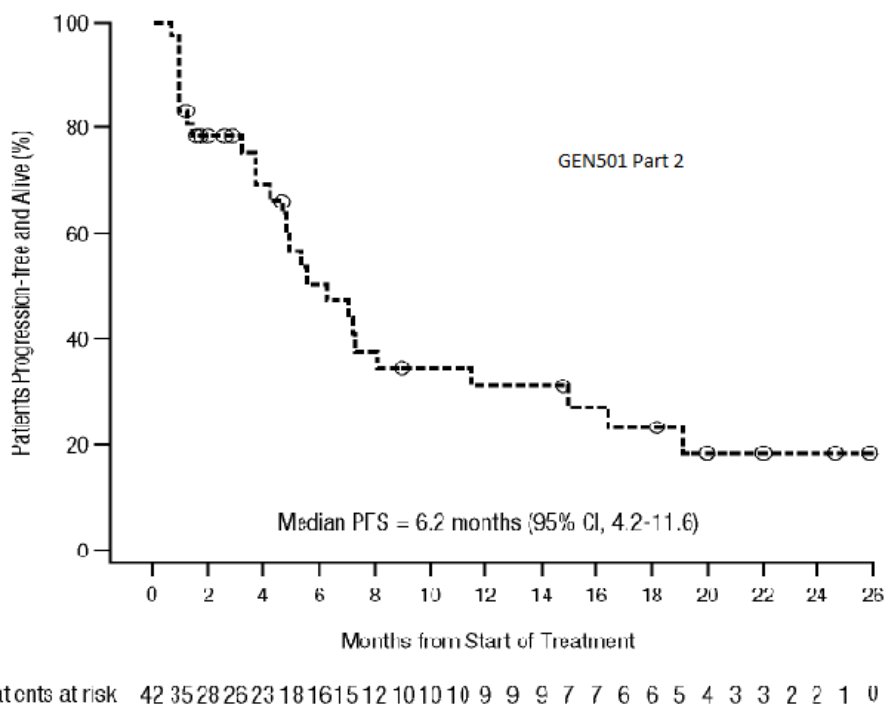
	MMY2002		GEN501 Part 2	
	Dara 8mg/kg (n=18)	**Dara 16mg/kg (n=106)**	**Dara 8mg/kg (n=30)**	**Dara 16mg/kg (n=42)**
Median PFS, months (95% CI)	4.9 (1.8, not reached)	3.7 (2.8, 4.6)	2.4 (1.4, 3.5)	6.2 (4.2, 11.6)
Number of events, n (%)	6 (33.3)	75 (70.8)	27 (90.0)	27 (64.3)
3 month PFS rate, % (95% CI)	63.5 (28.9, 84.7)	50.2 (39.8, 59.6)	-	78.3 (62.4, 88.1)
6 month PFS rate, % (95% CI)	25.4 (1.6, 63.7)	36.7 (27.0, 46.4)	16.2 (5.3, 32.5)	50.5 (32.9, 65.6)
12 month PFS rate, % (95% CI)	25.4 (1.6, 63.7)	18.3 (10.7, 27.5)	4.1 (0.3, 17.1)	31.2 (16.4, 47.2)

Key: CI, confidence interval; Dara, daratumumab; IRC, independent review committee; PFS, progression-free survival.
Notes: Analysis based on 9 January 2015 data cut-off for MMY2002 and the 8mg/kg arm of GEN501 Part 2, 31 December 2015 data cut-off for the 16mg/kg arm of GEN501 Part 2.
Source: Lonial et al. 2016[70]; Lokhorst et al. 2015[69]; Janssen et al. 2015[95]; Janssen et al. 2015[96]; Usmani et al. 2016.[71]

The KM plots for PFS in daratumumab 16mg/kg arms of MMY2002 and GEN501 Part 2 are presented in Figure 12.

Figure 12: KM plot for PFS, daratumumab 16mg/kg arms of MMY2002 and GEN501 Part 2 (IRC assessed; various data cut-offs)





Key: CI, confidence interval; IRC, independent review committee; PFS, progression-free survival.
Notes: Circles represent censoring; analysis based on 9 January 2015 data cut-off for MMY2002, 31 December 2015 data cut-off for GEN501 Part 2.
Source: Usmani et al. 2016.[71]

4.7.3 Subsequent therapy

In both MMY2002 and GEN501, treatment ended with disease relapse or progression, and most patients went on to receive subsequent therapy.

Of the 75 patients (71%) who went on to receive subsequent therapy in the daratumumab 16mg/kg arm of MMY2002, and the 32 patients (76%) who went on to receive subsequent therapy in the daratumumab 16mg/kg arm of GEN501 Part 2 (and for whom data were available at the time of the analysis), the most common subsequent therapies received are summarised in Table 18.

Table 18: Most common first subsequent anticancer therapies following daratumumab 16mg/kg monotherapy, MMY2002 and GEN501 Part 2 (31 December 2015 data cut-off)

First subsequent therapy	Percentage of patients, n (%)	
	MMY2002	**GEN501 Part 2**
Dexamethasone	60 (56.6)	26 (61.9)
Pomalidomide	34 (32.1)	16 (38.1)
Cyclophosphamide	33 (31.1)	14 (33.3)
Carfilzomib	31 (29.2)	11 (26.2)
Bortezomib	27 (25.5)	9 (21.4)
Lenalidomide	8 (7.5)	15 (35.7)
Source: Usmani et al. 2016.[71]; 18-month integrated efficacy analysis.[97]		

Of these patients, 30 (40%) and 12 (38%) had at least a partial response (PR) to first subsequent therapy and a further 31 (41%) and 9 (28%) demonstrated stabilisation of disease (SD or MR) following first subsequent therapy in MMY2002 and GEN501 Part 2, respectively, as summarised in Table 19.

Table 19: Summary of BOR to first subsequent anticancer therapy post daratumumab 16mg/kg monotherapy, MMY2002 and GEN501 (investigator assessed; 31 December 2015 data cut-off)

	Patients with subsequent anti-cancer therapy	
	MMY2002	**GEN501**
Patients with subsequent anticancer therapy	75	32
sCR, n (%)	2 (2.7)	0
CR, n (%)	2 (2.7)	1 (3.1)
VGPR, n (%)	9 (12.0)	2 (6.3)
PR, n (%)	17 (22.7)	9 (28.1)
MR, n (%)	6 (8.0)	2 (6.3)
SD, n (%)	25 (33.3)	7 (21.9)
PD, n (%)	9 (12.0)	5 (15.6)
NE, n (%)	1 (1.3)	1 (3.1)
Unknown, n (%)	4 (5.3)	5 (15.6)

Key: BOR, best overall response; CR, complete response; MR, minimal response; NE, not evaluable PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.
Source: Usmani et al. 2016.[71]

4.8 Subgroup analysis

In the MMY2002 study, the ORR was consistent across all clinically relevant pre-specified subgroups including patients who were refractory to their last line of therapy (ORR of 27%), patients who were refractory to a PI and an IMiD (ORR of 30%) and patients who were refractory to a PI, IMiD and an alkylating agent (ORR of 23%). A forest plot of these analyses is presented in Appendix 5.

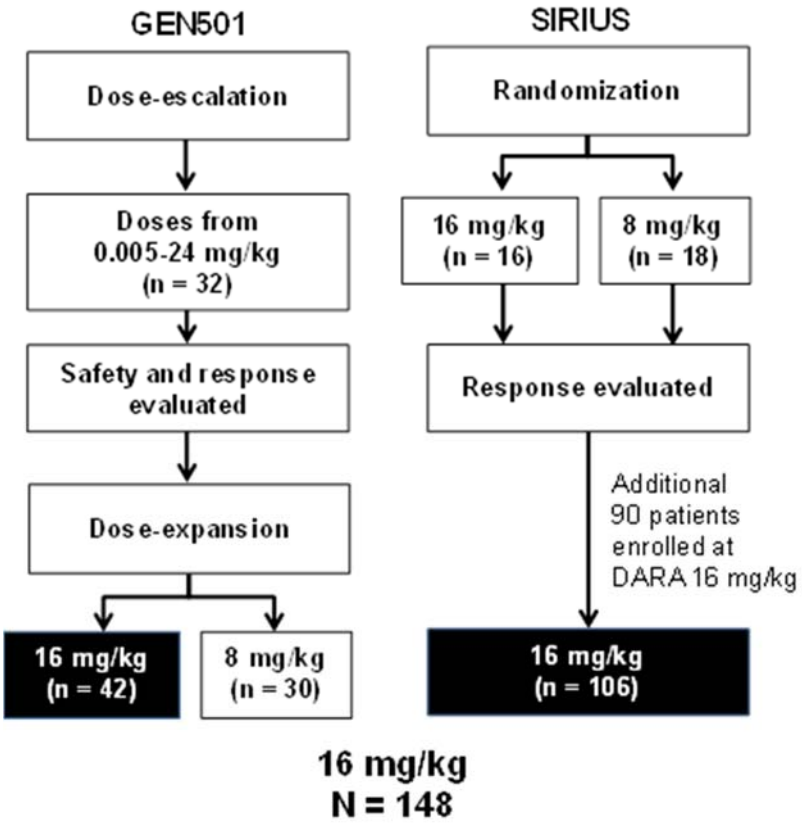
In the GEN501 study, the ORR was also consistent across all clinically relevant subgroups, including patients who were refractory to all available therapies. This is presented in Appendix 5. However, these results should be interpreted with caution due to the low patient numbers in some subgroups.

4.9 Meta-analysis

4.9.1 Summary of methodology

An integrated analysis of patients treated with daratumumab 16mg/kg monotherapy across the MMY2002 and GEN501 trials (see Sections 4.3 to 4.9) was conducted, as outlined in Figure 13.

Figure 13: Study schematic for the integrated analysis



Source: Usmani et al. 2016.[71]

This meta-analysis was conducted post-hoc across the two studies; however, in both studies, disease evaluations were conducted using IMWG criteria and as such are suitable for integrated analysis. For all outcomes except safety, which is reassessed in all patients from the integrated analysis set based on a data cut-off of 31 December 2015, the integrated analysis pools the latest data available from individual trials (see Section 4.9). Across datasets, the median follow-up for the 31 December 2015 data cut-off was 20.7 months (range: 0.5, 27.1).

4.9.2 Participant flow

All 148 patients who received daratumumab 16mg/kg across MMY2002 and GEN501 were included in the integrated analysis. At the time of the 31 December 2015 data cut-off, 136 patients (92%) had discontinued treatment (Table 20); 123 patients (83%) due to progressive disease, six patients (4%) due to an AE, four patients (3%) due to physician choice, and three patients (2%) due to patient choice.

Table 20: Patient disposition, integrated analysis (31 December 2015 data cut-off)

	Daratumumab 16mg/kg
Analysis set, n	148
Discontinued from treatment, n (%)	136 (91.9)
Progressive disease	123 (83.1)
Physician decision	4 (2.7)
Adverse event	6 (4.1)
Withdrawal of consent	3 (2.0)
Death	-
Source: Usmani et al. 2016.[71]	

At the latest data cut-off (31 December 2015; median follow-up 20.7 months), the median treatment duration for daratumumab 16mg/kg was 3.4 months, and the median number of infusions was 12 (equating to four months of treatment), as presented in Table 21.

Table 21: Duration of exposure and relative dose intensity, integrated analysis of MMY2002/GEN501 (31 December 2015 data cut-off)

	Daratumumab 16mg/kg (n=148)
Duration of treatment, median months (range):	3.4 (0.03-26.0)
Total dose received, mean mg/kg (SD)	223.8 (141.1)
Total number of daratumumab infusions, median (range)	12.0 (1.0-40.0)
Relative dose intensity, mean % (SD)	98.1 (9.2)
Key: Dara, daratumumab; SD, standard deviation **Source:** Usmani et al. 2016[71]; 18-month integrated efficacy analysis.[97]	

Baseline demographics and disease characteristics of patients treated with daratumumab 16mg/kg across the MMY2002 and GEN501 studies are presented in Table 22. Patients were heavily pre-treated and highly refractory, with 76% of patients having received >3 prior lines of therapy (median [range]: 5 [2-14]) and 87% of patients being double-refractory (refractory to both a PI and an IMiD). The time since initial diagnosis was 5.1 years (range: 0.8, 23.8), highlighting the aggressive course of disease in these patients; that is, on average, patients had received one line of therapy per year prior to trial enrolment.

Of note, most patients (98%) had received prior lenalidomide and were refractory to lenalidomide (84%). Consequently, even if this was a relevant comparator in the treatment setting for which daratumumab monotherapy is intended, a sensible comparison could not be made from this evidence base.

Table 22: Baseline demographics and disease characteristics, integrated analysis

	Daratumumab 16mg/kg (n=148)
Age, median (range)	64.0 (31-84)
Male, n (%)	78 (53)
ECOG score, n (%)	0: 41 (28) 1: 97 (66) 2: 10 (7)
Extramedullary plasmacytomas, n (%)	0: 130 (88) ≥1: 18 (12)
Time since initial diagnosis, median years (range)	5.1 (0.8-23.8)

	Daratumumab 16mg/kg (n=148)
Number of lines of prior therapy, median (range)	5 (2-14)
>3 prior lines of therapy, n (%)	113 (76)
Prior PI, n (%):	148 (100)
Bortezomib	147 (99)
Carfilzomib	61 (41)
Prior IMiD, n (%)	146 (99)
Lenalidomide	145 (98)
Pomalidomide	82 (55)
Thalidomide	66 (45)
Refractory to last line of therapy, n (%)	135 (91)
Refractory to PI/IMiD, n (%)	128 (87)
PI only	6 (4)
IMiD only	5 (3)
Refractory to PI + IMiD + alkylating agent, n (%)	100 (68)
Refractory to, n (%):	
Bortezomib	125 (85)
Carfilzomib	58 (39)
Lenalidomide	124 (84)
Pomalidomide	82 (55)
Thalidomide	41 (28)
Alkylating agent	107 (72)

Key: Dara, daratumumab; ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory agent; ISS, International Staging System; NR, not reported; PI, proteasome inhibitor.
Source: Usmani et al. 2016.[71]

4.9.3 Clinical effectiveness results

4.9.3.1 Response analysis

The ORR of patients treated with daratumumab 16mg/kg was 31%, with 44% of all responders experiencing at least a VGPR, as summarised in Table 23. When assessing paraprotein (M-protein) response, 40% and 19% of patients treated with daratumumab 16mg/kg achieved ≥50% and ≥90% reductions from baseline, respectively, as depicted in Figure 14. A greater reduction in M-protein reflects a

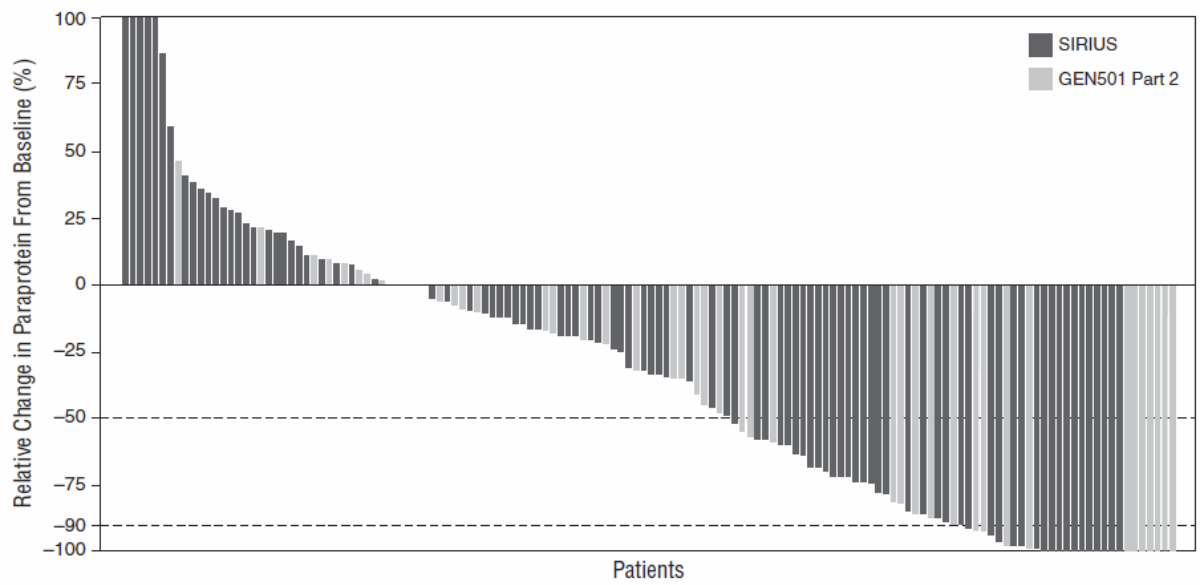
greater response to treatment. M-protein levels are more often assessed in clinical practice than the full IMWG criteria (of which M-protein levels are a key component). Further to ORR, the clinical benefit rate (ORR + Minimal Response [MR]) was 37%, and stabilisation of disease or better was achieved in 83% of patients; these are both important and clinically meaningful endpoints for these heavily pre-treated and highly refractory end-of-life patients (see Section 4.13).

Table 23: Summary of overall response rate, integrated analysis (IRC assessed; various data cut-offs)

	Daratumumab 16mg/kg (n=148)
ORR, n (%)	46 (31.1)
Clinical benefit rate, n (%)	55 (37.2)
BOR, n (%):	
Stringent complete response (sCR)	3 (2)
Complete response (CR)	4 (2.7)
Very good partial response (VGPR)	13 (8.8)
Partial response (PR)	26 (17.6)
Minimal response (MR)	9 (6.1)
Stable disease (SD)	68 (45.9)
Progressive disease (PD)	18 (12.2)
Not evaluable	7 (4.7)

Key: BOR, best overall response; IRC, independent review committee; ORR, overall response rate.
Notes: Analysis based on 9 January 2015 data cut-off for MMY2002, 31 December 2015 data cut-off for GEN501 Part 2.
Source: Usmani et al. 2016.[71]

Figure 14: Maximum change in paraprotein, integrated analysis (central laboratory data; various data cut-offs)



Key: IRC, independent review committee; IMWG, International Myeloma Working Group; PR, partial response; VGPR, very good partial response.
Notes: In addition to reduction in paraprotein, IMWG criteria require results from 2 consecutive tests demonstrating the necessary percent reduction in paraprotein, reduction of paraprotein in both serum and urine if measurable disease was determined by both serum and urine paraprotein, and a ≥50% reduction in the size of soft tissue plasmacytomas if these were present at baseline; thus, ≥50% and ≥90% reductions in paraprotein do not directly correlate with PR and VGPR; analysis based on 9 January 2015 data cut-off for MMY2002, 31 December 2015 data cut-off for GEN501 Part 2.
Source: Usmani et al. 2016.[71]

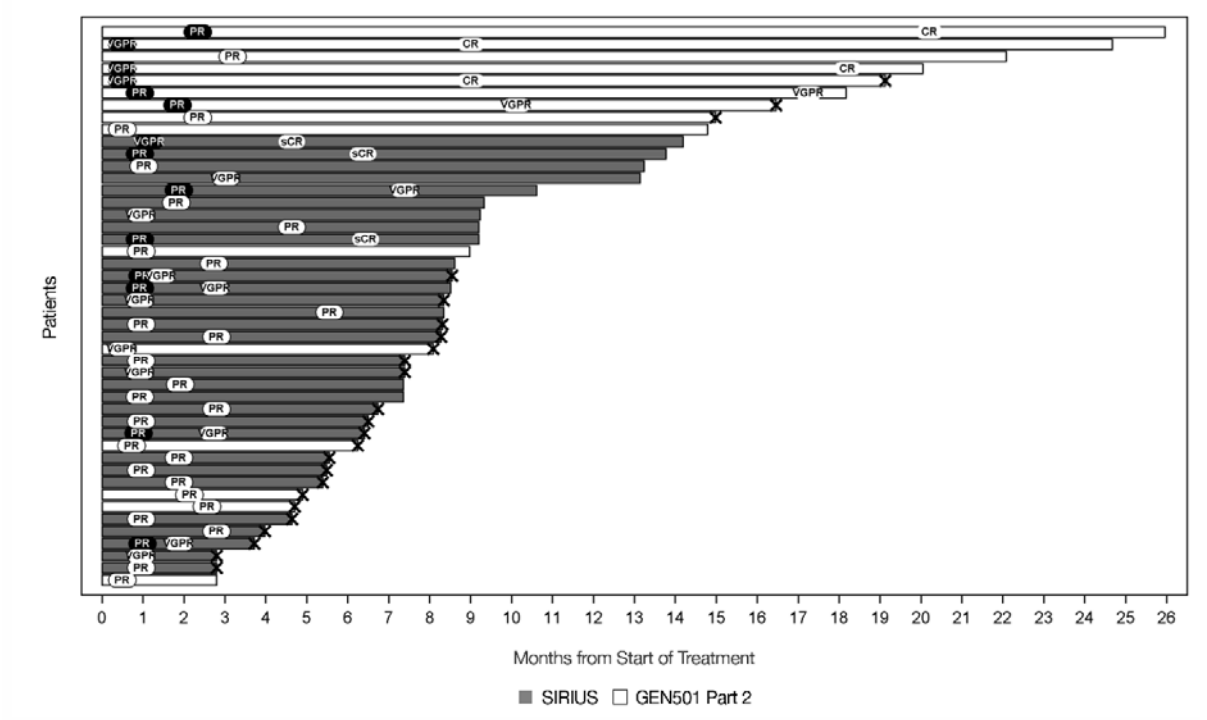
The median time to response (TTR) in patients with PR or better was 1.0 month (range: 0.5 - 5.6 months). At the latest data cut-off (31 December 2015; median follow-up 20.7 months), the median DoR in patients responding to treatment with daratumumab 16mg/kg was 8.0 months, and 22% of patients remained progression-free at two years, as summarised in Table 24.

Table 24: Duration of response, integrated analysis (IRC assessed; 31 December 2015 data cut-off)

	Daratumumab 16mg/kg (n=46)
Median DoR, months (95% CI)	8.02 (6.47, 14.65)
3-month progression-free rate, % (95% CI)	86.5 (72.3, 93.7)
6-month progression-free rate, % (95% CI)	68.3 (52.4, 79.8)
12-month progression-free rate, % (95% CI)	40.6 (26.1, 54.6)
18-month progression-free rate, % (95% CI)	30.6 (17.5, 44.6)
24-month progression-free rate, % (95% CI)	22.0 (9.6, 37.7)
Key: CI, confidence interval; DoR, duration of response; IRC, independent review committee. **Source:** 18-month integrated efficacy analysis.[97]	

Responses deepened with continued exposure to daratumumab in 14 patients. Of 10 patients with an initial PR, seven achieved a VGPR with further treatment; additionally, three patients with an initial PR achieved deeper responses of complete response (CR) (one patient) and stringent complete response (sCR) (two patients). Responses in four patients with VGPR continued to deepen to CR (three patients) and sCR (one patient). The impressive depth and duration of response with daratumumab 16mg/kg monotherapy can be seen in the swimmer plot presented as Figure 15. These results suggest daratumumab continues to elicit clinical benefit for patients achieving different magnitudes of initial response.

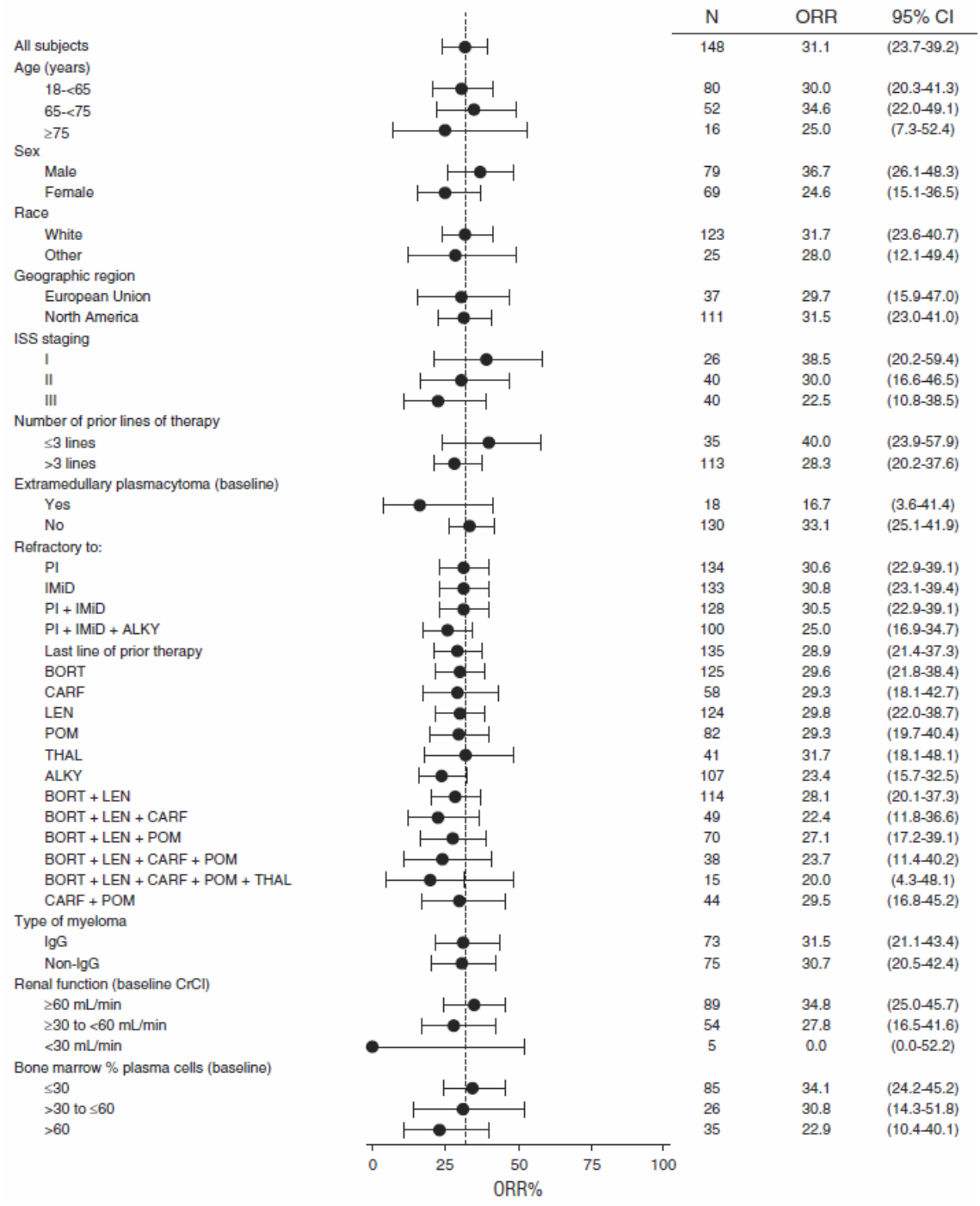
Figure 15: Depth and duration of response, integrated analysis (IRC assessed; 31 December 2015 data cut-off)



Key: CR, complete response; DoR, duration of response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
Notes: Black oval indicates first response; grey oval indicates best response; X indicates disease progression.
Source: Usmani et al. 2016.[71]

Response benefit was consistent across patient subgroups, regardless of prior lines of therapy, refractory status, renal function and baseline percentage of plasma cells in the bone marrow, as presented in Figure 16. Such robust results are highly beneficial given the heterogeneity of rrMM.

Figure 16: ORR in patient subgroups in the daratumumab 16mg/kg group, integrated analysis (31 December 2015 data cut-off)



Key: ALKY, alkylating agents, including autologous stem cell transplant; BORT, bortezomib; CARF, carfilzomib; CI, confidence interval; CrCl, creatinine clearance; IMiD, immunomodulatory drug; LEN, lenalidomide; ORR, overall response rate; PI, proteasome inhibitor; POM, pomalidomide; THAL, thalidomide.
Source: Usmani et al. 2016.[71]

4.9.3.2 Survival analysis

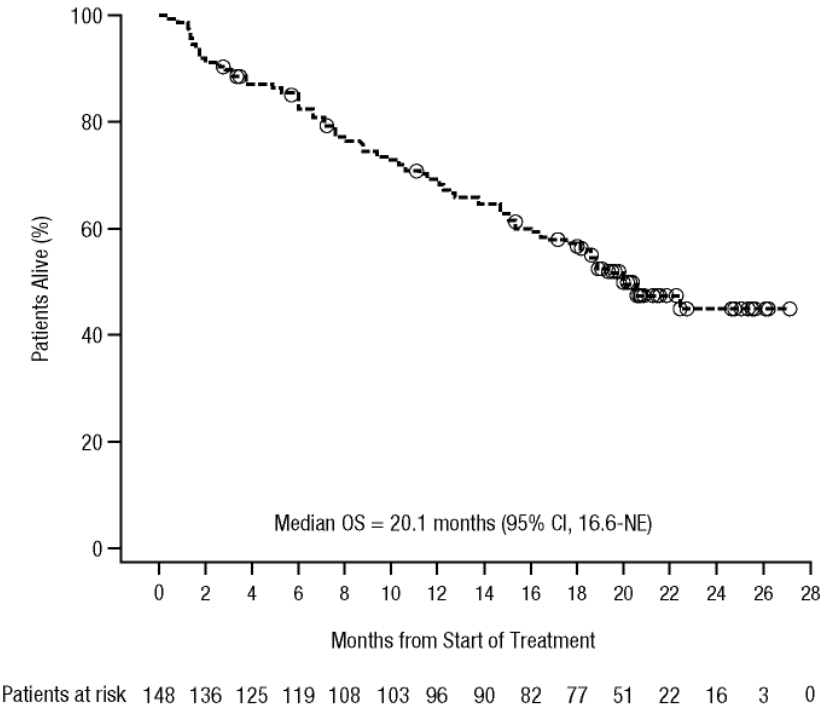
At the latest data cut-off (31 December 2015; median follow-up 20.7 months), patients treated with daratumumab 16mg/kg demonstrated a median OS of 20.1 months and a 2-year OS rate of 45% (Table 25). These survival data are unprecedented in this indication where patients are approaching the end of their active treatment pathway and their life.

Table 25: Summary of OS, integrated analysis (31 December 2015 data cut-off)

	Daratumumab 16mg/kg (n=148)
Median OS, months (95% CI)	20.1 (16.6, not reached)
Number of events, n (%)	73 (49.3)
6 month OS rate, % (95% CI)	83.6 (76.5, 88.7)
12 month OS rate, % (95% CI)	68.7 (60.5, 75.6)
18 month OS rate, % (95% CI)	56.5 (47.9, 64.2)
24 month OS rate, % (95% CI)	45.0 (35.5, 54.1)
Key: CI, confidence interval; Dara, daratumumab; Dec, December; IRC, independent review committee; OS, overall survival. **Source:** Usmani et al. 2016[71]; 18-month integrated efficacy analysis.[97]	

The KM plot for OS is presented in Figure 17.

Figure 17: KM plot for OS, integrated analysis (31 December 2015 data cut-off)



Key: CI, confidence interval; NE, not estimable; OS, overall survival.
Notes: Circles represent censoring.
Source: Usmani et al. 2016.[71]

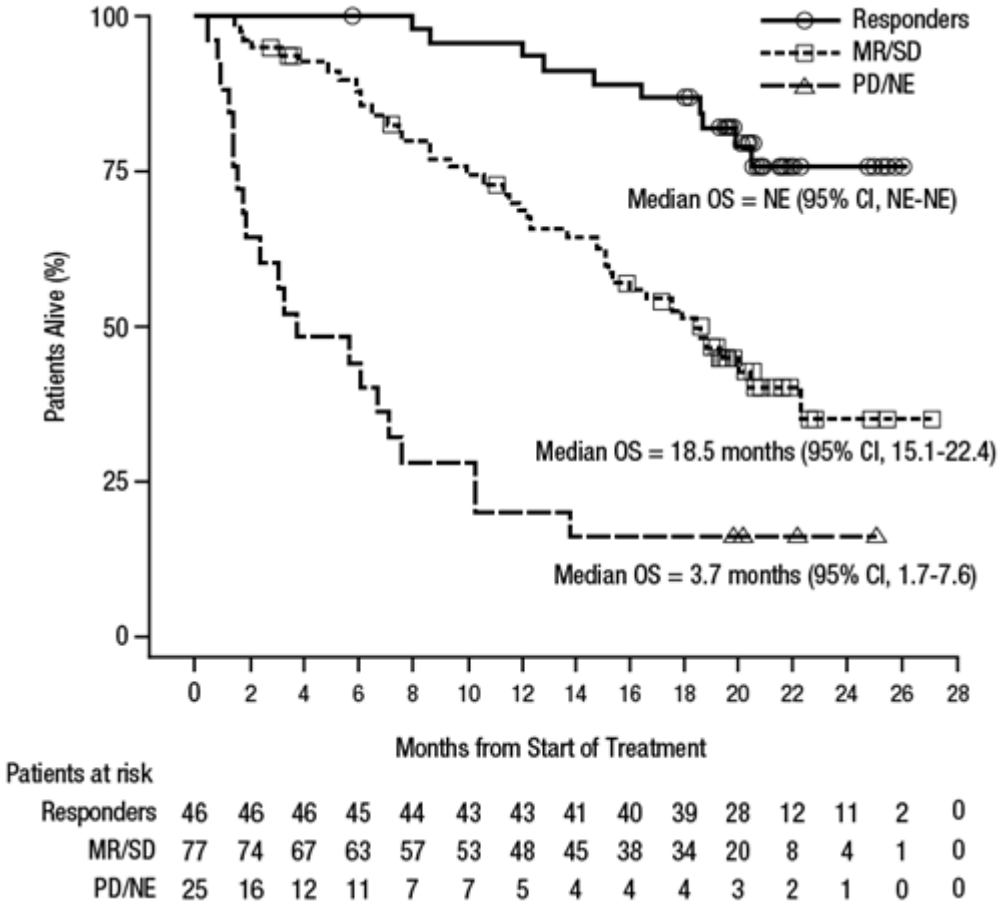
Subgroup analyses demonstrate clear differences in OS when patients are stratified by type of response, as can be clearly observed in the KM plot presented in Figure 18.

As may be expected *a priori*, patients with at least a PR to therapy demonstrate the greatest OS benefit with median OS yet to be reached and a 2-year OS rate of 76%. At the latest data cut-off (31 December 2015; median follow-up 20.7 months), 78% of patients (36/46) who responded to daratumumab 16mg/kg were alive.

A clear OS benefit was also observed in patients achieving stable disease (SD) or minimal response (MR), with median OS of 18.5 months (95% CI: 15.1, 22.4) and a 2-year OS rate of 35%. Such results support the fact that in this highly relapsed and refractory patient population, stabilisation of disease elicits clinically meaningful benefit. Conversely, patients with early progression (i.e. best overall response [BOR] of progressive disease [PD]) despite active treatment with daratumumab 16mg/kg

monotherapy demonstrated a median OS of only 3.7 months (95% CI: 1.7, 7.6) and a 2-year OS rate of 16%.

Figure 18: KM plot for OS stratified by response, integrated analysis (31 December 2015 data cut-off)



Key: CI, confidence interval; MR, minimal response; NE, not estimable; OS, overall survival; PD, progressive disease; SD, stable disease.
Notes: Circles, squares and triangles represent censoring.
Source: Usmani et al. 2016.[71]

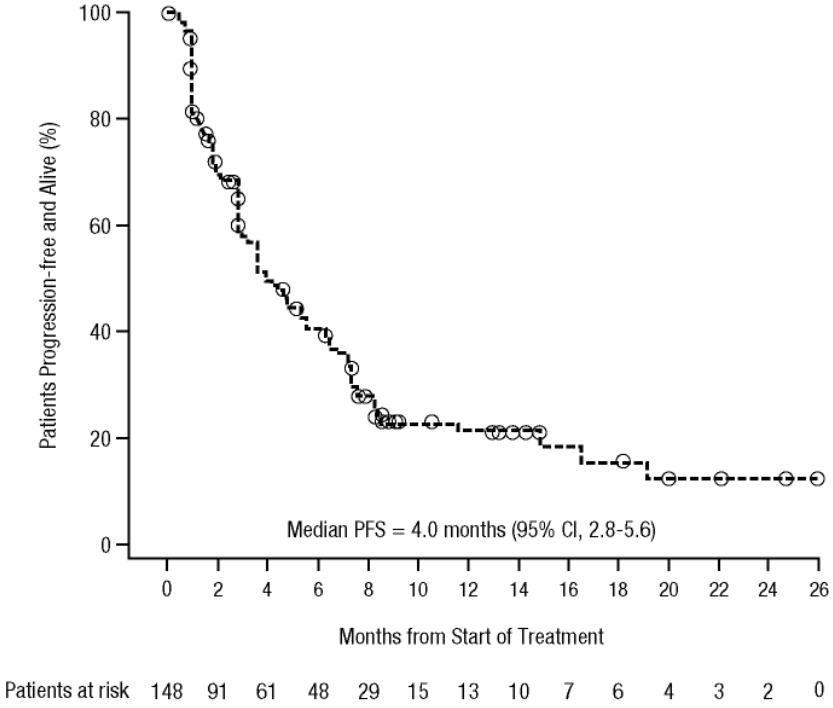
PFS data from the integrated analysis, as assessed by IRC, is presented in Table 26 and a KM plot is presented in Figure 19. Investigator-assessed PFS data are provided in Appendix 6.

Patients treated with daratumumab 16mg/kg demonstrated a median PFS of 4.0 months (95% CI: 2.8, 5.6) and a 1-year PFS rate of 22% (IRC assessed). As noted previously, this may appear relatively short on face value, considering the median OS of 20.1 months. There is some precedence for such observations with immunomodulatory therapy in rrMM.[50] This is further discussed in Section 4.13.

Table 26: Summary of PFS, integrated analysis (IRC assessed; various data cut-offs)

	Daratumumab 16mg/kg (n=148)
Median PFS, months (95% CI)	4.0 (2.8, 5.6)
Number of events, n (%)	102 (68.9)
3 month PFS rate, % (95% CI)	57.8 (49.0, 65.7)
6 month PFS rate, % (95% CI)	40.5 (32.0, 48.9)
12 month PFS rate, % (95% CI)	21.6 (14.4, 29.8)
Key: CI, confidence interval; Dara, daratumumab; IRC, independent review committee; PFS, progression-free survival. **Notes:** Analysis based on 9 January 2015 data cut-off for MMY2002, 31 December 2015 data cut-off for GEN501 Part 2. **Source:** Usmani et al. 2016[71]; 18-month integrated analysis.[97]	

Figure 19: KM plot for PFS, integrated analysis (IRC assessed; various data cut-offs)

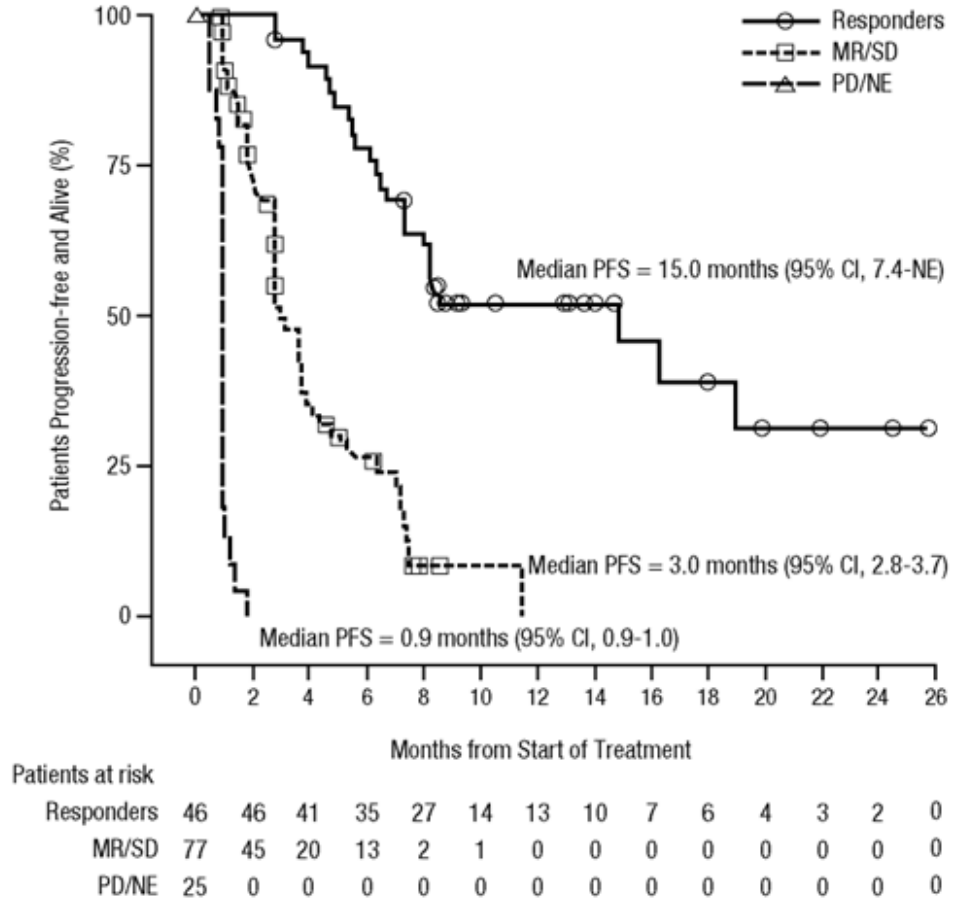


Key: CI, confidence interval; IRC, independent review committee; PFS, progression-free survival.
Notes: Circles represent censoring; integrated analysis based on 9 January 2015 data cut-off for MMY2002, 31 December 2015 data cut-off for GEN501 Part 2.
Source: Usmani et al. 2016.[71]

As was observed in subgroup analysis of OS, clear differences in PFS were observed when patients were stratified by type of response, as depicted in Figure 20.

Patients with at least a PR to therapy demonstrated a median PFS of 15.0 months (95% CI: 7.4, not reached). This was markedly longer than the median PFS observed in patients with stabilisation of disease (3.0 months), and of course in patients with early progression (0.9 months). In patients responding to treatment, the 1-year PFS rate was 52%, compared with a contrasting 1-year PFS rate of 0% in patients with stabilisation of disease or early progression.

Figure 20: KM plot for PFS stratified by response, integrated analysis (IRC assessed; various data cut-offs)



Key: CI, confidence interval; MR, minimal response; NE, not estimable; PD, progressive disease; PFS, progression-free survival; SD, stable disease.
Notes: Circles, squares and triangles represent censoring; integrated analysis based on 9 January 2015 data cut-off for MMY2002, 31 December 2015 data cut-off for GEN501 Part 2.
Source: Usmani et al. 2016.[71]

4.9.3.3 Subsequent therapy

Of the 107 patients (72%) who went on to receive subsequent therapy (and for whom data were available at the time of the integrated analysis), the most common subsequent therapies received are summarised in Table 27.

Table 27: Most common first subsequent anticancer therapies following daratumumab 16mg/kg monotherapy, integrated analysis (31 December 2015 data cut-off)

First subsequent therapy	Percentage of patients (%)
Dexamethasone	86 (58.1)
Pomalidomide	50 (33.8)
Cyclophosphamide	47 (31.8)
Carfilzomib	42 (28.4)
Bortezomib	36 (24.3)
Lenalidomide	23 (15.5)
Source: Usmani et al. 2016[71]; 18-month integrated efficacy analysis.	

Of these patients, 42 (39%) had at least a PR to first therapy post daratumumab and a further 40 (37%) demonstrated stabilisation of disease (SD or MR), as summarised in Table 28.

Table 28: Summary of BOR to first subsequent anticancer therapy post daratumumab 16mg/kg monotherapy, integrated analysis (investigator assessed; 31 December 2015 data cut-off)

	Daratumumab 16mg/kg
Patients with subsequent anticancer therapy	107
sCR, n (%)	2 (1.9)
CR, n (%)	3 (2.8)
VGPR, n (%)	11 (10.3)
PR, n (%)	26 (24.3)
MR, n (%)	8 (7.5)
SD, n (%)	32 (29.9)
PD, n (%)	14 (13.1)
NE, n (%)	2 (1.9)
Unknown, n (%)	9 (8.4)
Key: BOR, best overall response; CR, complete response; MR, minimal response; NE, not evaluable PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response. **Source:** Usmani et al. 2016.[71]	

4.9.4 Adverse reactions

Summary safety data from the integrated analysis are provided in Table 29.

Daratumumab monotherapy was shown to be well tolerated with clinically manageable side effects, evidenced by the fact that no patients died or discontinued treatment due to study drug toxicity.

Three deaths were attributed to TEAEs (one case each of viral HIN1 infection, pneumonia and aspiration pneumonia), but in all cases, it was determined that deaths due to TEAEs were not related to study treatment.

Table 29: Overview of TEAEs, integrated analysis (31 December 2015 data cut-off)

	Daratumumab 16mg/kg (n=148)
Any TEAE	147 (99.3)
Drug-related	117 (79.1)
Any serious TEAE	48 (32.4)
Drug-related	13 (8.8)
Maximum severity of any TEAE	
Grade 1	9 (6.1)
Grade 2	55 (37.2)
Grade 3	56 (37.8)
Grade 4	17 (11.5)
Grade 5	10 (6.8)
DC due to TEAE	6 (4.1)
Drug-related	0
Death due to TEAE	3 (2.0)
Drug-related	0
Key: Dara, daratumumab; DC, discontinuation; Dec, December; TEAE, treatment-emergent adverse event. **Source:** 18-month integrated efficacy analysis.[97]	

Subgroup analyses confirmed that this safety profile was consistent across patient groups, including those defined by age, gender, race, renal or hepatic function.

4.9.4.1 Treatment-emergent adverse events

Details of TEAEs reported at the latest data cut-off (31 December 2015) are provided in Table 30.

The TEAE profile for daratumumab is consistent with the underlying disease state of advanced MM with common TEAEs including blood and lymphatic disorders (particularly anaemia [28%]), fatigue (42%), back pain (27%) and cough (26%).

Table 30: Common TEAEs (≥10%) by system organ class, integrated analysis (31 December 2015 data cut-off)

	Daratumumab 16mg/kg (n=148)		
	Any grade	**Grade 3**	**Grade 4**
Total TEAEs, n (%)	147 (99.3)	61 (41.2)	21 (14.2)
General disorders and administration site conditions	103 (69.6)	9 (6.1)	0
Fatigue	62 (41.9)	3 (2.0)	0
Pyrexia	29 (19.6)	1 (0.7)	0
Chills	15 (10.1)	0	0
Respiratory, thoracic, and mediastinal disorders	98 (66.2)	8 (5.4)	0
Cough	38 (25.7)	0	0
Nasal congestion	29 (19.6)	0	0
Dyspnoea	25 (16.9)	1 (0.7)	0
Musculoskeletal and connective tissue disorders	97 (65.5)	10 (6.8)	2 (1.4)
Back pain	40 (27.0)	4 (2.7)	0
Arthralgia	27 (18.2)	0	0
Pain in extremity	26 (17.6)	1 (0.7)	0
Musculoskeletal chest pain	19 (12.8)	2 (1.4)	0
Bone pain	15 (10.1)	1 (0.7)	0
Musculoskeletal pain	15 (10.1)	1 (0.7)	0
Gastrointestinal disorders	88 (59.5)	3 (2.0)	1 (0.7)
Nausea	44 (29.7)	0	0
Diarrhoea	27 (18.2)	1 (0.7)	0
Constipation	22 (14.9)	0	0

	Daratumumab 16mg/kg (n=148)		
	Any grade	**Grade 3**	**Grade 4**
Vomiting	21 (14.2)	0	0
Infections and infestations	87 (58.8)	13 (8.8)	2 (1.4)
Upper respiratory tract infection	32 (21.6)	1 (0.7)	0
Nasopharyngitis	22 (14.9)	0	0
Blood and lymphatic system disorders	76 (51.4)	37 (25.0)	11 (7.4)
Anaemia	42 (28.4)	26 (17.6)	0
Thrombocytopenia	32 (21.6)	13 (8.8)	8 (5.4)
Neutropenia	31 (20.9)	11 (7.4)	4 (2.7)
Metabolism and nutrition disorders	62 (41.9)	9 (6.1)	4 (2.7)
Decreased appetite	23 (15.5)	1 (0.7)	0
Hypercalcaemia	18 (12.2)	3 (2.0)	2 (1.4)
Nervous system disorders	55 (37.2)	6 (4.1)	1 (0.7)
Headache	18 (12.2)	2 (1.4)	0
Vascular disorders	30 (20.3)	9 (6.1)	0
Hypertension	15 (10.1)	7 (4.7)	0

Key: TEAE, treatment-emergent adverse event.
Source: Usmani et al. 2016[71]; 18-month integrated efficacy analysis.[97]

Blood and lymphatic disorders (thrombocytopenia, anaemia and neutropenia) that did occur were managed effectively with platelet transfusions, red blood cell (RBC) transfusions and prophylactic use of granulocyte colony-stimulating factor (GCSF). In total, 199 transfusions were administered to 46 patients (31%); of those, platelet and RBC transfusions were received by 14 (10%) and 44 patients (30%), respectively. Prophylactic treatment with GCSF was required by 12 patients (8%).

Although it has previously been reported that daratumumab binds to CD38 expressed on the surface of RBCs,[100, 101] and this additional activity may interfere with blood typing and cross-matching, no TEAEs related to haemolysis were reported.

4.9.4.2 Infusion-related reactions

Infusion-related reactions (IRRs) reported in the integrated analysis are summarised in Table 31.

At the time of the latest data cut-off (31 December 2015; median follow-up 20.7 months), IRRs were observed in 48% of patients, but very few patients had a Grade ≥3 IRR (four patients). IRRs that occurred in ≥5% of patients were mainly respiratory conditions including nasal congestion, cough, allergic rhinitis, throat irritation, and dyspnoea; non-respiratory IRRs that occurred in ≥5% of patients of patients comprised of chills and nausea. Most IRRs were observed during the first infusion (95.8%), and incidence markedly decreased during the second (7.0%) and subsequent (7.0%) infusions (some patients experienced >1 IRR).

IRRs were safely managed with pre- and post-infusion medications, which consisted of antihistamines, corticosteroids and paracetamol/acetaminophen, and all patients who experienced an IRR were able to continue full-dose therapy with supportive treatment.

Table 31: Common IRRs (≥5%) by system organ class, integrated analysis (31 December 2015 data cut-off)

	Daratumumab 16mg/kg			
	First infusion (n=148)	**Second infusion (n=145)**	**Subsequent infusions (n=141)**	**Total (n=148)**
Total IRRs, n (%)	68 (45.9)	5 (3.4)	5 (3.5)	71 (48.0)
Respiratory, thoracic and mediastinal disorders	53 (35.8)	4 (2.8)	0	54 (36.5)
Nasal congestion	17 (11.5)	1 (0.7)	0	17 (11.5)
Cough	11 (7.4)	1 (0.7)	0	12 (8.1)
Rhinitis allergic	10 (6.8)	0	0	10 (6.8)
Throat irritation	8 (5.4)	1 (0.7)	0	9 (6.1)
Dyspnoea	7 (4.7)	1 (0.7)	0	8 (5.4)
General disorders and administration site conditions	15 (10.1)	1 (0.7)	1 (0.7)	16 (10.8)
Chills	10 (6.8)	0	0	10 (6.8)

	Daratumumab 16mg/kg			
	First infusion (n=148)	**Second infusion (n=145)**	**Subsequent infusions (n=141)**	**Total (n=148)**
Gastrointestinal disorders	10 (6.8)	1 (0.7)	1 (0.7)	11 (7.4)
Nausea	7 (4.7)	1 (0.7)	1 (0.7)	8 (5.4)

Key: IRR, infusion related reaction.
Source: Usmani et al. 2016[71]; 18-month integrated efficacy analysis.[97]

4.10 Indirect and mixed treatment comparisons

4.10.1 Study selection

The SLR methods used to identify trials for potential inclusion in an ITC are described in Sections 4.1 and 4.12.

4.10.1.1 Pomalidomide

A number of trials provided evidence for POM+DEX that could potentially be utilised for ITC, as summarised in Appendix 7.

The trial providing the highest quality (based on assessment of study design, sample size and data availability) and most comparable evidence base (based on assessment of patient characteristics) to that available for daratumumab monotherapy was the Phase III RCT, MM-003. This trial investigated the efficacy and safety of POM+DEX compared with high-dose dexamethasone in patients with rrMM who had failed at least two previous treatments, including bortezomib and lenalidomide. In consideration of their lower quality (based on assessment of study design, sample size and data availability) or comparability to MMY2002/GEN501, all other trials investigating the efficacy and safety of POM+DEX were excluded from the statistical analysis plan for base-case ITC. Sensitivity analyses utilising data pooled from MM-003 and STRATUS data have been conducted as detailed in Appendix 9.

Full methodological details for MM-003 and a quality assessment of this trial are presented in Appendix 8.

In addition to trial data, real-world data from the IMF chart review were used in sensitivity analyses. The IMF is a large myeloma-specific organisation which spans 140 countries worldwide, supporting patients and carers, while providing significant contribution to medical research. A key benefit of utilising this source of RWE was the ability to access IPD to inform comparative analyses. Location of sites encompassed North & South America, Asia Pacific and Europe, including the UK (n=3).

Patients with rrMM who had received ≥3 prior lines of therapy, were refractory to both a PI and an IMiD, and who had been exposed to an alkylating agent were identified for inclusion in the study. Hence, the IMF cohort was closely aligned to the integrated IPD from the daratumumab trial populations. Follow-up of patients started on the date they fulfilled eligibility criteria in terms of refractory status and exposure (T_0), and OS was the main endpoint of the study; defined as the time between treatment initiation and death. Patients who were lost to follow-up or did not reach the event of interest were censored at the date of their final assessment. From the IMF cohort, 963 treatment lines from 550 patients were included in the analysis, with 42% of patients providing data for more than one treatment line post T_0. Of the 963 treatment lines identified, 226 (23%) included pomalidomide (the most frequently used treatment).

4.10.1.2 Panobinostat

Two trials provided evidence for PANO+BORT+DEX that could potentially be used for ITC; these trials are summarised in Appendix 7.

The trial providing the highest quality (based on assessment of study design, sample size and data availability) evidence base was the Phase III RCT PANORAMA 1. However, this trial enrolled patients with rrMM who had received 1-3 prior treatments, and the median number of prior treatments was one, with limited data reported for patients who had received at least two prior regimens. Therefore, more comparable data (based on assessment of patient characteristics) from the Phase II trial, PANORAMA 2, were utilised for ITC. This trial investigated the efficacy and safety of PANO+BORT+DEX in patients with rrMM who had received at least two prior treatments, including an IMiD, and who had progressed on or within 60 days of

their last bortezomib-based therapy; however, these patients were still less heavily pre-treated (median number of prior therapies of four versus five) than those in the daratumumab trials (see Section 4.10.3.3).

Full methodological details for PANORAMA 2 and a quality assessment for this trial are provided in Appendix 8.

4.10.1.3 Bendamustine

As summarised in Appendix 7, a number of trials that provide evidence for the off-label use of bendamustine-based therapy were identified. However, since bendamustine is unlicensed for the treatment of rrMM, the majority of studies investigating bendamustine-based therapy were retrospective in nature (reflective of its off-label use). The few prospective trials that were identified were small and only reported at conferences with minimal informative data. Based on assessment of study design, sample size and data availability; no trials were of suitable quality or comparability to inform an ITC.

Of note, in the recent technology appraisal of POM+DEX, the manufacturer presented a comparison to bendamustine utilising data from the MUKone trial.[102] This trial did not meet the eligibility criteria of the SLR presented in Section 4.1 as the inclusion criteria for MUKone was ‘confirmed relapsed/refractory MM with measurable disease’ (i.e., there was no required number of prior treatment regimens) and subgroup data were not provided for patients who had received at least two prior regimens. As such, the MUKone trial is unsuitable to inform comparison of daratumumab versus bendamustine.

In order to fill this substantial evidence gap, RWE studies were assessed for potential use in ITC. Of those identified through systematic review, no survival data were specifically available for bendamustine-based therapy; rather, data were more generally reported for ’available care’. In attempt to obtain further details on RWE studies conducted in the UK, authors were contacted but it was not possible to access the individual patient-level data (IPD) required for comparative analyses. A summary of data available from RWE studies identified through systematic review is presented in Table 32.

Table 32: Clinical effectiveness data from RWE studies identified through systematic review

Study ID	Population	Setting	Interventions	Effectiveness outcomes	Data availability
Gooding 2015	DRMM defined as relapsed and/or refractory to BORT and LEN N=39	UK	First DRMM treatment, n (%): Bendamustine plus THAL/DEX: 17 (43.6) Subsequent treatments, n (%): Bortezomib: 6 (15.4) Lenalidomide: 13 (33.3)	From start of DRMM treatment, median months: OS: 5.6 PFS: 5.6 Deaths, n (%): 24 (61.5)	Full published manuscript[26]
Jagannath 2016	MM patients with relapsed/refractory disease who had received ≥3 lines of prior therapy N=391 Prior BORT and IMiD, n=239	US	3rd line with prior BORT and IMiD, n (%): Bortezomib ± non-IMID: 69 (28.9) Lenalidomide ± non-PI: 45 (18.8) Bortezomib ± IMiD: 39 (16.3) Thalidomide ± non-PI: 7 (2.9) Melphalan ± non-IMiD, non-PI: 7 (2.9) Melphalan + thalidomide: 4 (1.7) Carfilzomib ± IMiD/other: 34 (14.2) Pomalidomide PI/other:15 (6.3) Other: 19 (7.9)	Median PFS, months (95% CI): 7.3 (4.2, 10.8) 4.9 (3.0, 8.6) 7.3 (5.0, 15.0) 9.8 (0.1, 50.4) 3.4 (0.6, NR) 25.2 (0.7, 29.4) 3.7 (2.8, 8.4) 5.8 (1.4 13.8) 7.9 (1.9, 14.0)	Full published manuscript[93]
Kistler 2012	MM patients previously treated with ≥3 regimens including BORT and an IMiD N=1,723	US	-	-	Conference abstract[94]
Kumar 2012	MM patients refractory to BORT	US, Europe,	Drugs included in 1st regimen following T0, n (%):	From T0, median months (95% CI): OS: 9 (7, 11)	Full published

Study ID	Population	Setting	Interventions	Effectiveness outcomes	Data availability
	and relapsed/ refractory, intolerant or ineligible for/to an IMiD N=286 Treated, n=213	Asia	Corticosteroids: 140 (66) Cyclophosphamide: 66 (31) Bortezomib: 55 (26) Doxorubicin: 43 (20) Lenalidomide: 41 (19) Melphalan: 31 (15) Thalidomide: 29 (14) Etoposide: 25 (12) Cisplatin: 22 (10) Corticosteroids alone: 17 (8) BCNU: 4 (2)	EFS: 5 (4, 6) From T0 for treated patients: Median OS, months (95% CI): 12 (10, 14) ≥PR, n (%): 50 (24) ≥MR, n (%): 73 (213) BR with a regimen without BORT, THAL or LEN, n/N (%): 26/107 (24)	manuscript[27]
Streetly 2014	DRMM defined as relapsed and/or refractory to BORT and LEN N=29 Treated, n=11	UK	-	Median OS following failure of BORT and LEN: 5.9 months PR or better at first treatment post-DRMM: <50%	Conference abstract[29]
Tarrant 2013	MM patients sequentially exposed to THAL, BORT and LEN N=55	UK	1st-line post T0, n (%): LEN-based, n (%): 3 (11.5) BORT-based, n (%): 3 (11.5) THAL-based, n (%): 13 (50.0) Clinical trial, n (%): 5 (19.2) Patients receiving further therapy, n: 2nd-line post T0: 12	From T0, median months (range): OS: 3.9 (0-33) PD as maximum response to 1st-line post T0, n (%): 13 (50) PR or better to 2nd-line post T0, n: 2 (4)	Conference abstract[28]

Study ID	Population	Setting	Interventions	Effectiveness outcomes	Data availability
			3rd-line post T0: 2		
Usmani 2016	MM patients previously treated with ≥3 regimens including a PI and an IMiD, or double-refractory to a PI and an IMiD N=662 IMS, n=500 Optum, n=162	US	IMS dataset: Patients who received at least 1 line of therapy after T0, %: BORT monotherapy: 16.8 LEN+THAL: 20.4 BORT plus LEN+THAL: 14.8 BORT plus cytotoxic agent: 7.2 Any cytotoxic agent: 9.0 Carfilzomib: 15.6 Steroid: 8.0 Pomalidomide: 6.0 LEN+THAL plus cytotoxic agent: 1.4 Bendamustine: 0.8 OPTUM dataset: Patients who received at least 1 line of therapy after T0, %: BORT monotherapy: 18.5 LEN+THAL: 19.1 BORT plus LEN+THAL: 9.9 BORT plus cytotoxic agent: 4.9 Any cytotoxic agent: 14.8 Carfilzomib: 12.3	IMS dataset: Median OS, months (95% CI): Total population: 7.9 (6.2, 9.1) Double refractory population: 7.5 (5.1, 8.9) ≥Double refractory population: 6.7 ≥3 LOT population: 11.5 Triple/quadruple refractory population: 5.1 (3.5, 8.7) OPTUM dataset: Median OS, months (95% CI): Total population: 7.9 (6.4, 10.3) Double refractory population: 8.5 (6.2, 11.3) ≥Double refractory population: 7.3 ≥3 LOT population: 10.3 Triple/quadruple refractory population: 3.1 (1.6, 13.4)	Full published manuscript [31]

Study ID	Population	Setting	Interventions	Effectiveness outcomes	Data availability
			Steroid: 13.6 Pomalidomide: 8.0 LEN/THAL plus cytotoxic agent: 0.6 Bendamustine: 0		
Wang 2014	Dual refractory/intolerant MM defined as refractory or intolerant to both BORT and LEN N=65 Treated, n=59	US	Number of treatments lines after T0, median (range): 2 (0-6) Alkylating agents: 55% Pomalidomide: 23% Carfilzomib: 17% Anthracyclines: 14% Stem-cell transplant: 14%	Median OS from T0, months (range): 10.2 (0.5-59.4)	Full published manuscript[30]

Key: BORT, bortezomib; DRMM, double relapsed refractory multiple myeloma; IMiD, immunomodulatory drug; LEN, lenalidomide; LEN+THAL, lenalidomide plus thalidomide; LOT, lines of treatment; MM, multiple myeloma; PI, proteasome inhibitor; THAL, thalidomide; THAL+DEX, thalidomide plus dexamethasone.
Notes: [a], T0 is the time at which patients met study eligibility.

Due to the scarcity of suitable RWE in the published literature, Janssen commissioned a retrospective chart review of participating International Myeloma Foundation (IMF) sites in order to obtain real-world outcomes that provide important insights into current care.[103, 104]

As anticipated, the number of treatment lines which included bendamustine were very small; only 96/963 treatment lines (10%) from the total IMF cohort. This reduced further to 49/518 treatment lines (9%) when only considering the European subset. Median PFS and OS in all patients receiving bendamustine-based therapy were 2.7 and 10.0 months, respectively.

Further methodological details and a quality assessment of this study are provided in Appendix 8.

While the IMF chart review provides a rich source of RWE for outcomes associated with clinical practice across Europe and the US, Janssen recognises that UK specific data is preferred for decision making in the UK. Therefore, Janssen also commissioned a retrospective review of UK-specific RWE from the Haematological Malignancy Research Network (HMRN). The HMRN is an ongoing population-based cohort that was established in the UK in 2004 to provide robust, generalisable data to inform clinical practice and contribute to research in haematological malignancies. The HMRN region comprises a total population of 3.8 million (covering the area formerly served by the Yorkshire and the Humber & Yorkshire Coast Cancer Networks). Janssen initiated a study with HMRN in which their data was used to characterise disease management for a population-based cohort of patients with rrMM who had received ≥3 prior lines of therapy including a PI and an IMiD, or who had disease double refractory to a PI and an IMiD. Hence, the HMRN cohort was closely aligned to the integrated IPD from the daratumumab trial populations. Patients were included in the analysis if they were newly diagnosed between 2008-2013 (with the view that the treatment pathway prior to 2008 would not be reflective of current practice), and thereafter reached the specific eligibility criteria. The number of patients receiving each treatment was detailed in the HMRN report along with response, OS and PFS outcomes by line of therapy.

Importantly, due to data governance, IPD were unobtainable from the HMRN group, and therefore the extent to which this could be used in ITC and subsequent cost-effectiveness modelling was limited (see Section 5.3).

Within the HMRN cohort, only two patients were treated with bendamustine-based therapy. While outcomes specific to these patients are not provided, prognosis of the the total cohort (n=69) was very poor, with a median PFS of 2.7 months and a median OS of 7.1 months. Further details from the HMRN report are provided in Appendix 9.

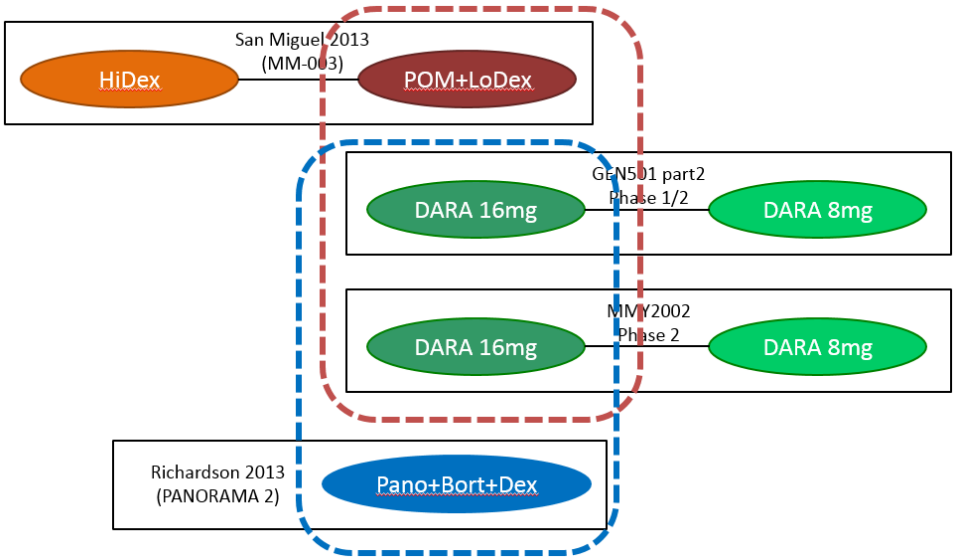
Janssen also considered commissioning a retrospective review of data from Public Health England (PHE), in the UK. However, following several discussions with PHE it was concluded that current data are not mature enough to provide robust estimates in rrMM patients. This is because data owned by PHE, particularly systemic anti-cancer treatment (SACT) data, were not formally and consistently collected prior to 2011 and as such it would be challenging to identify patients by line of therapy. This in turn would preclude an MAIC versus MMY2002/GEN501 as the number/type of prior therapies are key prognostic factors required for matching (see Section 4.10.3.2).

4.10.2 Indirect comparison

In the absence of head-to-head trials between daratumumab monotherapy, POM+DEX, PANO+BORT+DEX and bendamustine, an ITC is required to synthesise the relative differences in OS and PFS between treatments, while accounting for variation in trial populations.

As previously mentioned (see Section 4.10.1) the most robust sources of efficacy in the patient population of interest to this appraisal for POM+DEX and for PANO+BORT+DEX are the MM-003 trial and PANORAMA 2 trial, respectively. The network of evidence utilised for ITC of daratumumab monotherapy versus POM+DEX and versus PANO+BORT+DEX is presented in Figure 21.

Figure 21: Network of evidence



Key: Bort, bortezomib; DARA, daratumumab; Dex, dexamethasone; HiDex, high-dose dexamethasone; LoDex, low-dose dexamethasone; Pano, panobinostat; POM, pomalidomide.

Given the lack of a common comparator between the daratumumab trials (MMY2002/GEN501) and the MM-003 and PANORAMA 2 trials, a standard ITC could not be undertaken. Moreover, an unadjusted comparison would derive biased estimates of relative efficacy due to variation across trial populations; therefore, a more sophisticated approach to indirect comparison is required. A matching-adjusted indirect comparison (MAIC), based on the methodology published by Signorovitch et al.[105, 106], was used to compare IPD from the MMY2002 and GEN501 trials to aggregate data from published trials for comparator treatments. This method accounts for cross-trial differences in patients' baseline characteristics, which may bias an unadjusted indirect comparison. After matching, by excluding patients who have no overlap in characteristics and using an approach similar to propensity score weighting (a tool widely used in observational research)[105] for remaining patients, treatment outcomes are compared across balanced trial populations. Thus the following analyses were conducted:

- MAIC of daratumumab monotherapy versus POM+DEX by adjusting IPD from the integrated cohort of MMY2002 and GEN501 (Part 2) to match the

pomalidomide-treated population, as represented by the published aggregate KM data from MM-003.

- MAIC of daratumumab monotherapy versus PANO+BORT+DEX by adjusting IPD from the integrated cohort of MMY2002 and GEN501 (Part 2) to match the panobinostat-treated population, as represented by the published aggregate KM data from PANORAMA 2.

In addition to trial data, real-world data on the effectiveness of pomalidomide from the IMF chart review were used in sensitivity analyses.

Trial data for the use of bendamustine-based therapy in the patient population of interest to this appraisal are scarce and of low quality; no data identified were appropriate to inform a MAIC for use in an economic evaluation (see Section 4.10.1). In the absence of robust trial data, alternative sources were consulted to provide effectiveness estimates for the use of bendamustine (see Section 4.10.1.2). However, as a consequence of the restricted (only available on the CDF for patients for whom no other options exist) and off-label use of bendamustine, effectiveness evidence specific to the UK is scarce. The retrospective chart review of data from participating IMF sites was selected as the most robust source of real-world outcomes from which to derive estimates of relative effectiveness, and thus the following analysis was conducted:

- Multivariate regression analysis of daratumumab monotherapy versus bendamustine-based therapies comparing the IPD from the integrated cohort of MMY2002 and GEN501 (Part 2) and the real-world IMF cohort.

The methods used for each of the comparisons of interest to this appraisal are summarised in Table 33.

Table 33: Summary of ITC methods adopted

Treatment/Comparator	Source	Evidence level	Method
Daratumumab	Integrated MMY2002/GEN501	Integrated IPD	-
vs POM+DEX	MM-003	Aggregate data	MAIC
	IMF	IPD	Multivariate regression
vs PANO+ BORT+DEX	PANORAMA 2	Aggregate data	MAIC
vs bendamustine	IMF	IPD	Multivariate regression
Key: BORT/DEX, bortezomib plus dexamethasone; IPD, individual patient-level data; MAIC, matching-adjusted indirect comparison; POM+DEX, pomalidomide plus dexamethasone.			

4.10.3 Matching-adjusted indirect comparison

4.10.3.1 Rationale

There is precedent for the use of MAIC in HTA; the approach has been employed in a number of oncology HTAs submitted to and accepted by NICE, including those evaluating bortezomib for induction treatment of MM[49]; and dasatinib, high-dose imatinib and nilotinib for frontline treatment of chronic myeloid leukaemia.[107] It has also been used and accepted in other disease areas where there was a lack of head-to-head data.[108]

4.10.3.2 Methods

MAIC is a method developed by Signorovitch et al.[105, 106] to enable indirect comparison of competing treatments across trials. Standard ITCs, using aggregate data reported in the trial publications, not only depend on a common comparator, but also assume consistency in the relative treatment effect across trials; thus, differences in treatment effect modifiers between trials may result in biased ITCs. While IPD for all trials in a specific decision-problem are rarely attainable, IPD for at least one comparator may be available (in this case, daratumumab monotherapy). MAIC leverages and re-weights the IPD from one source, so that average baseline characteristics match aggregate baseline characteristics reported in a published comparator trial, with the aim of eliminating (or reducing) any bias due to differences

in the baseline characteristics of patients. Closely following the methodology developed by Signorovitch et al.[105, 106], a MAIC was conducted using the IPD from the integrated MMY2002/GEN501 cohort (see Section 4.9) and the most up to date aggregate data published from MM-003 and PANORAMA 2, as summarised in Table 34.

Table 34: Data sources used in the MAICs

Treatment	Data source	
	OS	PFS
Daratumumab	18-month integrated efficacy analysis[97] Analysis based on Dec 2015 data cut-off	18-month integrated efficacy analysis[97] Analysis based on Jan 2015 data cut-off for MMY2002; Dec 2015 data cut-off for GEN501 Part 2 IRC assessed; IMWG criteria
POM+DEX	Manufacturers submission to NICE[50] Analysis based on Sep 2013 data cut-off	Manufacturers submission to NICE[50] Analysis based on Mar 2013 data cut-off IRC assessed; IMWG criteria
PANO+ BORT+DEX	Manufacturers submission to G-BA[109] Analysis based on Dec 2012 data cut-off	Manufacturers submission to G-BA[109] Analysis based on Dec 2012 data cut-off mEBMT criteria

Key: BORT+DEX, bortezomib plus dexamethasone; G-BA, Federal Joint Committee; IMWG, International Myeloma Working Group; IRC, independent review committee; mEBMT, modified European Group for Blood and Marrow Transplant; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.

To match the patient populations of interest, the inclusion and exclusion criteria of both the daratumumab and comparator trials were compared and aligned, with the aim of excluding any patients in the daratumumab cohort who would not have been eligible for inclusion in the comparator trial from further consideration. In the comparison of daratumumab monotherapy and POM+DEX, although the majority of the patients in the daratumumab trials were previously exposed and even refractory to POM+DEX (55%), excluding POM+DEX experienced patients from the daratumumab dataset (to align with MM-003) resulted in a much smaller sample size. Therefore, POM+DEX experienced patients were included in the base-case

analysis, but a sensitivity analysis was conducted that excluded POM+DEX experienced patients in the comparison of daratumumab monotherapy and POM+DEX. In regards to the comparison against PANO+BORT+DEX, patients that were not refractory to bortezomib were excluded (as per the eligibility criteria for PANORAMA 2).

Following alignment of inclusion and exclusion criteria across trials, IPD from the remaining patients in the daratumumab cohort were then weighted such that the mean values for relevant baseline parameters reflected the means reported in the comparator studies. This was achieved through a propensity score model, in which patients from the daratumumab cohort were weighted by the inverse odds of being in the daratumumab trials, rather than MM-003 or PANORAMA 2, respectively. The weighting used the generalised method of moments to estimate propensity scores and has previously been described in detail by Signorovitch et al.[105] It should be noted that the algorithm does not directly match median values; rather, it calculates the weights such that the proportion of patients with a value below the median is matched to the proportion with a value above the median.

Ideally, matching should be based on clinically relevant risk factors that impact the relative treatment effects. Characteristics upon which to match were identified through literature review[110] and consultation with clinical experts in haematology. Those which were considered of most importance were refractory status (in regard to both treatment type and number of treatments), number of prior treatments (which also reflects time since diagnosis), Eastern Cooperative Oncology Group (ECOG) status, age, cytogenetics and International Staging System (ISS) staging. Cytogenetics and ISS staging data are not available for GEN501 patients and could not be incorporated into the matching, and age is considered comparable across trials (and less important if ECOG is included). Characteristics were clustered by 'type' (see Table 35) and the types of characteristics reported for MM-003 and PANORAMA 2 were broadly comparable, however, the level of granularity differed.

After matching, continuous, binary, or time-to-event outcomes could be compared across the balanced trial populations using weighted statistical tests that incorporated the same weights applied during the matching process.

Table 35: Baseline characteristics (in order of relevance to effect on survival) available for matching by comparator treatment

PANO+ BORT+DEX		POM+DEX	
Baseline variable	**n**	**Baseline variable**	**N**
Refractory to bortezomib (%)	1	Refractory to lenalidomide (%) Refractory to bortezomib (%) Refractory to both (%)	3
Median number of prior regimens >3 prior regimens (%)	2	Mean number of prior regimens >2 prior regimens (%)	2
-	0	Creatinine clearance <30 (%) Creatinine clearance 30-60 (%) Creatinine clearance ≥60 (%)	3
ECOG 0 (%) ECOG 1 (%) ECOG 2 (%)	3	ECOG 0 (%) ECOG 1 (%) ECOG 2 (%)	3
Median time since diagnosis (years)	1	Median time since diagnosis (years)	1
Myeloma subtype, IgA (%) Myeloma subtype, IgG (%) Myeloma subtype, IgM (%)	3	Myeloma subtype, IgA (%) Myeloma subtype, IgG (%) Myeloma subtype, IgM (%) Myeloma subtype, IgD (%) Light chain Kappa (%) Light chain lambda (%)	6
-	0	White (%) Asian (%) Black (%)	3
-	0	Bone lesions (%)	1
Prior ASCT (%)	1	Prior ASCT (%)	1
Median age (years) Age ≥65 years (%)	2	Mean age (years) Age >65 years (%) Age >75 years (%)	3
Total number of characteristics to match	**13**	Total number of characteristics to match	**26**
Key: ASCT, autologous stem-cell transplant; BORT+DEX, bortezomib plus dexamethasone; ECOG, Eastern Cooperative Oncology Group; Ig, immunoglobulin; POM+DEX, pomalidomide plus dexamethasone.			

The ability to adjust for multiple baseline factors depends on having IPD for a sufficient number of patients. In general, matching larger numbers of baseline characteristics and adjusting for greater cross-trial baseline differences will require more extreme weights and will reduce the effective sample size. Accordingly, to examine the differences in matched populations, clusters of independent baseline characteristics associated with survival outcomes were identified for POM+ DEX and PANO+BORT+DEX, as detailed in Table 36 and Table 37, respectively.

Table 36: Clusters of independent baseline characteristics in MM-003

Baseline Variable	**nrbl**	**Number of matched patients (Neff), POM+DEX**								
Refractory status	3	110	108	106	84	82	71	63	62	58	55
Number of prior therapies	5									
Creatinine clearance	8									
ECOG score	11									
Time since diagnosis	12									
Myeloma subtype	18									
Race	21									
Bone lesions	22									
ASCT	23									
Age	26									
Key: ASCT, autologous stem-cell transplant; ECOG, Eastern Cooperative Oncology Group; nrbl, cumulative number of baseline variables.										

Table 37: Clusters of independent baseline characteristics in PANORAMA 2

Baseline variable	**nrbl**	**Number of matched patients (Neff), PANO+BORT+DEX**					
Number of prior therapies	2	91	80	79	67	52	46
ECOG score	5						
Time since diagnosis	6						
Myeloma subtype	9						
ASCT	10						

Baseline variable	nrbl	Number of matched patients (Neff), PANO+BORT+DEX					
Age	12						
Key: ASCT, autologous stem-cell transplant; ECOG, Eastern Cooperative Oncology Group; nrbl, cumulative number of baseline variables.							

In order to balance appropriate adjustment with reduction in effective sample size, only the most important factors were adjusted for in the base-case analyses. As a consequence of the differing levels of granularity in the reported baseline characteristics across MM-003 and PANORAMA 2, the numbers of characteristics used to match MMY2002/GEN501 data with MM-003 and with PANORAMA 2 differed. While the types of characterisitics upon which data were matched are similar across the MAICs, it was not possible to adjust for refractory status (except to bortezomib) or creatinine clearance in the MAIC versus PANO+BORT+DEX.

Therefore, in the base-case, 11 characteristics were matched in the comparison of daratumumab monotherapy and POM+DEX (i.e., refractory status [to lenalidomide, to bortezomib, to both], prior treatments [mean number, received >2] creatinine clearance [<30, 30-60, ≥60], ECOG score [0, 1, 2]) and five characteristics were matched in the comparison of daratumumab monotherapy and PANO+BORT+DEX (i.e., prior treatments [median number, received >3] and ECOG score [0, 1, 2]).

To calculate HRs for PFS and OS in the reweighted daratumumab monotherapy arm versus POM+DEX and versus PANO+BORT+DEX, IPD were first simulated for POM+DEX and for PANO+BORT+DEX based on the published KM curves. DigitizeIt 2.0.5 was used to estimate the co-ordinates of the published KM curves for PFS and OS. Individual time-to-event data were generated on the basis of the algorithm proposed by Guyot et al.[111], which maps digitised KM curves to IPD using an iterative numerical method. The reweighted IPD from the daratumumab monotherapy arm were then combined with the simulated IPD for POM+DEX and for PANO+BORT+DEX and analysed together using Cox proportional hazard (PH) models. The impact of reweighting on the uncertainty was assessed using the robust sandwich estimator for standard errors and consequently the confidence intervals for

the HRs.[112] All MAIC analyses were conducted in SAS; coding is supplied in Appendix 9.

In addition to the base-case analysis, five sets of sensitivity analyses were undertaken:

- Exclusion of patients with previous exposure to POM+DEX in the comparison of daratumumab monotherapy and POM+DEX.
- Inclusion of patients who are not refractory to bortezomib in the comparison of daratumumab monotherapy and PANO+BORT+DEX.
- Utilising data solely from the MMY2002 trial, which had a greater number of attributes on which to match populations.
- Varying the number of baseline characteristics matched for the analysis against PANO+BORT+DEX and against POM+DEX.
- Utilising data pooled from MM-003 and STRATUS for POM+DEX.

4.10.3.3 Results

A total of 148 patients received daratumumab 16mg/kg monotherapy in the integrated MMY2002/GEN501 cohort. Individual baseline characteristics before and after adjusting daratumumab data to match the aggregate POM+DEX and PANO+BORT+DEX baseline characteristics are presented in Table 38 and Table 39, respectively.

Differences between patient characteristics at baseline are observed in treatment history, performance status and median time since diagnosis meaning that the populations of MM-003 and MMY2002/GEN501 are more closely aligned than the populations of MMY2002/GEN501 and PANORAMA 2. Specifically, patients treated with PANO+BORT+DEX were less heavily pre-treated than patients treated with daratumumab or POM+DEX and had more recently been diagnosed. Patients treated with PANO+BORT+DEX or POM+DEX also had better performance status than patients treated with daratumumab. These observations suggest the daratumumab trial populations had a worse prognosis at baseline.

Of note, the sample size used for matching with POM+DEX was reduced from 148 to 136 patients as 12 patients had missing values for one or more baseline characteristics used in the process and therefore could not be included. In the sensitivity analysis, patients who had previous exposure to POM+DEX were removed from the daratumumab cohort, reducing sample size further to 66 patients (Table 38).

In addition, 23 patients who were not refractory to bortezomib in the integrated MMY2002/GEN501 cohort were excluded at the first stage of the MAIC process, when aligning the inclusion criteria to daratumumab trials. Thus, the sample size for the MAIC against PANO+BORT+DEX is 125 (Table 39). In the sensitivity analyses, these patients are included in order to test the impact of matching a larger if less comparable sample.

Table 38: Baseline characteristics used in the MAIC, matching daratumumab monotherapy and POM+DEX trial populations, both before and after excluding the POM+DEX experienced patients

	POM+DEX MM-003	**Daratumumab monotherapy** MMY2002/GEN501	**Daratumumab monotherapy** MMY2002/GEN501; matched	**Daratumumab monotherapy** MMY2002/GEN501; excluding POM+DEX exposed	**Daratumumab monotherapy** MMY2002/GEN501; excluding POM+DEX exposed; matched
N	302	148	136	66	66
Refractory to lenalidomide (%) Refractory to bortezomib (%) Refractory to both (%)	95 79 75	84 84 77	95 79 75	76 77 67	95 79 75
Mean no. of prior regimens >2 prior regimens (%)	5.0 94	5.4 93	5.0 94	4.4 85	5.0 94
Creatinine clearance <30 (%) Creatinine clearance 30-60 (%) Creatinine clearance ≥60 (%)	1 31 68	3 36 60	1 31 68	5 30 65	1 31 68
ECOG 0 (%) ECOG 1 (%) ECOG 2 (%)	37 46 17	28 66 7	37 46 17	30 65 5	37 46 17
Median time since diagnosis (years)	6.2	6.3	6.2	6.0	6.2
Myeloma subtype, IgA (%) Myeloma subtype, IgG (%) Myeloma subtype, IgM (%)	26 62 0	18 49 1	26 62 0	15 47 0	26 62 0

	POM+DEX MM-003	**Daratumumab monotherapy** MMY2002/GEN501	**Daratumumab monotherapy** MMY2002/GEN501; matched	**Daratumumab monotherapy** MMY2002/GEN501; excluding POM+DEX exposed	**Daratumumab monotherapy** MMY2002/GEN501; excluding POM+DEX exposed; matched
Myeloma subtype, IgD (%) Light chain Kappa (%) Light chain lambda (%)	1 8 3	3 15 11	1 8 3	3 15 15	1 8 3
White (%) Asian (%) Black (%)	96 2 2	85 3 12	96 2 2	93 0 7	-
Bone lesions (%)	68	75	68	79	-
Prior ASCT (%)	71	78	71	70	-
Mean age (years) Age >65 years (%) Age >75 years (%)	63.6 45 8	63.2 41 9	63.6 45 8	62.9 41 12	-
Key: ASCT, autologous stem-cell transplantation; ECOG, Eastern Cooperative Oncology Group; Ig, immunoglobulin; MAIC, matching-adjusted indirect comparison; POM+DEX, pomalidomide plus dexamethasone.					

Table 39: Baseline characteristics used in the MAIC, matching daratumumab monotherapy and PANO+BORT+DEX trial populations after excluding non-bortezomib refractory patients

	PANO+BORT+DEX PANORAMA 2	**Daratumumab monotherapy** MMY2002/ GEN501	**Daratumumab monotherapy** MMY2002/GEN501; excluding non-BORT refractory	**Daratumumab monotherapy** MMY2002/GEN501; excluding non-BORT refractory; matched
N	55	148	125	125
Refractory to bortezomib (%)	100	84	100	100
Median number of prior regimens	4	5	5	4
>3 prior regimens (%)	67	76	78	67
ECOG 0 (%)	47	28	30	47
ECOG 1 (%)	46	66	63	46
ECOG 2 (%)	7	7	7	7
Median time since diagnosis (years)	4.57	5.12	4.93	4.62
Myeloma subtype, IgA (%)	22	18	19	22
Myeloma subtype, IgG (%)	64	49	49	64
Myeloma subtype, IgM (%)	2	1	1	2
Prior ASCT (%)	56	78	79	56
Median age (years)	61	64	64	61
Age ≥65 years (%)	38	46	46	38

Key: ASCT, autologous stem-cell transplantation; BORT, bortezomib; BORT+DEX, bortezomib plus dexamethasone; ECOG, Eastern Cooperative Oncology Group; Ig, immunoglobulin; MAIC, matching-adjusted indirect comparison.

Digitisation of the POM+DEX and PANO+BORT+DEX curves using estimates of reconstructed IPD resulted in an accurate imitation of the published KM curves, presented in Appendix 9.

Daratumumab monotherapy versus POM+DEX

A summary of the results for the comparison of daratumumab versus POM+DEX is provided in Table 40. The KM plots for base-case analyses (based on matching to the top 11 characteristics) are presented in Figure 22 and Figure 23. Log-log plots for these analyses are presented as part of the discussion around how MAIC results were applied in the economic model (see Section 5.3).

Daratumumab monotherapy demonstrated a statistically significantly reduced risk of death compared with POM+DEX, irrespective of number of characteristics matched. Matching to the top 11 characteristics resulted in a HR for death of 0.57 (95% CI: 0.41, 0.81); a clinically meaningful OS benefit to patients. This is an improved point estimate compared with naïve (unadjusted) comparison that gives a HR for death of 0.61 (95% CI: 0.46, 0.81) supporting the face validity of the matched comparison that accounts for the worse prognosis of the daratumumab trial population (Table 38).

Daratumumab monotherapy was also associated with a reduced risk of disease progression or death compared with POM+DEX. Although the difference did not reach statistical significance, matching to the top 11 characteristics resulted in a HR for death or disease progression of 0.81 (95% CI: 0.60, 1.09). Given that both daratumumab and pomalidomide are immunomodulatory agents, a relatively short period of PFS compared with OS is not unexpected. However, daratumumab's novel and multifactorial MoA provides further benefit leading to superior OS.

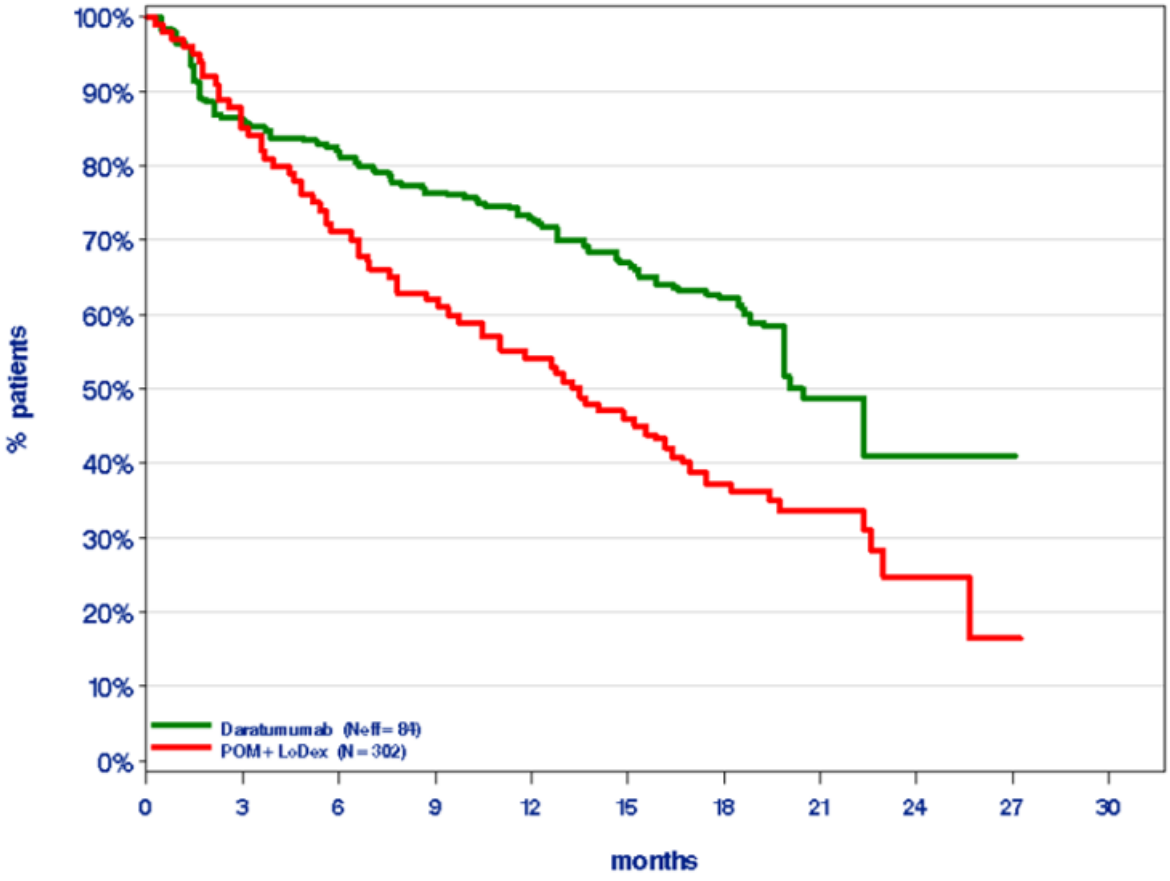
- Sensitivity analyses utilising data solely from the MMY2002 trial for daratumumab monotherapy, and sensitivity analyses utilising pooled MM-003, and STRATUS data for POM+DEX generally supported the base-case analyses.

Table 40: MAIC base-case results for OS and PFS before and after matching, daratumumab monotherapy versus POM+DEX

Number of matched characteristics	N	Neff	HR (95% CI)	
			OS	PFS
Unadjusted	148		0.61 (0.46, 0.81)	0.88 (0.69, 1.12)
26	136	55	0.56 (0.38, 0.83)	0.72 (0.50, 1.05)
23	136	58	0.57 (0.34, 0.84)	0.75 (0.52, 1.08)
22	136	62	0.59 (0.41, 0.86)	0.81 (0.58, 1.13)
21	137	63	0.59 (0.41, 0.86)	0.81 (0.59, 1.13)
18	148	71	0.55 (0.39, 0.78)	0.78 (0.57, 1.07)
12	148	82	0.55 (0.39, 0.77)	0.78 (0.58, 1.05)
11	**148**	**84**	**0.57 (0.41, 0.81)**	**0.81 (0.60, 1.09)**
8	148	106	0.56 (0.41, 0.76)	0.83 (0.63, 1.09)
5	148	108	0.60 (0.45, 0.81)	0.85 (0.64, 1.12)
3	148	110	0.61 (0.45, 0.83)	0.84 (0.64, 1.11)

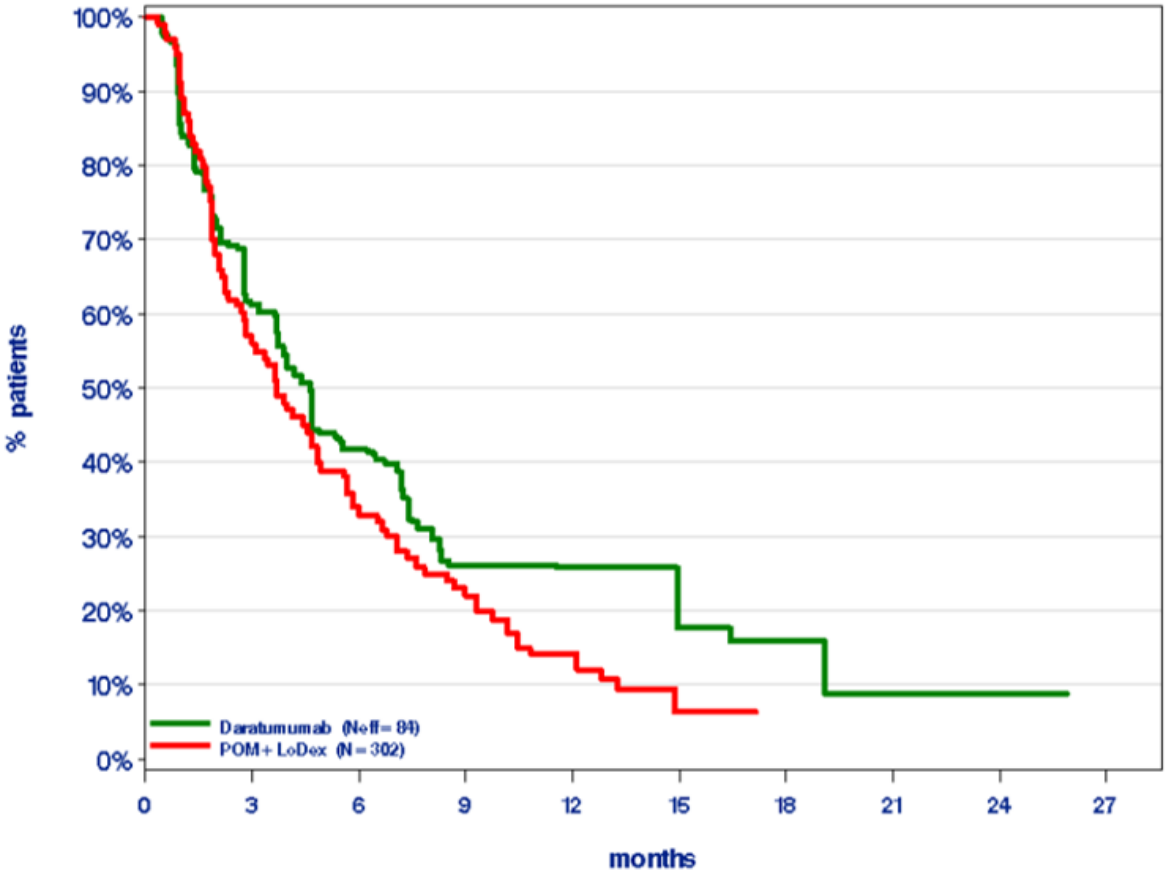
Key: BORT, bortezomib; BORT+DEX, bortezomib plus dexamethasone; CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; Neff, net effective sample size, OS, overall survival; PFS, progression-free survival.

Figure 22: Adjusted KM plot for OS, daratumumab monotherapy versus POM+DEX (base-case MAIC)



Key: MAIC, matching-adjusted indirect comparison; OS, overall survival; POM+DEX, pomalidomide plus dexamethasone; POM+LoDex, pomalidomide plus low-dose dexamethasone.

Figure 23: Adjusted KM plot for PFS, daratumumab monotherapy versus POM+DEX (base-case MAIC)



Key: MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone; POM+LoDex, pomalidomide plus low-dose dexamethasone.

When patients with previous exposure to POM+DEX were excluded from the comparison, daratumumab monotherapy demonstrated a greater reduction in the risk of death versus POM+DEX than estimated in the base-case, as summarised in Table 41.

As was observed in the base-case, this difference was statistically significant irrespective of the number of characteristics matched. Matching of the top 11 characteristics resulted in a HR for death of 0.40 (95% CI: 0.20, 0.80) and a HR for death or disease progression of 0.57 (95% CI: 0.31, 1.05). These results

demonstrate that daratumumab monotherapy is clinically effective regardless of previous exposure to POM+DEX, although the benefit is greater when used earlier.

Table 41: MAIC results for OS and PFS before and after matching, daratumumab monotherapy versus POM+DEX in POM+DEX-naïve patients

Number of matched characteristics	N	Neff	HR (95% CI)	
			OS	PFS
Unadjusted	66		0.38 (0.25, 0.60)	0.77 (0.55, 1.09)
18	66	19	0.33 (0.17, 0.66)	0.51 (0.24, 1.06)
12	66	29	0.40 (0.20, 0.80)	0.57 (0.31, 1.05)
11	**66**	**29**	**0.40 (0.20, 0.80)**	**0.57 (0.31, 1.05)**
8	66	44	0.40 (0.24, 0.67)	0.72 (0.47, 1.10)
5	66	46	0.46 (0.29, 0.74)	0.73 (0.49, 1.11)
3	66	51	0.47 (0.30, 0.74)	0.78 (0.53, 1.16)

Key: BORT, bortezomib; BORT+DEX, bortezomib plus dexamethasone; CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; Neff, net effective sample size, OS, overall survival; PFS, progression-free survival.

Daratumumab monotherapy versus PANO+BORT+DEX

A summary of the results for the comparison of daratumumab versus PANO+BORT+DEX is provided in Table 42. The KM plots for base-case analyses (based on matching to the top five characteristics for the bortezomib-refractory cohort) are presented in Figure 24 and Figure 25. Log-log plots for these analyses are presented in Appendix 11.

Daratumumab monotherapy demonstrated a reduced risk of death compared with PANO+BORT+DEX, irrespective of the number of characteristics matched. Although the difference did not reach statistical significance, this is most likely a result of the small number of patients for which clinical effectiveness data were available for PANO+BORT+DEX (n=55) in the fourth line setting. Matching to the top five characteristics in the base-case analysis resulted in a HR for death of 0.84 (95% CI: 0.52, 1.37) which represents a clinically meaningful OS benefit to patients. This is an improved point estimate compared with naïve (unadjusted) comparison of the crudely matched trial populations (based on trial eligibility) that gave a HR for death

of 0.93 (95% CI: 0.60, 1.44) hence supporting the face validity of the matched comparison that accounts for the worse prognosis of the daratumumab trial population (Table 39).

Daratumumab monotherapy did not demonstrate a statistically significant reduction in the risk of disease progression or death compared with PANO+BORT+DEX. This is not unexpected as the PFS benefit associated with immunomodulatory agents can be relatively short compared with the OS benefit (see Sections 4.9 and 4.13); such a phenomenon is not associated with pan-deacetylase inhibitor therapy (i.e., panobinostat). Similarly, the impact of response to daratumumab on PFS is not as far-reaching as the impact of response to daratumumab on OS, which extended from responding patients to patients whose disease stabilised following treatment with daratumumab (see Section 4.9). Differences between criteria used to assess disease progression across trials also warrant caution when interpreting PFS analysis.

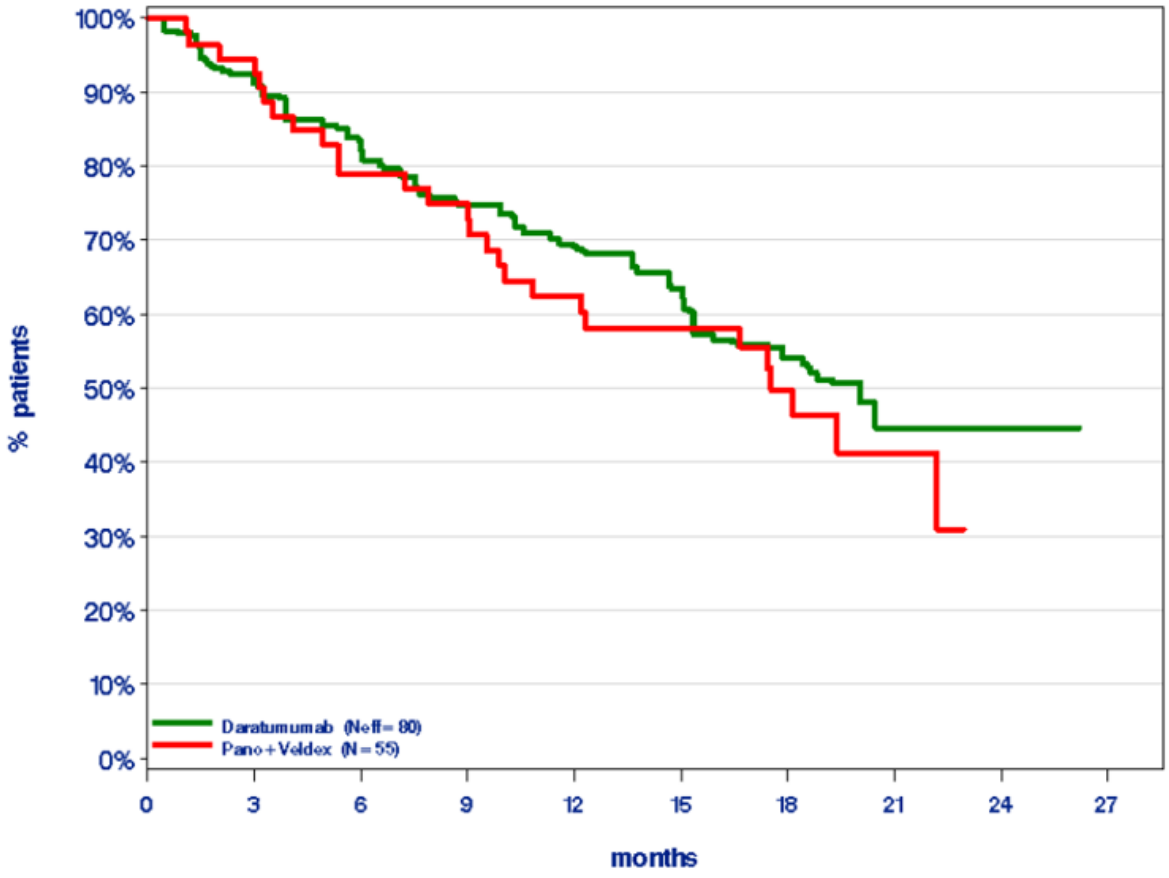
Sensitivity analyses utilising data solely from the MMY2002 trial, which had a greater number of attributes on which to match populations generally supported the base-case analyses, as summarised in Appendix 9.

Table 42: MAIC base-case results for OS and PFS before and after matching, daratumumab monotherapy versus PANO+BORT+DEX

Number of matched characteristics	N	Neff	HR (95% CI)	
			OS	PFS
Non-BORT refractory included Unadjusted	148	-	0.82 (0.53, 1.26)	1.05 (0.75, 1.47)
Non-BORT refractory excluded Unadjusted	125	-	0.93 (0.60, 1.44)	1.09 (0.77, 1.56)
12	125	46	0.76 (0.44, 1.30)	0.96 (0.60, 1.55)
10	125	52	0.81 (0.48, 1.37)	0.98 (0.63, 1.53)
9	125	67	0.84 (0.51, 1.38)	1.04 (0.69, 1.58)
6	125	79	0.83 (0.51, 1.35)	1.08 (0.73, 1.59)
5	**125**	**80**	**0.84 (0.52, 1.37)**	**1.09 (0.74, 1.61)**

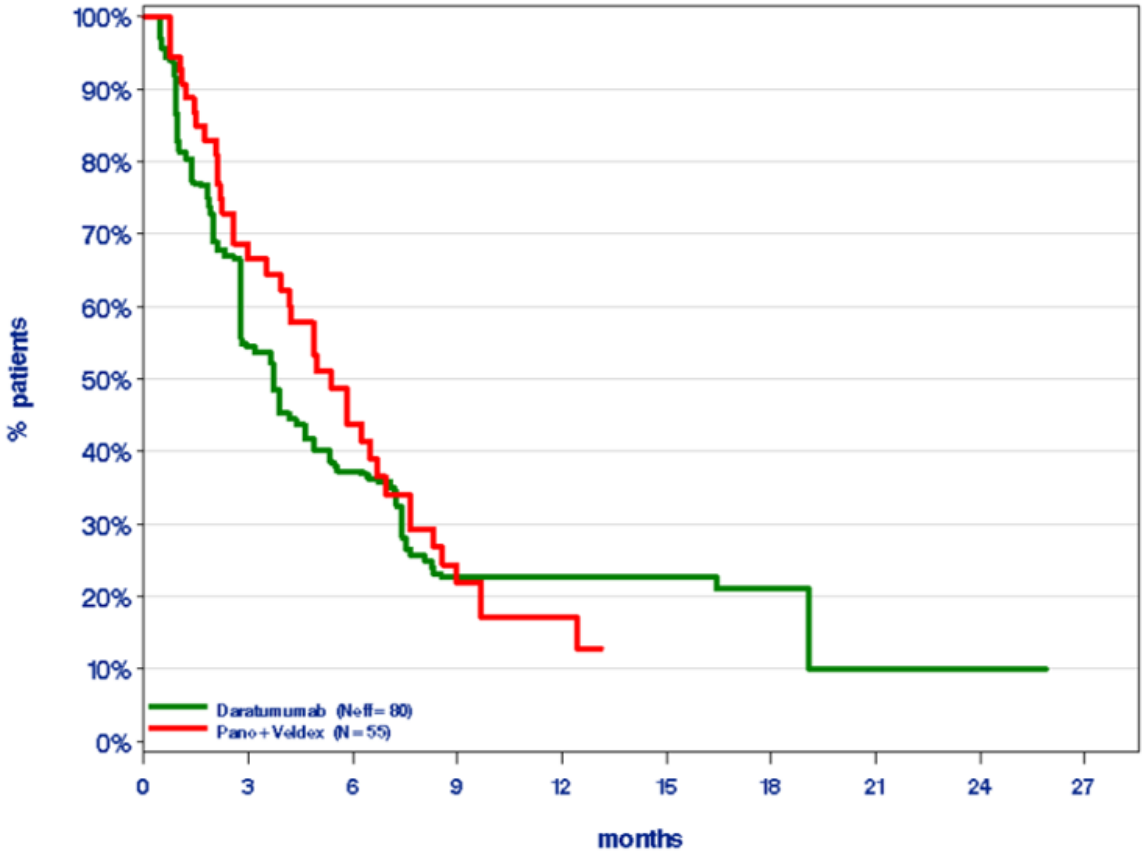
Number of matched characteristics	N	Neff	HR (95% CI)	
			OS	PFS
2	125	91	0.91 (0.57, 1.45)	1.19 (0.83, 1.72)
Key: BORT, bortezomib; BORT+DEX, bortezomib plus dexamethasone; CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; Neff, net effective sample size, OS, overall survival; PFS, progression-free survival.				

Figure 24: Adjusted KM plot for OS, daratumumab monotherapy versus PANO+ BORT+DEX (base-case MAIC)



Key: BORT+DEX, bortezomib plus dexamethasone; MAIC, matching-adjusted indirect comparison; OS, overall survival; Pano+Veldex, panobinostat in combination with bortezomib and dexamethasone.

Figure 25: Adjusted KM plot for PFS, daratumumab monotherapy versus PANO+ BORT+DEX (base-case MAIC)



Key: BORT+DEX, bortezomib plus dexamethasone; MAIC, matching-adjusted indirect comparison; Pano+Veldex, panobinostat in combination with bortezomib and dexamethasone; PFS, progression-free survival.

Strengths and limitations of MAIC

The MAIC presented utilises the most robust sources of efficacy in the patient population of interest to this appraisal, while accounting for cross-trial differences in patient characteristics. This is imperative across the evidence base for daratumumab monotherapy, POM+DEX and PANO+BORT+DEX as patients treated with daratumumab have a worse prognosis at baseline, which would negatively bias an unadjusted indirect comparison. As a consequence of the similarity of MMY2002/GEN501 and MM-003 trials, results of MAIC are robust. However,

differences in the patient populations of MMY2002/GEN501 and PANORAMA 2, along with limitations in the reporting of baseline characteristics (particularly refractory status) may bias MAIC results against daratumumab.

There are other sources of potential bias that are not accounted for within the MAIC that should be acknowledged. Unfortunately, it is not possible to adjust for differences in study design, that is, randomised versus non-randomised. However, as the aim of the MAIC is to adjust for prognostic factors to retrospectively minimise bias, whereas the aim of randomisation is to prospectively minimise bias, bias introduced by differences in study design is thought to be minimal. It is also not possible to adjust for differences in outcome definitions, as observed in assessments of disease progression that were based on the IMWG criteria in MMY2002/GEN501 and MM-003 were comparable with the modified European Blood and Marrow Transplant (EBMT) criteria in PANORAMA 2. Although definitions for progression are similar across these criteria, this difference alongside the different mechanisms of agents warrant some caution when interpreting PFS analysis of daratumumab monotherapy versus PANO+BORT+DEX.

A further difference is observed in the number of patients who went on to receive subsequent therapy. Of the 148 patients treated with daratumumab 16mg/kg monotherapy in the MMY2002/GEN501 cohort, 72% went on to receive subsequent therapy compared with 39% of the 302 patients randomised to POM+DEX in MM-003.[50] This is thought to be a result of the novel and unique MoA associated with daratumumab, alongside the favourable safety profile, that culminate in an improved health status of patients. This is discussed further in Section 4.13. Subsequent therapy data were not identified for the PANORAMA 2 trial.

Importantly, treatments available to patients following daratumumab monotherapy in MMY2002/GEN501 or POM+DEX in MM-003 were broadly similar, with the exception of carfilzomib and pomalidomide that were not available to patients in MM-003. Although these treatments are not routinely reimbursed in England, it was not possible to adjust the MAIC for subsequent treatment with pomalidomide or carfilzomib. Pomalidomide is however being appraised by NICE at present and may become available in the NHS in England forthwith. Due to the heterogeneity of the

treatment pathway it is not unreasonable to suggest treatment with POM+DEX following daratumumab monotherapy. Furthermore, when assessed as a single agent in heavily pre-treated rrMM patients (FOCUS trial), carfilzomib failed to show an overall survival benefit over low-dose dexamethasone with or without cyclophosphamide.[113] Therefore, the impact of subsequent treatment with carfilzomib on estimates of relative effectiveness is expected to be minimal.

4.10.4 Multivariate regression analysis

4.10.4.1 Rationale

Since IPD with a satisfactory degree of overlap were available from the daratumumab trials and the IMF cohort, it was possible to conduct a multivariate regression analysis to derive comparative effectiveness estimates for daratumumab monotherapy versus pomalidomide and versus bendamustine-based therapy. Utilising this method ensured that variation in patient populations between data sources were adjusted for to minimise risk of bias when making inferences on treatment effect. Multivariate regression analysis is a method recognised by NICE as a robust way in which observational data can be used to inform estimates of treatment effectiveness in technology appraisals.[114]

4.10.4.2 Methods

Analysis of OS was conducted on the ITT population from the IMF and the integrated daratumumab monotherapy cohort (MMY2002/GEN501) using KM curves and Cox proportional hazards regression. To account for variation in patient characteristics between the daratumumab trials and the IMF cohort due to lack of randomisation, a multivariate Cox regression model was used to estimate the HR of daratumumab monotherapy versus pomalidomide and versus bendamustine-based therapy. This enabled a measure of relative efficacy/effectiveness while adjusting for differences in baseline prognostic factors, which were included as covariates in the model. The list of characteristics included as covariates in the multivariate model was determined by clinical importance and availability across both data sources. Similar to parameters used for patient matching in the MAIC, these included age, gender, prior therapies (and relapse), number of prior therapies, and criteria used to assess ISS disease stage (albumin and β2 microglobulin).

Baseline values for the covariates for each patient were specific to treatment line. The clustering of observations at treatment line level within patients was controlled for using the robust sandwich estimate for the covariance matrix.[115, 116] Adjusted HRs and 95% CIs for the treatments in the total IMF cohort, reflecting 'available care', relative to daratumumab were calculated alongside the comparison of daratumumab versus pomalidomide and versus bendamustine. For PFS analysis, investigator assessed results from the integrated MMY2002/GEN501 cohort were used for daratumumab monotherapy to align with the investigator assessed nature of the real-world, IMF cohort. HRs and prognostic co-variates are presented graphically as forest plots, representing point estimates and 95% CIs. All statistical analyses were performed using the statistical software package SAS 9.2.

4.10.4.3 Results

All 148 patients receiving daratumumab 16mg/kg monotherapy in the integrated MMY2002/GEN501 cohort were included in the analysis, alongside 550 patients that made up the IMF cohort. A summary of patient characteristics from both cohorts are detailed in Table 43.

Table 43: Baseline demographics and disease characteristics for the IMF and daratumumab monotherapy cohorts

	Daratumumab 16mg/kg MMY2002/GEN501 (n=148)	Total IMF cohort (n=963)	IMF cohort pomalidomide (n=226)	IMF cohort bendamustine-based therapy (n=96)
Age, median	64	63	64	64
Male, %	53	59	62	64
Region, %				
EU	25	50	69	
US	60	39	22	
Other	15	11	9	
Albumin, %				
<3.5 g/dl	39	31	37	39
≥3.5g/dl	61	28	38	31
Unknown	0	41	26	30
β2 microglobulin, %				
<3.5 g/dl	25	14	18	10
3.5-5.5 g/dl	20	8	11	5
>5.5 g/dl	26	14	16	12
Unknown	28	63	54	73
Prior therapy, n (%)				
Pomalidomide	55	18	3	29
Carfilzomib	41	15	11	2
>3 prior lines of therapy, %	76	96	100	100

	Daratumumab 16mg/kg MMY2002/GEN501 (n=148)	Total IMF cohort (n=963)	IMF cohort pomalidomide (n=226)	IMF cohort bendamustine-based therapy (n=96)
Refractory status, %:				
Double	23	73	82	68
Triple	37	24	17	28
Quadruple	28	3	1	3

Key: Dara, daratumumab; ECOG, Eastern Cooperative Oncology Group; IMF, International Myeloma Foundation; IMiD, immunomodulatory agent; ISS, International Staging System; NR, not reported; PI, proteasome inhibitor.
Source: Usmani et al. 2016[71]; IMF population data.[117]

Numerous treatments were administered within the total IMF cohort, reflecting the lack of an established standard of care for this difficult to treat patient population. Alongside treatments more often used in the UK, such as POM+DEX (n=226), bendamustine-based therapy was represented (n=96) and provided an appropriate source to utilise in comparative analysis. Across the IMF cohort (n=963), treatment lines were included in the analysis for 'available care', details of which are provided in Table 44.

Table 44: Therapies used to treat patients with rrMM who had received ≥3 prior lines of therapy, were refractory to both a PI and an IMiD, and who had been exposed to an alkylating agent in clinical practice (IMF cohort)

Treatment	Proportion across all treatment lines administered (n=963)
Pomalidomide	24%
Bendamustine	10%
Carfilzomib	6%
Bortezomib plus chemotherapy[a]	5%
Cyclophosphamide	5%
Thalidomide plus chemotherapy[a]	4%
Bortezomib	4%
Lenalidomide plus chemotherapy[a]	3%
Dexamethasone	3%

Treatment	Proportion across all treatment lines administered (n=963)
Lenalidomide	3%
Bortezomib plus lenalidomide	3%
Carfilzomib plus lenalidomide	3%
Thalidomide	2%
Pomalidomide plus chemotherapy[a]	2%
Bortezomib plus thalidomide	2%
Carfilzomib plus chemotherapy[a]	2%
Bortezomib plus pomalidomide	1%

Key: IMF, International Myeloma Foundation; IMiD, immunomodulatory agent; PI, proteasome inhibitor; rrMM, relapsed refractory multiple myeloma.
Notes: [a], chemotherapy represented by a mix of treatments with cisplatin plus cyclophosphamide plus dexamethasone plus etoposide plus melphalan and dexamethasone plus melphalan.
Source: IMF population data.[117]

Pomalidomide

Daratumumab monotherapy was associated a statistically significant reduction in the risk of death versus pomalidomide; HR for death of 0.42 (95% CI: 0.30, 0.60); p<0.001. In the European cohort, 164 pomalidomide treatment regimens were received; the adjusted HR for death in this patient group for the comparison of daratumumab monotherapy versus pomalidomide was 0.41 [95% CI: 0.27-0.63]; p<0.001.

Daratumumab monotherapy was also associated with a reduction in the risk of disease progression or death versus POM+DEX; HR 0.83 (95% CI: 0.63, 1.10); p<0.191. In the European cohort, the adjusted HR for disease progression or death for the comparison of daratumumab monotherapy versus bendamustine-based therapy was 0.90 (95% CI: 0.64, 1.27); p=0.536.

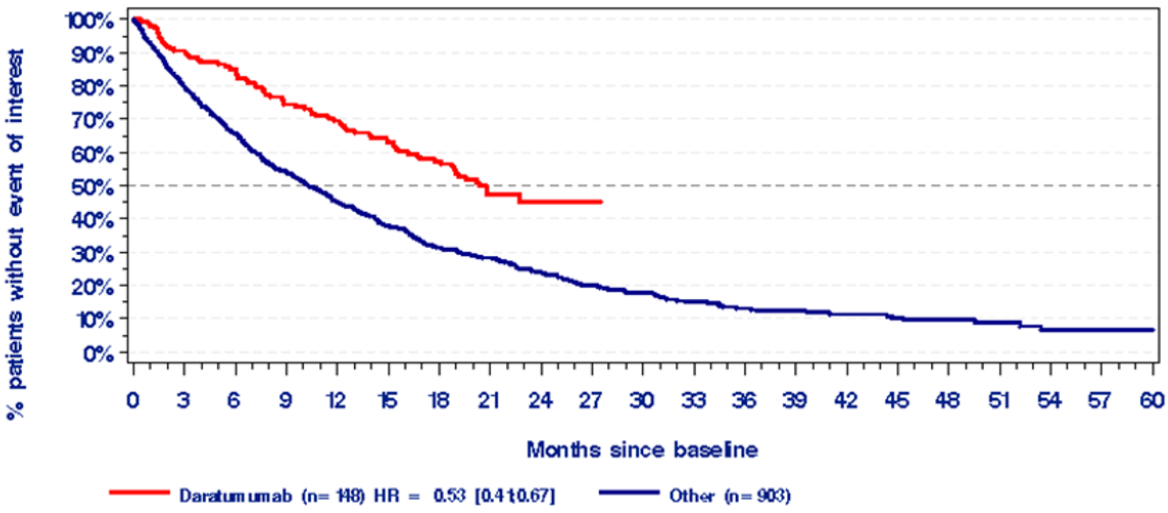
Bendamustine-based therapy

Daratumumab monotherapy was associated with a statistically significant reduction in the risk of death versus bendamustine-based therapy; HR for death of 0.43 (95% CI: 0.30, 0.63); p<0.001. In the European cohort, 49 bendamustine-based treatment regimens were received; the adjusted HR for death in this patient group for the comparison of daratumumab monotherapy versus bendamustine was 0.43 (95% CI: 0.26, 0.69); p<0.001.

Daratumumab monotherapy was also associated with a statistically significant reduction in the risk of disease progression or death versus bendamustine-based therapy; HR 0.59 (95% CI: 0.43, 0.81); p<0.001. In the European cohort, the adjusted HR for disease progression or death for the comparison of daratumumab monotherapy versus bendamustine-based therapy was 0.65 (95% CI: 0.43, 0.98); p=0.041.

Daratumumab monotherapy also demonstrated a significantly reduced risk of death compared with the total IMF cohort, reflective of 'available care', based on a naïve, unadjusted comparison of MMY2002/GEN501 data and the IMF data. This is illustrated in Figure 26 and derived a HR for death of 0.42 (95% CI: 0.31, 0.57).

Figure 26: Naïve, unadjusted KM plot for OS, daratumumab monotherapy versus available care (IMF cohort)



Key: IMF, International Myeloma Foundation; HR, hazard ratio; OS, overall survival.

The estimated impact of each characteristic included in the multivariate model on OS is provided in Appendix 9. Increased mortality was observed in older patients, males, patients with low albumin and high β2 microglobulin levels, patients with prior pomalidomide exposure and patients with a higher level of refractory status.

After adjustment for differences in baseline characteristics included in the multivariate model, daratumumab monotherapy demonstrated a greater reduction in the risk of death versus the total IMF cohort (i.e., 'available care') than estimated in the naïve comparison, with a HR for death of 0.42 (95% CI: 0.31, 0.57). When restricting the comparative analysis to European patients, results are very similar with an adjusted HR for death of 0.40 (95% CI: 0.28, 0.58).

Daratumumab monotherapy also demonstrated a reduced risk of disease progression or death compared with the total IMF cohort (i.e., 'available care') with an adjusted HR of 0.79 (95% CI: 0.62, 1.01); p<0.001. As was observed in multivariate regression analysis of OS, results were very similar when the IMF cohort was restricted to European patients; HR for disease progression or death of 0.79 (95% CI: 0.58, 1.08).

Strengths and limitations of Multivariate regression

The eligibility criteria for assessment of real world data from the IMF were closely aligned with the integrated data from MMY2002/GEN501. This resulted in broadly comparable datasets, reducing the risk of bias commonly seen between trial data and real-world evidence. However, imbalances in key prognostic variables remained for which adjustment was required.

Multivariate regression is recommended as an option by NICE DSU (TSD 17) when IPD from real world evidence is available and the assumption of 'no unobserved confounding' is reasonable. In addition to this, the DSU recommends that multivariate regression is appropriate when there is sufficient overlap in covariates between the treated and untreated groups.

As per the MAIC, covariates of prognostic significance were identified through literature review and consultation with clinical experts. Given that data were available for covariates considered of most importance, the assumption of 'no unobserved

confounding' is reasonable. However, as with any observational study, residual confounding due to unobserved risk factors cannot be excluded. For both the comparison with pomalidomide and with bendamustine-based therapy, there was a satisfactory degree of overlap in the covariates of interest. However, patient numbers were lower in the comparison with bendamustine and as such this comparison is associated with greater uncertainty.

The IMF cohort includes patients from many countries and it is possible that heterogeneity in the relative treatment effect exists. However, when compared with UK specific datasources (see Section 5.3.1); outcomes from the IMF were shown to be consistent.

In conclusion, the multivariate regression of IMF data is likely to provide robust estimates of comparative effectiveness, particularly with respect to pomalidomide, the key comparator of interest.

4.11 Non-randomised and non-controlled evidence

Relevant non-randomised and non-controlled evidence is presented in Sections 4.3 to 4.8 in the absence of relevant RCT evidence.

4.12 Adverse reactions

4.12.1 Identification and selection of relevant studies

Search strategy

To ensure all relevant safety evidence for daratumumab and potential comparator therapies was identified, systematic searches for additional AE data were also initiated in January 2016. It was anticipated that additional safety data would be minimal as assessments of safety were included in the review of clinical evidence (see Section 4.1); literature searches were therefore limited to key data sources of MEDLINE and EMBASE.

The search strategies used for AE searches are provided in Appendix 2.

AE data search terms were adapted from the British Medical Journal (BMJ) clinical evidence filter, chosen as a validated source as they cover all AE terms used in filters referred to by the ISSG search filter resource.

As was the case with the search strategies for clinical effectiveness data, prior to running, systematic search strategies for AE data were critiqued and refined by a team of information specialists at ScHARR.

Study selection

Methods for study selection were identical to those adopted for the review of clinical effectiveness data (see Section 4.1); including the eligibility criteria applied to the evidence base (Table 6).

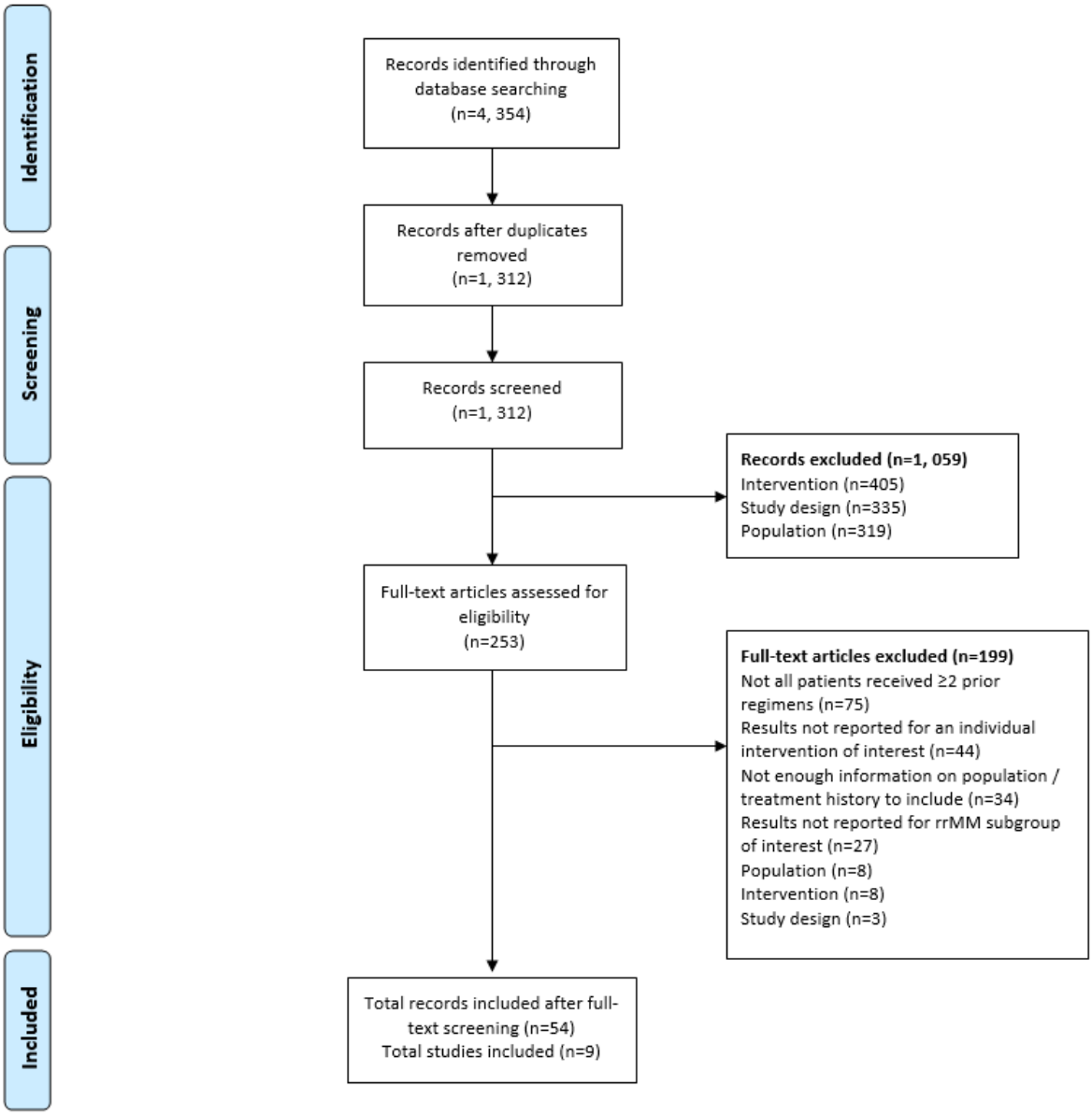
Original search results

Original systematic searches were conducted in January 2016.

A PRISMA flow diagram showing the number of studies included and excluded at each stage of the review is presented in Figure 27.

Electronic database searches identified 4,354 citations in total; after cross-referencing with citations identified in clinical effectiveness searches and removing duplicates, a total of 1,312 citations remained. During primary screening, a total of 1,059 were excluded as they were clearly not of relevance to the research question. A total of 253 citations were accessed in full for further evaluation. Of these citations, nine were primary publications of trials meeting the eligibility criteria of the review, one was a secondary publication providing an additional data source for one of these trials, and a further 44 were secondary publications providing additional data sources to studies identified in the review for clinical effectiveness evidence. Of note, nine of the 44 secondary publications were also identified through hand searching of conference proceedings as part of the clinical effectiveness searches, and one was a secondary data source for two trials (MM-002 and MM-003).

Figure 27: PRISMA flow diagram of the adverse event literature search process (January 2016)



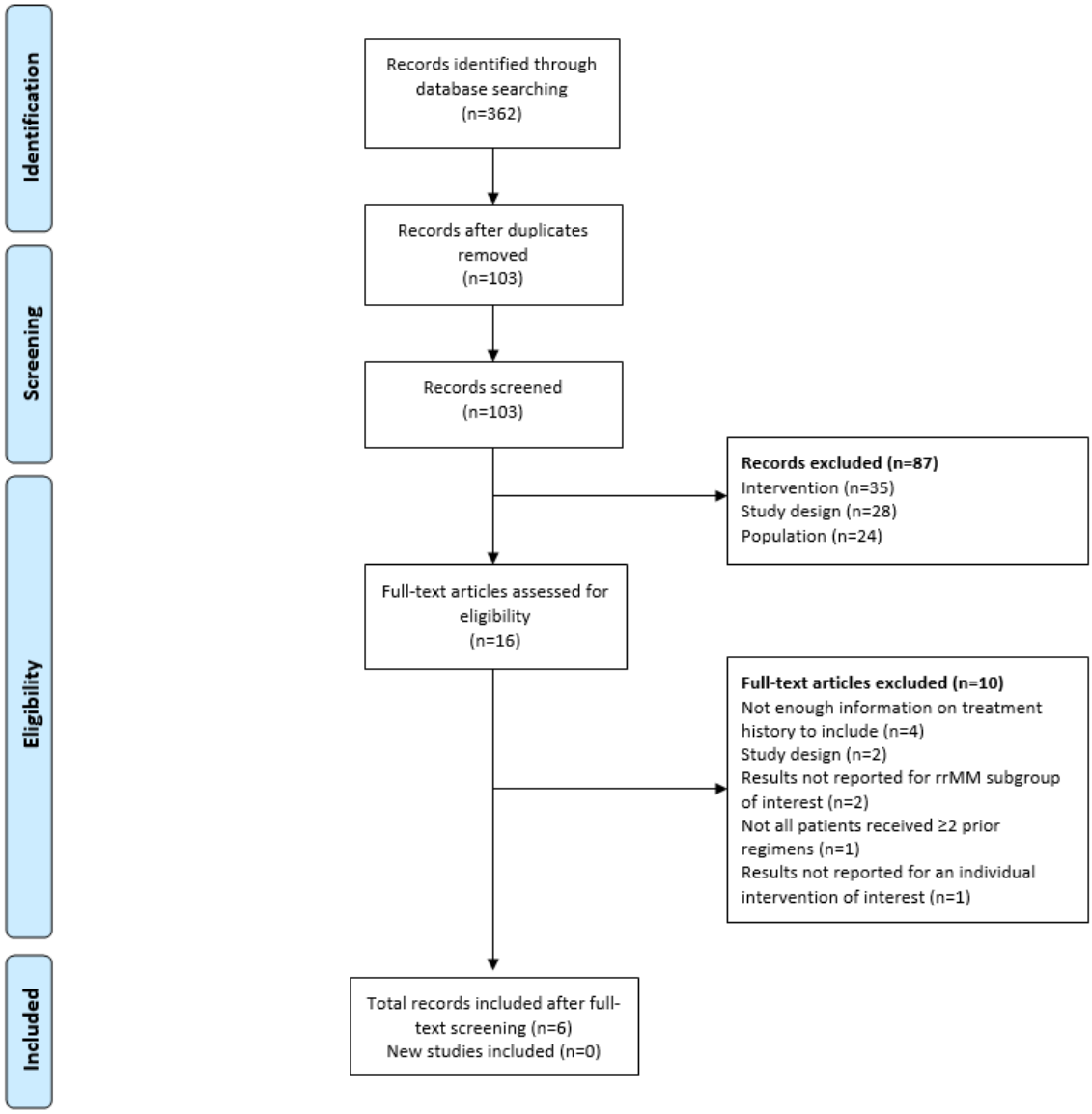
Key: AE, adverse events; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; rrMM, relapsed and refractory multiple myeloma.

Updated search results

A PRISMA flow diagram showing the number of studies included and excluded at each stage of the review update, initiated in July 2016, is presented in Figure 28.

Electronic database searches identified 362 citations in total; after cross-referencing with citations identified in clinical effectiveness searches and removing duplicates, a total of 103 citations remained. During primary screening, a total of 87 were excluded as they were clearly not of relevance to the research question. A total of 16 citations were accessed in full for further evaluation. Of these citations, 6 provided additional data sources for trials identified in the original review.

Figure 28: PRISMA flow diagram of the adverse event literature search process (July 2016)



Key: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Of the nine new studies identified through SLR, five studies investigated interventions including POM+DEX and bendamustine. Primary data sources for these studies are listed in Table 45. No secondary data sources were identified for these studies and no additional studies were identified for PANO+BORT+DEX.

Table 45: Primary data sources for trials identified through AE searches that investigated interventions of interest

Intervention	Trial name	Treatment arm(s)	Primary data source
Pomalidomide	UARK Pom	Pomalidomide 4mg + dexamethasone 12-40mg	Usmani et al. 2011[118]
Bendamustine	Zepeda 2014	Pomalidomide 2-4mg + dexamethasone 20 or 40mg	Zepeda et al. 2014[119]
	Krieger 2010	Bendamustine 70-90mg/m^2 + corticosteroids	Krieger et al. 2010[120]
	Gentilini 2014	Bendamustine 60mg/m^2 + dexamethasone 20mg	Gentilini et al. 2014[121]

No additional clinical evidence for daratumumab monotherapy was identified; therefore, safety data are only presented from MMY2002 and GEN501 Part 2. Evidence providing data for comparator therapies are only utilised in comparative safety analysis and are therefore presented in Section 4.12.1.

Safety data for daratumumab 16 mg/kg from the integrated analysis of MMY2002/GEN501 are presented in Section 4.9.4 and represent the most up-to-date safety data available. Safety data from the individual MMY2002 and GEN501 trials are detailed in Appendix 16.

4.12.2 Comparative safety

Common safety data reported for daratumumab 16mg/kg monotherapy, PANO+ BORT+DEX and POM+DEX, are provided in Table 46.

Compared to PANO+BORT+DEX and POM+DEX, daratumumab demonstrates markedly reduced rates of serious TEAEs, discontinuations due to TEAEs, dose modifications for AE management, and deaths due to TEAEs. Considering patients enrolled in the daratumumab trials were more heavily pre-treated, they could represent a higher risk patient group due to accumulation of toxicity than patients enrolled in comparator trials, particularly the PANORAMA 1 population in which most patients had only received one prior treatment. This qualitative synthesis may therefore provide a conservative estimate of comparative safety in patients of equal risk.

Importantly, in the daratumumab monotherapy trials, no discontinuations or deaths due to drug-related TEAEs were reported. In MM-003, 11 patients (4%) discontinued POM+DEX treatment due to drug-related TEAEs, and 11 patients (4%) died as a result of drug-related TEAEs. Discontinuations due to drug-related TEAEs are not reported for PANORAMA 2, but in PANORAMA 1, 90 patients (24%) had to discontinue PANO+BORT+DEX treatment due to a drug-related TEAE, and 11 patients (3%) died as a result of drug-related TEAEs. In terms of common TEAEs, POM+DEX was associated with markedly higher rates of Grade 3 or 4 TEAEs of neutropenia and infections and infestations compared with daratumumab, which could require hospitalisation. PANO+BORT+DEX treatment was associated with markedly higher rates of diarrhoea, neutropenia and thrombocytopenia compared to daratumumab. As part of the ongoing technology appraisal for POM+DEX, the NICE committee heard from a patient who described the debilitating effects of AEs they experienced on PANO+BORT+DEX, particularly the effects of diarrhoea that markedly impacts normal living.

Safety data were not captured for the IMF cohort. The tolerability of bendamustine has therefore been reviewed based on data reported in trials identified through systematic review (see Appendix 7). In the majority, common TEAEs appear to be related to events of myelosuppression (cytopenia, leukopenia, neutropenia, thrombocytopenia), that increase risk of infection that could require hospitalisation.[86-89, 92, 121, 122]

While being mindful of cross-trial naïve comparisons, this qualitative synthesis suggests daratumumab monotherapy offers a favourable safety profile compared with alternative treatments that could be used in the fourth-line setting in clinical practice. This favourable safety profile, alongside the unique mechanism of action associated with daratumumab, is thought to contribute to the observation that a higher proportion of patients treated with daratumumab monotherapy are able to receive subsequent therapy compared with patients treated with more toxic agents, due to a reduction in cumulative toxicity.

Table 46: Summary safety data and common TEAEs (≥10%) from the MM-003, PANORAMA and MMY2002/GEN501 studies

	POM+DEX	PANO+ BORT+DEX		Daratumumab
	MM-003 (n=300) n(%)	PANORAMA 1 (n=387) n(%)	PANORAMA 2 (n=55) n(%)	MMY2002/GEN501 (n=148) n(%)
Any serious TEAE	183 (61)	228 (60)	37 (67)	48 (32)
DC due to TEAE	21 (7)	138 (36)	10 (18)	6 (4)
Drug-related	11 (4)	90 (24)	NR	0
Dose modifications for AE management	NR	194 (51)	NR	48 (32)[a]
Dose interruption	201 (67)	NR	32 (58)	48 (32)[a]
Dose reduction	82 (27)	NR	35 (64)	0 (not permitted)
Death due to TEAE	144 (48)	NR	1 (2)	3 (2)
Drug-related	11 (4)	11 (3)	0	0

TEAEs reported in ≥10% patients, n (%)								
	Total	**Grade 3/4**	**Total (n=381)**	**Grade 3/4 (n=381)**	**Total**	**Grade 3/4**	**Total**	**Grade 3/4**
Abdominal pain	NR	NR	50 (13)	8 (2)	NR	NR	NR	NR
Abdominal distension	NR	NR	NR	NR	11 (20.0)	4 (7.3)	NR	NR
Anaemia	157 (52)	99 (33)	236 (62)	68.6 (18)	26 (47.3)	8 (14.5)	42 (28)	26 (18)
Asthenia	48 (16)	11 (3)	217 (57)[b]	91 (24)[b]	11 (20.0)	5 (9.1)	NR	NR
Back pain	59 (20)	15 (5)	50 (13)	3 (1)	NR	NR	40 (27)	4 (3)
Bone pain	52 (17)	21 (7)	NR	NR	NR	NR	15 (10)	1 (1)

	POM+DEX		PANO+ BORT+DEX				Daratumumab	
	MM-003 (n=300) n(%)		PANORAMA 1 (n=387) n(%)		PANORAMA 2 (n=55) n(%)		MMY2002/GEN501 (n=148) n(%)	
Bronchitis	30 (10)	3 (1)	NR	NR	NR	NR	NR	NR
Constipation	65 (22)	7 (2)	103 (27)	4 (1)	NR	NR	22 (15)	0
Cough	61 (20)	1 (<1)	80 (21)	3 (1)	NR	NR	38 (26)	0
Decreased appetite	36 (12)	2 (1)	107 (28)	11 (3)	NR	NR	23 (16)	1 (1)
Diarrhoea	66 (22)	3 (1)	259 (68)	95 (29)	37 (70.9)	11 (20)	27 (18)	1 (1)
Dizziness	37 (12)	4 (1)	72 (19)	11 (3)	NR	NR	NR	NR
Dyspepsia	NR	NR	46 (12)	3 (1)	NR	NR	NR	NR
Dyspnoea	59 (20)	15 (5)	57 (15)	8 (2)	NR	NR	25 (17)	1 (1)
Epistaxis	28 (9)	3 (<1)	NR	NR	NR	NR	NR	NR
Fatigue	103 (34)	16 (5)	NR	NR	38 (69.1)	11 (20)	62 (42)	3 (2)
Febrile neutropenia	29 (10)	28 (10)	NR	NR	NR	NR	NR	NR
Headache	NR	NR	53 (14)	3 (1)	NR	NR	NR	NR
Herpes zoster	NR	NR	18 (5)	4 (<1)	NR	NR	NR	NR
Hypercalcaemia	21 (7)	13 (4)	NR	NR	NR	NR	18 (12)	5 (3)
Hypokalaemia	NR	NR	NR	NR	12 (21.8)	4 (7.3)	NR	NR
Hypotension	NR	NR	53 (14)	11 (3)	11 (20.0)	5 (9.1)	NR	NR
Infections and infestations	203 (68)	91 (30)	NR	NR	NR	NR	87 (59)	15 (10)
Insomnia	31 (10)	3 (1)	72 (19)	0	NR	NR	NR	NR
Leukopenia	38 (13)	26 (9)	NR	NR	NR	NR	NR	NR

	POM+DEX		PANO+ BORT+DEX				Daratumumab	
	MM-003 (n=300) n(%)		PANORAMA 1 (n=387) n(%)		PANORAMA 2 (n=55) n(%)		MMY2002/GEN501 (n=148) n(%)	
Muscle spasms	47 (16)	1 (<1)	NR	NR	NR	NR	NR	NR
Muscle weakness	11 (4)	3 (1)	NR	NR	NR	NR	NR	NR
Nasopharyngitis	NR	NR	50 (13)	0	NR	NR	NR	NR
Nausea	45 (15)	2 (1)	137 (36)	23 (6)	33 (60)	3 (5.5)	44 (30)	0
Neutropenia	152 (51)	143 (48)	286 (75)	130 (34)	10 (18.2)	8 14.6)	31 (21)	15 (10)
Pain in extremity	NR	NR	40 (10)	3 (1)	NR	NR	NR	NR
Peripheral oedema	52 (17)	4 (1)	111 (29)	8 (2)	NR	NR	NR	NR
Peripheral neuropathy	NR	NR	232 (61)	69 (18)	NR	NR	NR	NR
Pneumonia	46 (15)	38 (13)	NR	NR	NR	NR	NR	NR
Pyrexia	80 (27)	9 (3)	99 (26)	3 (1)	NR	NR	29 (20)	1 (1)
Sepsis	NR	NR	NR	NR	16 (9)	16 (9)	NR	NR
Syncope	NR	NR	NR	NR	16 (9)	16 (9)	NR	NR
Thrombocytopenia	90 (30)	67 (22)	373 (98)	255 (67)	36 (65.5)	35 (63.6)	32 (22)	21 (14)
Upper abdominal pain	NR	NR	50 (12)	3 (1)	NR	NR	NR	NR

	POM+DEX		PANO+ BORT+DEX				Daratumumab	
	MM-003 (n=300) n(%)		PANORAMA 1 (n=387) n(%)		PANORAMA 2 (n=55) n(%)		MMY2002/GEN501 (n=148) n(%)	
Upper respiratory tract infection	48 (16)	5 (2)	69 (18)	8 (2)	NR	NR	32 (22)	1 (1)
Vomiting	NR	NR	99 (26)	27 (7)	NR	NR	NR	NR
Weight decrease	NR	NR	50 (12)	3 (1)	NR	NR	NR	NR

Key: DC, discontinuation; NR, not reported; POM+DEX, pomalidomide plus dexamethasone; TEAE, treatment-emergent adverse event.
Notes: [a], not assessed in the integrated analysis, data are a crude pooling from primary analysis of individual trials (9 January 2015 data cut-off); [b], asthenia or fatigue.
Source: San Miguel et al. 2013[57]; Lonial et al. 2016[70]; Lokhorst et al. 2014[123]; Novartis 2015[60]; San Miguel et al. 2014[59]; Richardson et al. 2013.[58]

4.13 Interpretation of clinical effectiveness and safety evidence

Patients with rrMM whose prior therapy included a PI and an IMiD agent, and who have demonstrated disease progression on the last therapy, have an overall poor prognosis, and people who have received three or more prior therapies have restricted treatment options in current clinical practice. There is a recognised unmet medical need for such patients that daratumumab has great potential to fulfil.

Principal findings from the clinical evidence base

The clinical benefits and safety profile associated with daratumumab 16mg/kg monotherapy have been demonstrated with clinical data from the pivotal Phase II trial, MMY2002, and earlier Phase I/II trial data from GEN501. Principal findings from this evidence base are summarised below:

Daratumumab monotherapy is associated with a deep and durable response

In an integrated analysis (n=148), daratumumab monotherapy demonstrated an ORR of 31% which is comparable to the level of response observed with multi-agent regimens in less refractory MM populations.[57, 58] Moreover, daratumumab monotherapy demonstrated a clinical benefit rate of 37% and a disease stabilisation rate of 83%; these are both important and clinically meaningful endpoints for these heavily pre-treated and highly relapsed end-of-life patients. The median TTR was 1.0 month and at the latest data cut-off the median DoR was 8.0 months with 22% of patients remaining progression-free at 2 years. When assessing paraprotein (M-protein) response, 40% and 19% of patients treated with daratumumab 16mg/kg achieved ≥50% and ≥90% reductions from baseline, respectively. Recent evidence has demonstrated that such depth of response is positively associated with improvement in OS in MM.[124] Benefit with respect to response was also consistent across patient subgroups. Such robust results are highly beneficial given the heterogeneity of rrMM.

Daratumumab monotherapy is associated with unprecedented survival benefit

Median OS in all patients treated with daratumumab monotherapy was 20.1 months (95% CI: 16.6, not reached). These survival data are unprecedented and, even within the limitations of an integrated analysis of early Phase data, are extraordinary

when considering the poor prognosis of the patients enrolled in MMY2002/GEN501. Survival benefit was not only observed in responding patients, in whom median OS is yet to be reached, but extended to patients with stabilisation of disease, in whom median OS was 18.5 months (95% CI: 15.1, 22.4). Furthermore, considering the poor prognosis of patients enrolled in MMY2002/GEN501, these survival data may be considered conservative estimates of the potential survival which may be achieved with daratumumab monotherapy in a less heavily pre-treated and less refractory population in clinical practice.

Given that daratumumab is an immunomodulatory agent, a relatively short PFS (4.0 months) relative to OS (20.1 months) is not unexpected. There is some precedence for such observations with immunomodulatory therapy in rrMM as discussed extensively during the original technology appraisal for POM+DEX.[50] It is also important to note that trial assessment methods for disease progression can be misleading as patients can have biochemical progression (as measured by IMWG criteria) without clinical progression. As assessment for disease progression is based on an increase from lowest response value rather than baseline, patients are often still in a better health state than they were prior to treatment despite biochemical progression.

In the absence of head-to-head data, indirect estimates of comparative efficacy suggest daratumumab monotherapy offers a superior survival benefit to alternative treatments that could be used for patients in the fourth-line setting in NHS England. Based on MAIC, daratumumab monotherapy demonstrated a reduced risk of death compared with PANO+BORT+DEX and a statistically significant reduction in the risk of death compared with POM+DEX that represents a clinically meaningful OS benefit to patients. Based on multivariate regression analysis, daratumumab monotherapy also demonstrated a statistically significant reduction in the risk of death compared with bendamustine-based therapy. However, bendamustine is not a relevant comparator.

Daratumumab monotherapy is well tolerated with a favourable safety profile

Across MMY2002 and GEN501, daratumumab monotherapy was shown to be well tolerated with clinically manageable side effects, as evidenced by the fact that no

patients died or discontinued treatment due to study drug toxicity. Common AEs were consistent with the underlying disease state of advanced MM, or the administration method of daratumumab. Blood and lymphatic disorders that did occur were effectively managed with platelet or RBC transfusions and prophylactic use of GCSF. IRRs were normally observed during the first infusion, and incidence markedly decreased during subsequent infusions. IRRs were safely managed with pre- and post-infusion medications, and all patients who experienced an IRR were able to continue full-dose therapy with supportive treatment.

While being mindful of cross-trial naïve comparisons, qualitative synthesis of safety data reported in the clinical evidence base presented suggests that daratumumab monotherapy offers a favourable safety profile compared to alternative treatments that could be used for patients in the fourth-line setting in the NHS in England. This is particularly important for these end-of-life patients who have been exposed to multiple prior regimens with cumulative toxicity.

Daratumumab monotherapy results in an improved health status that allows patients to receive further active treatment upon inevitable progression

While research is ongoing as to the exact biological processes involved, the novel and unique mechanism of action associated with daratumumab monotherapy appears to change the natural course of disease in rrMM. Coupled with its favourable safety profile, this disease reset culminates in an improved health status of patients, allowing them to receive further active treatment on inevitable progression (given rrMM is incurable) to re-stabilise their disease. In integrated analysis (n=148), 72% of patients treated with daratumumab monotherapy went on to receive subsequent therapy, and several patients responded to retreatment with therapies to which they were previously refractory.

Daratumumab has great potential to fulfil a recognised unmet medical need in rrMM

MM is a heterogeneous, re-occurring disease and in the absence of cure, all patients eventually relapse. With each successive relapse, the chance of durable response decreases with patients becoming refractory to treatment over time. Each relapse is therefore associated with a marked reduction in prognosis and health status. This

reduced health status is further exacerbated through cumulative toxicity of multiple regimens. Treatments that could be used for patients in the fourth-line setting in the NHS in England are associated with several limitations, including considerable toxicity concerns and limited clinical benefit, such that there are still a number of patients who are not receiving effective, tolerable therapy in clinical practice, optimal for their care. This is a clear unmet medical need, recently recognised by NICE as part of the ongoing technology appraisal for POM+DEX.

Daratumumab monotherapy offers a new treatment option with a novel mechanism of action, durable response, manageable safety profile and improved health staus that culminates in long-term survival benefit. As recognised by the COMP and the EMA during regulatory filing, daratumumab monotherapy therefore has great potential to fulfil this unmet medical need in rrMM.

Strengths and limitations of the clinical evidence base

Overall, the methods used to assess the clinical effectivess of daratumumab monotherapy in clinical practice utilised the limited available evidence appropriately.

Although the lack of an active-control arm in pivotal trials may be considered a limitation, it reflects of the lack of effective treatments for heavily pre-treated and highly refractory patients. In the absence of an obvious comparator at the time of trial design, it was considered infeasible and unethical to adopt an active control arm because any alternative would not be expected to benefit patients. Similarly, it was considered unethical to adopt placebo or best supportive care as a control arm given the poor prognosis of patients at this disease stage. In therapeutic areas where new and effective treatments are urgently needed, such as rrMM, a dose-controlled trial design such as MMY2002 is often considered appropriate. Indeed, the EMA approved daratumumab monotherapy under the accelerated assessment procedure in light of the unmet medical need and promising efficacy demonstrated in early Phase trials.

Clinical trials were conducted in line with GCP guidelines by qualified investigators using a single protocol to promote consistency across sites, and with measures taken to minimise bias. Data from MMY2002 and GEN501 have been presented from an integrated analysis that was conducted outside of the individual trial designs.

In both studies, disease evaluations were conducted using common assessment methods amenable to an integrated analysis. Data from all patients who received daratumumab 16mg/kg in MMY2002 and GEN501 Part 2 were included, and similar statistical parameters were applied. Although eligibility criteria differed slightly across individual trials, patient populations are considered generally comparable, and the integrated analysis population reflects the licence wording for daratumumab monotherapy. Pooling these data to provide a larger evidence base is therefore appropriate and the integrated analysis provides a clinically meaningful population size (n=148) when considering the orphan status of this indication. Upon consultation, clinical and health economic experts agreed with the approach of combining data from MMY2002 and GEN501, both for assessment of clinical effectiveness, and for assessment of cost effectiveness (see Section 5).

MMY2002 and GEN501 provide data directly relevant to clinical practice. Disease and safety evaluation methods are consistent with other studies of rrMM therapy, and outcome assessments were conducted in accordance with trial-validated methodologies. Disease evaluations were conducted every 28 days in order to adequately detect on-treatment effect with survival follow-up conducted every 12 weeks, in line with standard trial practice. Both studies are thought to adequately reflect routine clinical practice in England with respect to population, treatment administration and outcomes assessed, although patients represent a heavily pre-treated and highly refractory cohort within the licensed population and some treatments received are yet to be available in the NHS in England. Any bias caused by this would be against daratumumab monotherapy; that is, the severity of the trial populations mean the response and survival results may be considered conservative estimates of the clinical benefit which may be achieved in a less heavily pre-treated and less refractory population in clinical practice. Moreover, the fact that patients presented with progressive disease despite receiving newer agents (such as pomalidomide and carfilzomib) further highlights the need for novel treatment options with differentiating MoA’s compared to those used earlier in the treatment pathway. In the integrated analysis, almost half of the patient population were European (64/148 patients), and haematologists practicing in England have confirmed the generalisability of daratumumab monotherapy study results to patients in routine

clinical practice. Clinical experts also specifically noted that because trial patients were highly relapsed and refractory, outcomes are likely to be poorer than would be observed in clinical practice.[41]

In the absence of head-to-head data, ITC methods have been adopted to provide comparative efficacy estimates for daratumumab monotherapy versus alternative treatments that could be used at fourth-line in the NHS in England. While POM+DEX is currently under NICE appraisal, it has been widely used on the CDF in previous years, thus making it the most appropriate comparator for consideration There are numerous limitations with both the PANO+BORT+DEX and bendamustine evidence base, however they have been included as comparators in the submission to satisfy the NICE scope.

The ITC approaches adopted are a transparent attempt to estimate relative effectiveness using the most appropriate methods and evidence available. As a consequence of the similarity of MMY2002/GEN501 and MM-003 trials, results of MAIC are robust and further supported by multivariate regression analyses. Differences in the patient populations of MMY2002/GEN501 and PANORAMA 2, along with limitations in the reporting of baseline characteristics (particularly refractory status) may bias MAIC results against daratumumab. For multivariate regression analyses, eligibility criteria of the IMF data were aligned with the daratumumab trials. This, in combination with the availability and overlap of key prognostic variables across these datasets, is likely to result in robust assessments of relative treatment effect. Moreover, a statistically significant OS benefit of daratumumab monotherapy versus POM+DEX was identified in MAIC and through multivariate regression and as such the superior efficacy of daratumumab may be considered established.

End-of-life criteria

End-of-life criteria considerations are summarised in Table 47, and support the conclusion that daratumumab monotherapy offers a life-extending treatment option in the end-of-life setting.

Patients with rrMM whose prior therapy included a PI and an IMiD agent, and who have demonstrated disease progression on the last therapy, have a poor prognosis.

As observed in RWE, life expectancy of these patients does not exceed 12 months.[26-31] For patients who are refractory to both a PI and an IMiD, life expectancy is further reduced to 8-9 months, and for patients who are refractory to three or four of the common PIs and IMiDs, this decreases to only 3-5 months.[31]

Although PANO+BORT+DEX demonstrated a longer median OS (17.5 months) in PANORAMA 2, this still did not exceed 24 months. However, with restricted uptake reported due to considerable toxicity concerns, PANO+BORT+DEX is yet to demonstrate a significant impact on the life expectancy of patients with rrMM in clinical practice. Furthermore, it is important to note that the patient population of the PANORAMA 2 trial (from which these data are taken) were not as heavily pre-treated as the population intended for daratumumab monotherapy.

In the heavily pre-treated and highly refractory patient population of MMY2002 and GEN501, daratumumab monotherapy was associated with a median OS of 20.1 months. These survival data are unprecedented, and especially impressive considering the poor prognosis of patients at baseline. As cross-trial, naïve comparisons are inappropriate for assessment of relative effectiveness, estimates of life years gained from the model are used to compare the survival benefits expected if POM+DEX, PANO+BORT+DEX, or bendamustine-based therapy were given to the patient population of MMY2002/GEN501. Based on the economic model daratumumab is expected to provide 2.54 life years, exceeding life years expected for POM+DEX, PANO+BORT+DEX and bendamustine-based therapy by 12.8, 4.7 and 17.3 months, respectively.

Furthermore, in the original technology appraisal for POM+DEX [TA338] the committee could not definitively judge the incremental effectiveness of POM+DEX compared with current treatment because of limitations in the evidence base. Nevertheless, it was decided that POM+DEX indeed extends life for at least three months on average and the end-of-life criteria is applicable. Given that daratumumab monotherapy demonstrates a significant survival benefit compared with POM+DEX, end-of-life criteria should extend to daratumumab. As part of the ongoing technology appraisal for POM+DEX (ID985), there was still strong support from the clinical experts that effective treatment options in the fourth-line setting of rrMM should be considered as end-of-life treatments.

Table 47: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median life expectancy: less than 24 months, and is in fact closer to 12 months. Source: population studies[26-31]; Phase II/III clinical trials[57, 58, 71]
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Mean OS estimates: Daratumumab monotherapy: 2.54 life years (30.4 months) PANO+BORT+DEX: 2.14 life years (25.7 months) POM+DEX: 1.46 life years (17.5 months) Bendamustine: 1.10 life years (13.2 months) Extension to life estimate: ≥3 months Source: MMY2002/GEN501[71], PANORAMA 2[58], MM-003[125], IMF cohort[117, 126]

4.14 Ongoing studies

In addition to the MMY2002 and GEN501 clinical trials, an Early Access Programme (EAP) was initiated in the US and Europe (MMY3010; NCT02477891).

This programme was designed to provide early access to daratumumab and allow collection of additional safety and HRQL data for patients with MM who have received at least three prior lines of therapy including a PI and an IMiD or whose disease is double refractory to both a PI and an IMiD (while the medication was not commercially available or available through another protocol). Preliminary data for patient reported outcomes from this EAP are available and utilised in the cost-effectiveness modelling, as discussed in Section 5.4.

No further trials investigating daratumumab 16mg/kg monotherapy for the treatment of adult patients with rrMM are planned.

5 Cost effectiveness

5.1 Published cost-effectiveness studies

An SLR was performed in January 2016 to identify previous economic evaluations of daratumumab in MM. The search strategy and further details are fully documented in Appendix 10.

Each reference was first screened for inclusion based on title and abstract. All publications that met entry criteria for the review were obtained as full articles and reassessed against the review criteria. To be included, references had to meet the inclusion criteria (and none of the exclusion criteria) detailed in Table 48. Based on these criteria, the systematic review did not identify any suitable existing analyses.

Table 48: Inclusion criteria for cost-effectiveness studies

	Inclusion	**Exclusion**
Study population	Adult patients with MM	No adult MM patients
Intervention	Daratumumab	None
Outcome	Studies will include a comparison of costs between the intervention and comparator arms. Results should also include either incremental QALYs (or another measure of health outcome/clinical effectiveness), or be structured with a cost-minimisation argument	Cost-only outcomes (without a cost-minimisation argument, e.g. burden of illness studies)
Study types	Economic evaluations (including cost-consequence, cost-minimisations, cost-effectiveness, cost-utility and cost-benefit evaluations)	None
Publication Types	None	Letters and comment articles
Language	Studies reported in English	Studies not reported in English
Other	Studies must present sufficient detail of the methodology used and provide extractable results	Publications that fail to present sufficient methodological detail or extractable results
Key: MM, multiple myeloma; QALY, quality-adjusted life year; rrMM, relapsed/refractory multiple myeloma.		

5.2 De novo analysis

5.2.1 Patient population

Daratumumab monotherapy is indicated for the treatment of adult patients with rrMM, whose prior therapy included a PI and an IMiD agent, and who have demonstrated disease progression on the last therapy. The heterogeneity of the disease makes defining one sequential treatment pathway difficult, however, daratumumab monotherapy is anticipated to be used as a fourth-line treatment.

As discussed in Section 3.3, patients at this line of therapy have very few options for further treatment and those that are available in the NHS in England comprise POM+DEX, PANO+BORT+DEX, or off-label use of bendamustine (available for "relapsed disease where all other treatments contraindicated or inappropriate" via the CDF).

Daratumumab's orphan designation conveys the seriousness and low prevalence of rrMM which is amplified when considering patients at fourth-line. The tolerability, safety and efficacy profile of daratumumab provides substantial gains in key clinical and patient-relevant outcomes for the small number of patients who have exhausted conventional regimens. The economic analysis therefore compares daratumumab monotherapy with POM+DEX, PANO+BORT+DEX, and off-label bendamustine in these patients, estimating the incremental cost and benefit of introducing daratumumab into the patient pathway in England.

5.2.2 Model structure

A *de novo* model was developed in Microsoft Excel® using a semi-Markov partitioned survival structure. This type of model has precedence in previous NICE myeloma appraisals.[48, 51]

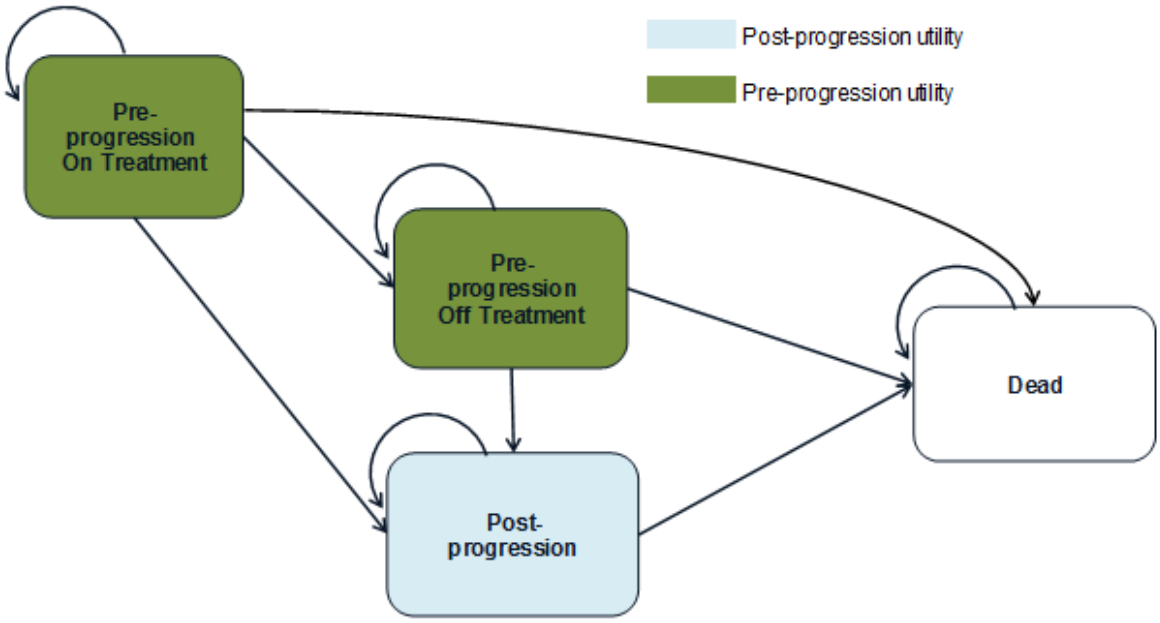
The model structure is depicted in Figure 29 and comprises four health states; two pre-progressive disease states (defined by treatment status), one post-progressive disease state, and a state for death.

In clinical practice, and reflected in the key clinical trials for daratumumab and its comparators, patients may withdraw from active treatment before disease

progression; defining separate pre-progression health states by treatment status allows treatment costs to be captured accurately in the economic model.

The proportion of patients in each health state over time is calculated using PFS, OS and time to treatment discontinuation (TTD) data from key clinical trials, as described in Section 5.3. Patients cannot transition back to the pre-progression state following progression; instead they remain in the post-progression health state until death. Patients in the post-progression health state may receive subsequent treatments.

Figure 29: Model structure



The health states are designed to capture key elements of the disease pathway that are relevant from a clinical, cost and patient perspective, including treatment status, disease progression status and survival. As patients receive active therapy, they incur treatment costs specific to drug, administration, resource use and AEs. Following treatment discontinuation, patients incur management costs that differ by pre-and post-progressive disease. Costs associated with subsequent treatment are also captured in the “post-progression” health state. As described in Section 5.4, evidence suggests that patients suffer a decline in health-related quality of life (HRQL) upon disease progression and a temporary decrement in HRQL in the event of certain AEs; the course of HRQL in rrMM patients is captured in the design of the

economic model through health state utilities and dis-utilities associated with AEs. Finally, upon entry to the death health state, patients incur a terminal care cost.

Model settings

Additional features key to the economic model are described and justified in Table 49. The time horizon and cycle length selected were guided by the clinical data, while other model settings including the perspective of the analysis and assumptions used to discount future model outcomes are based on the NICE Guidelines.[127]

Table 49: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	15 years	Fewer than 1% of cohort alive after 15 years in all arms in the base-case
Cycle length	1 week	Sufficiently short to accurately capture clinical outcomes from effectiveness trials and fit with dosing schedules
Half-cycle correction	Not applied	The cycle length is short (1 week)
Were health effects measured in QALYs; if not, what was used?	QALYs	NICE reference case[127]
Discount of 3.5% for utilities and costs	3.5%	NICE reference case[127]
Perspective (NHS/PSS)	NHS/PSS	NICE reference case[127]
Key: NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years.		

5.2.3 Intervention technology and comparators

The intervention, daratumumab monotherapy, is implemented within the model as per its marketing authorisation, and is given according to the recommended dosing regimen.[10] The comparative treatments, POM+DEX and PANO+BORT+DEX, are also implemented as per their respective marketing authorisations and are given according to their licensed dosing regimens.[128] [129] Since the third comparator of interest, bendamustine, is not licensed for use in patients with rrMM, it is implemented in the model according to the standard dosing regimen used in clinical practice, as advised by Professor Kwee Yong. [130, 131]

5.3 Clinical parameters and variables

To inform the economic analysis, OS, PFS and TTD KM curves were generated for daratumumab from integrated patient-level data from MMY2002 and GEN501, as described in 4.9. To facilitate extrapolation over the time horizon of the model, a variety of parametric curves were fitted to these data, in accordance with guidance from NICE Technical Support Document (TSD) 14.[132] For each clinical outcome used within the economic model, five standard parametric survival functions were estimated (exponential, Weibull, log-logistic, lognormal, generalised gamma), and the fit of each parametric model was compared with the observed data. Statistical fit was assessed using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Alongside visual inspection, these measures indicate the goodness of fit of each parametric survival function to the KM data observed during the trial period. Given the importance of long-term predictions, the clinical plausibility of each extrapolation was assessed by a consultant haematologist practicing within the NHS in England, and the parametric function to be used in the base-case was selected accordingly.[133]

In the absence of head-to-head trials, an ITC is required to synthesise the relative differences in OS and PFS between treatments, while accounting for variation in trial populations. Given the lack of a common comparator between the daratumumab trials (MMY2002/GEN501) and the POM+DEX (MM-003)[57] and PANO+BORT+DEX (PANORAMA2)[58] trials, a standard ITC could not be undertaken, and instead, an MAIC was required. The methods for the MAIC are described in 4.10. Weighted HRs derived from the MAIC were applied to the parametric curve for daratumumab monotherapy to generate the comparative parametric curves for POM+DEX and for PANO+BORT+DEX. TTD for daratumumab and POM+DEX was calculated by fitting parametric curves to the TTD KM curves from the relevant clinical trials; integrated MMY2002/GEN501 and MM-003[57] respectively. Reflective of the lower evidence base, TTD data are not available from PANORAMA2[58] for PANO+BORT+DEX or available for bendamustine and so it is assumed that patients are treated until progression or until the maximum number of treatment cycles is reached.

As detailed in 4.10, trial data for the use of bendamustine-based therapy in the patient population of interest to this appraisal are scarce and of low quality. To

satisfy the request to include bendamustine as a comparator in the absence of robust trial data, real-world data sources were consulted to provide efficacy estimates for bendamustine. Thus, as also reported in 4.10, the retrospective IMF chart review was used to derive estimates of relative effectiveness of daratumumab versus bendamustine, although bendamustine represented less than 10% of the total IMF cohort.[117] The availability of IPD from both the integrated daratumumab trials and the IMF chart review facilitated the use of multivariate regression analysis.

Of note, alternative study-level RWE from Gooding et al.[26] and the HMRN[134], were also considered as possible sources of efficacy for bendamustine-based therapy. However, no survival data specific to bendamustine were available from Gooding et al and only two patients in HMRN received treatment with bendamustine. These data are used to assess the generalisability of the IMF data by providing UK specific data sources with which to compare (see Section 5.3.1.5).

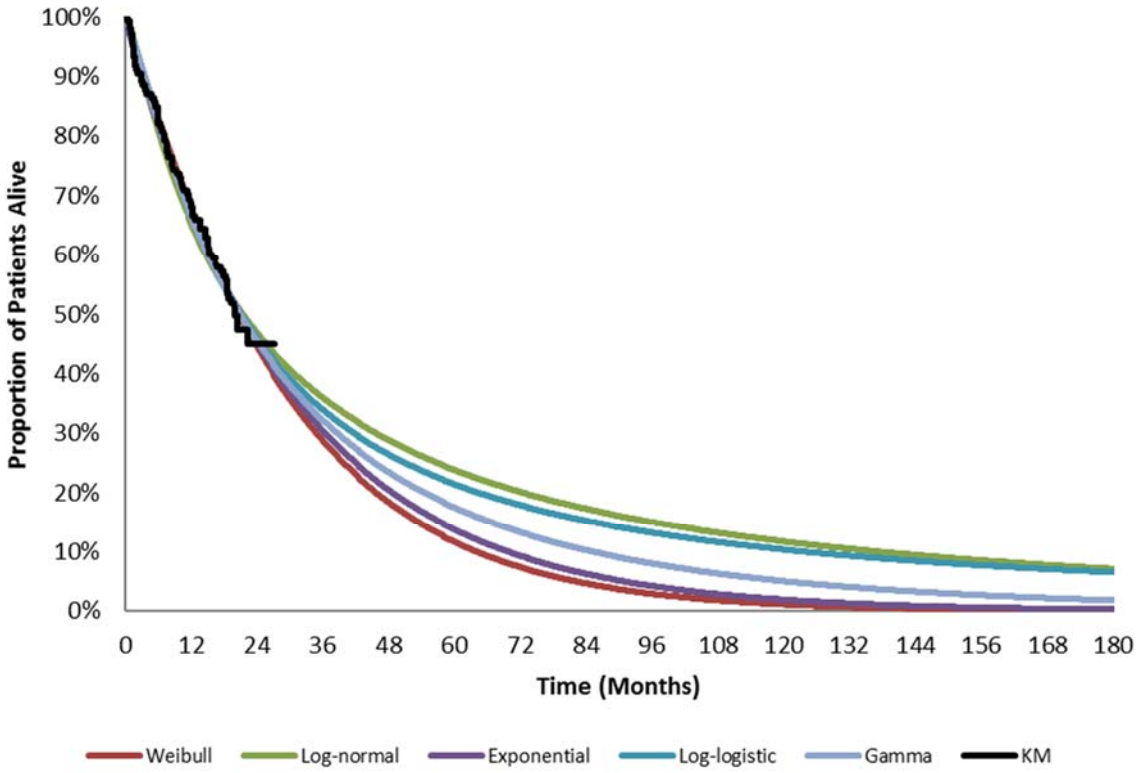
5.3.1 Overall survival

5.3.1.1 Daratumumab

The OS KM data for daratumumab, and the respective survival functions explored in the extrapolation, are presented in Figure 30. Since the OS KM data are 55% complete, the survival curves required extrapolation to predict future death events. For such predictions to be as accurate as possible, it was important to assess the clinical plausibility of the long-term survival projections, beyond study data. Thus, as aforementioned, in addition to the AIC and BIC statistics and visual inspection, clinical validation was sought from practicing NHS Consultant Haematologists with extensive experience of treating rrMM patients, to inform the choice of parametric distribution used in the base-case. Two NHS Consultant Haematologists advised that neither the log-logistic nor the log-normal curves were plausible as they predicted that 10% of patients receiving daratumumab would be alive after 10 years. By contrast, the exponential, gamma and Weibull distributions, estimating that 2% of daratumumab patients would be alive at 10 years, were deemed reasonable predictions of survival.

As indicated by the AIC and BIC statistics displayed in Table 50, the exponential survival function provides the best statistical fit to the daratumumab OS KM data, as well as demonstrating apt visual fit (Figure 30). Consequently, the exponential distribution was used in preference to the Weibull or Gamma model to estimate OS for daratumumab patients in the base-case. To test this structural assumption, alternative OS extrapolations are considered in scenario analyses, as presented in Section 5.8.

Figure 30: Parametric curve fits to OS data of the integrated MMY2002/GEN501 data



Key: KM, Kaplan–Meier; OS, overall survival.

Table 50: Goodness-of-fit statistics for OS of daratumumab

	Exponential	Weibull	Log-normal	Log-logistic	Gamma
AIC	361.69	363.33	363.78	363.67	364.89
BIC	364.32	369.32	369.77	369.66	373.89
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion.					

5.3.1.2 Pomalidomide + dexamethasone

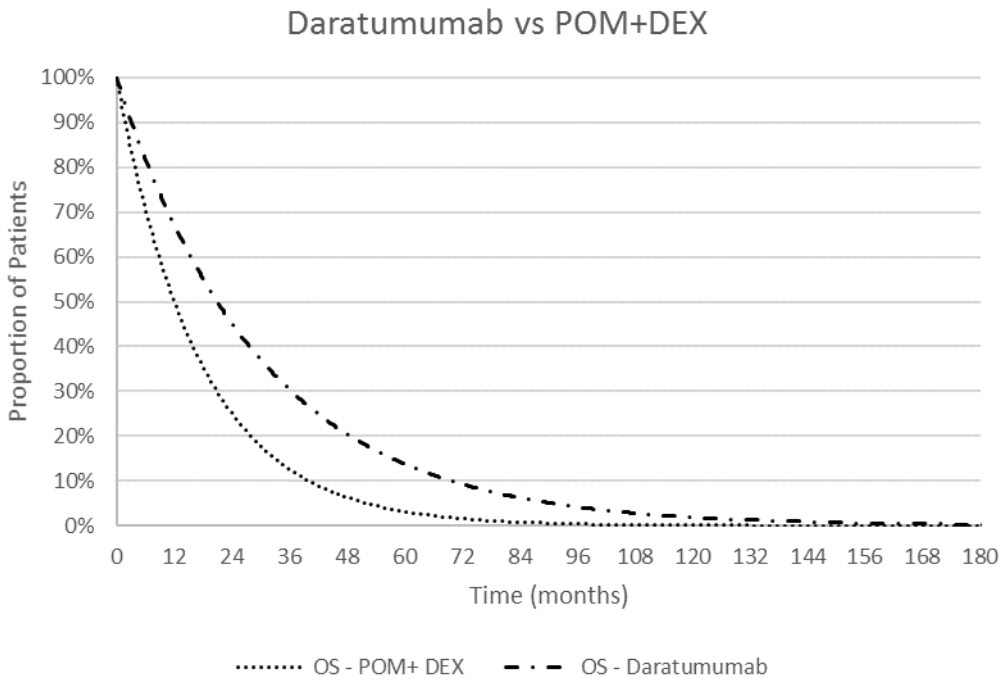
The adjusted KM curves derived from the MAIC are shown in Figure 22 (Section 4.10.3) and the weighted HR for OS, when matching to the most relevant 11 characteristics is 0.574 (95% CI: 0.407, 0.808).

As detailed and justified in Section 4.10, the number of characteristics chosen were based on clinical opinion; characteristics were ranked on their likely impact on survival and clinical experts in haematology confirmed those most important for matching[41]. Given the granularity of information reported on baseline characteristics in MM-003, these equated to matching the top 11 characteristics.

To assess uncertainty around these MAIC estimates, scenarios were tested where patients were matched by three, five and eighteen possible criteria. The weighted HRs used for these are presented in Section 4.10. A further scenario is presented, in which patients from the integrated daratumumab cohort who were pre-treated with POM+DEX are excluded from the analysis. In addition to scenario analyses uses MAIC, a scenario analysis using multivariate regression of MMY2002/GEN501 and IMF data for pomalidomide treated patients (see Section 4.10.4) was carried out. Modelled results from these scenario analyses are presented in Section 5.8.

Figure 31 displays the exponential curves used in the base-case economic model to inform the efficacy of daratumumab alongside the curve used to inform the efficacy of POM+DEX. The weighted OS HR (derived from the MAIC) was applied to the exponential curve chosen to model OS with daratumumab to calculate OS with POM+DEX. The results show that treatment with daratumumab monotherapy is expected to provide significantly greater OS than treatment with POM+DEX.

Figure 31: Exponential parametric curve fit to OS of daratumumab monotherapy and resulting OS of POM+DEX



Key: MAIC, matching-adjusted indirect comparison; OS, overall survival; POM+DEX, pomalidomide plus dexamethasone.

The proportional hazards assumption was tested for and these details are presented in Appendix 11. Results of this exploratory analysis were thereafter used to inform scenario analysis presented in Section 5.8.3.

5.3.1.3 Panobinostat + bortezomib + dexamethasone

The MAIC results for OS with PANO+BORT+DEX are implemented in are the same way as described for POM+DEX.

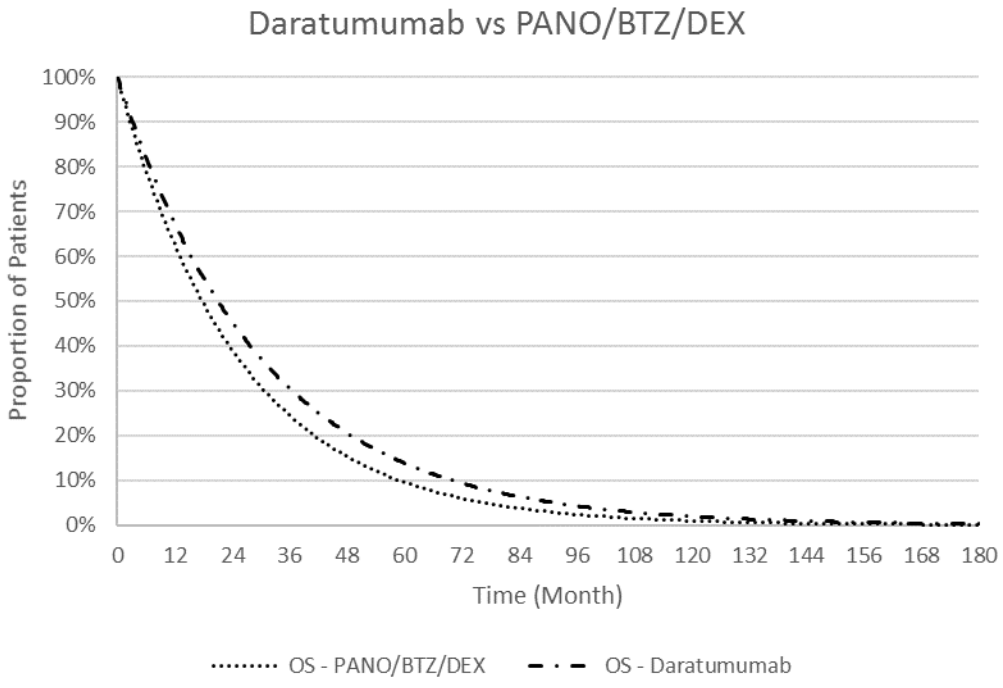
The adjusted KM curves derived from the MAIC are shown in Figure 24 (Section 4.10.3) and the weighted HR of OS, when matching to the top five characteristics, is 0.843 (95% CI: 0.521, 1.365). Similar to POM+DEX, characteristics were ranked on their likely impact on survival and clinical experts in haematology confirmed those most important for matching. Given the granularity of information reported on

baseline characteristics in PANORAMA 2, these equated to matching the top five characteristics.

To assess uncertainty around the MAIC estimates, scenarios were tested where patients were matched by two and twelve criteria, which represent the best and worst HRs. The weighted HRs used for these scenario analyses are previously presented in Section 4.10 and modelled results are presented in Section 5.8.

Figure 32 presents the exponential curves used in the base-case economic model to inform the efficacy of daratumumab and the efficacy of PANO+BORT+DEX. The weighted OS HR (derived from the MAIC) was applied to the exponential curve chosen to model OS with daratumumab to calculate OS with PANO+BORT+DEX. The results show that treatment with daratumumab monotherapy is expected to slightly improve survival versus treatment with PANO+BORT+DEX. Since patients in the daratumumab trials were more heavily pre-treated and refractory than patients in PANORAMA 2, and since refractory status for treatments other than bortezomib is not adjusted for in the MAIC as a consequence of the data reported for PANORAMA 2, such OS estimates may be considered conservative.

Figure 32: Exponential parametric curve fit to OS of daratumumab monotherapy and resulting OS of PANO+BORT+DEX



Key: BORT, bortezomib; DEX, dexamethasone; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; PANO, panobinostat.

The proportional hazards assumption was tested for and these details are presented in Appendix 11. Results of this exploratory analysis were thereafter used to inform scenario analysis presented in Section 5.8.3.

5.3.1.4 Bendamustine

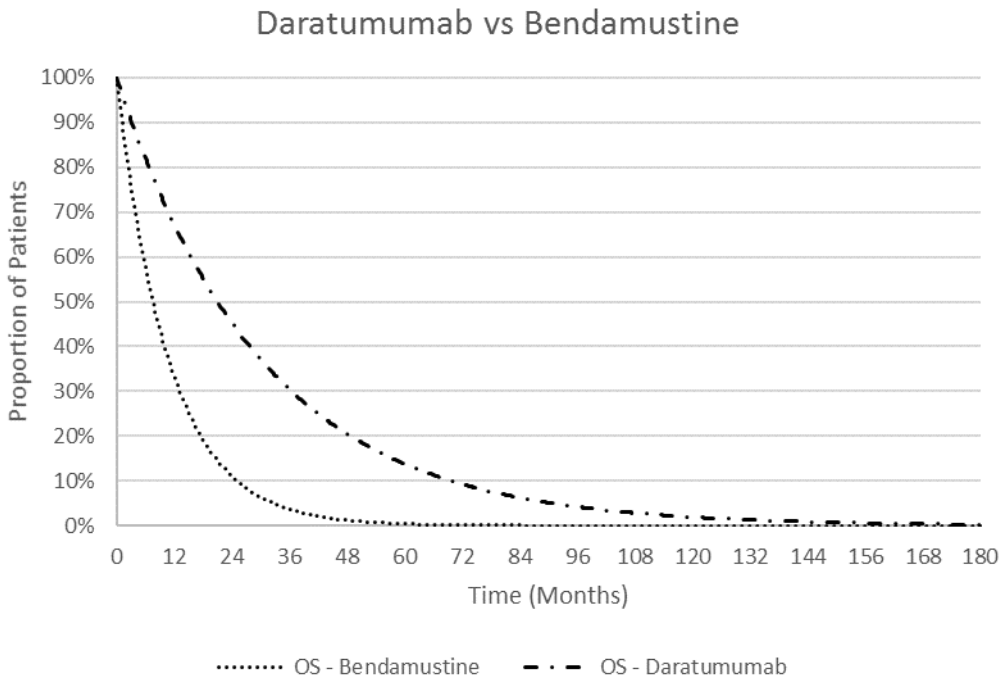
As described in Section 4.10.4, multivariate regression was conducted to estimate the comparative efficacy of daratumumab versus bendamustine using RWE from the IMF chart review the result of which is presented in Table 51.

Figure 33 displays the exponential curve used in the base-case to inform the efficacy of daratumumab alongside the curve used to inform the efficacy of bendamustine derived from application of the OS HR. The results show that treatment with daratumumab monotherapy is expected to provide significantly greater OS than treatment with bendamustine; this result is statistically significant.

Table 51: HR for OS for daratumumab vs. bendamustine

	Hazard ratio (95% CI)
Daratumumab vs bendamustine	0.43 (0.30, 0.63)
Key: CI, confidence interval; IMF, International Myeloma Foundation; MAIC, matching-adjusted indirect comparison; OS, overall survival. **Source**: IMF analysis.[117]	

Figure 33: Exponential parametric curve fit to OS of daratumumab monotherapy and resulting OS of bendamustine



Key: OS, overall survival.

The proportional hazards assumption was tested for and these details are presented in Appendix 11.

Further real-world evidence

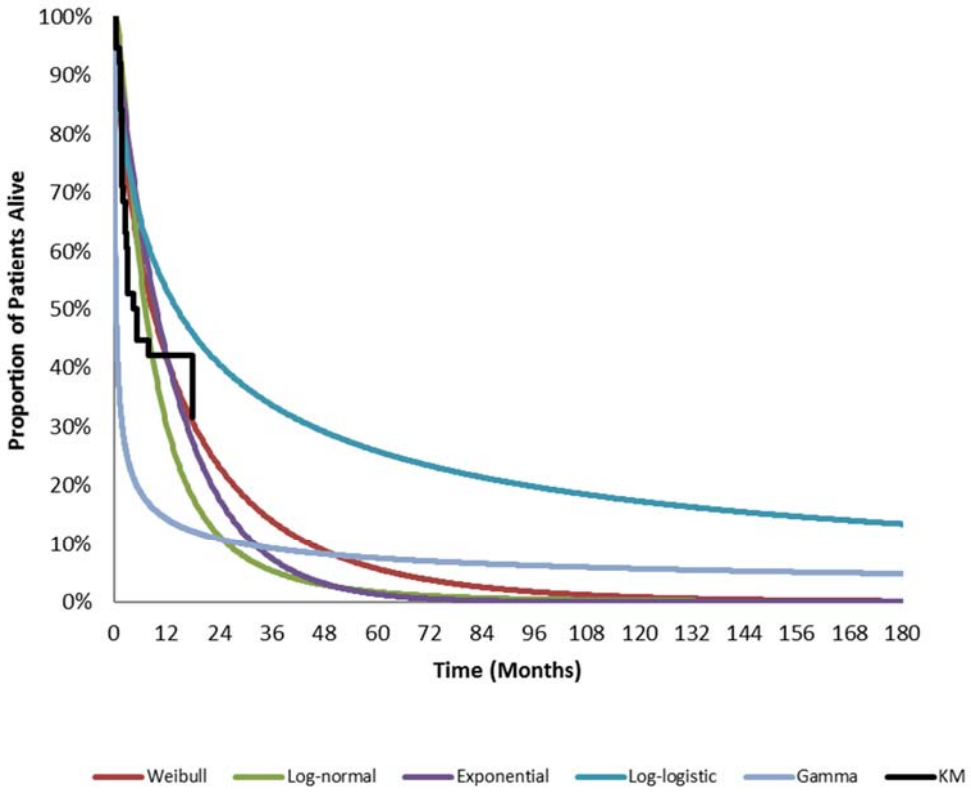
Alternative RWE from Gooding et al.[26] and HMRN[134] were compared to the IMF data to assess the generalisability of international real-world outcomes to the UK.

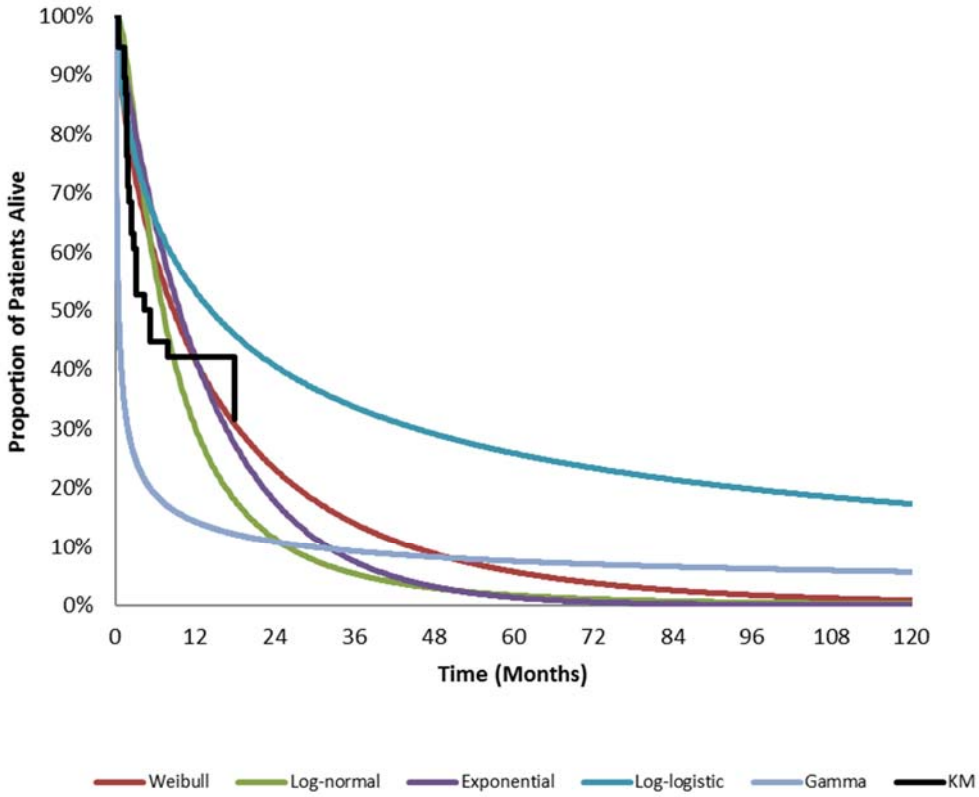
Gooding et al. is a study of 39 UK patients whose MM was relapsed and/or refractory to bortezomib and lenalidomide, and so includes patients at a comparable line of therapy to those in MMY2002/GEN501 trials. Patients at a comparable line in their treatment can also be identified through the HMRN (n=69).

IPD was reconstructed for each dataset using the Guyot algorithm[111], and five standard parametric survival functions were estimated for each dataset (exponential, Weibull, log-logistic, lognormal and generalised gamma). The OS extrapolations for

the data reported by Gooding et al.[26] are shown in Figure 34 and the OS extrapolations for the HMRN data[134] are shown in Figure 35. A comparison of these OS curves alongside the OS curves from the IMF multivariate regression analysis and the integrated daratumumab cohort is presented in Figure 36. The consistency in results between these HMRN and IMF data (the two largest datasets) supports the generalisability of the IMF chart data to the UK and indicates it is representative of current outcomes in the NHS in England.

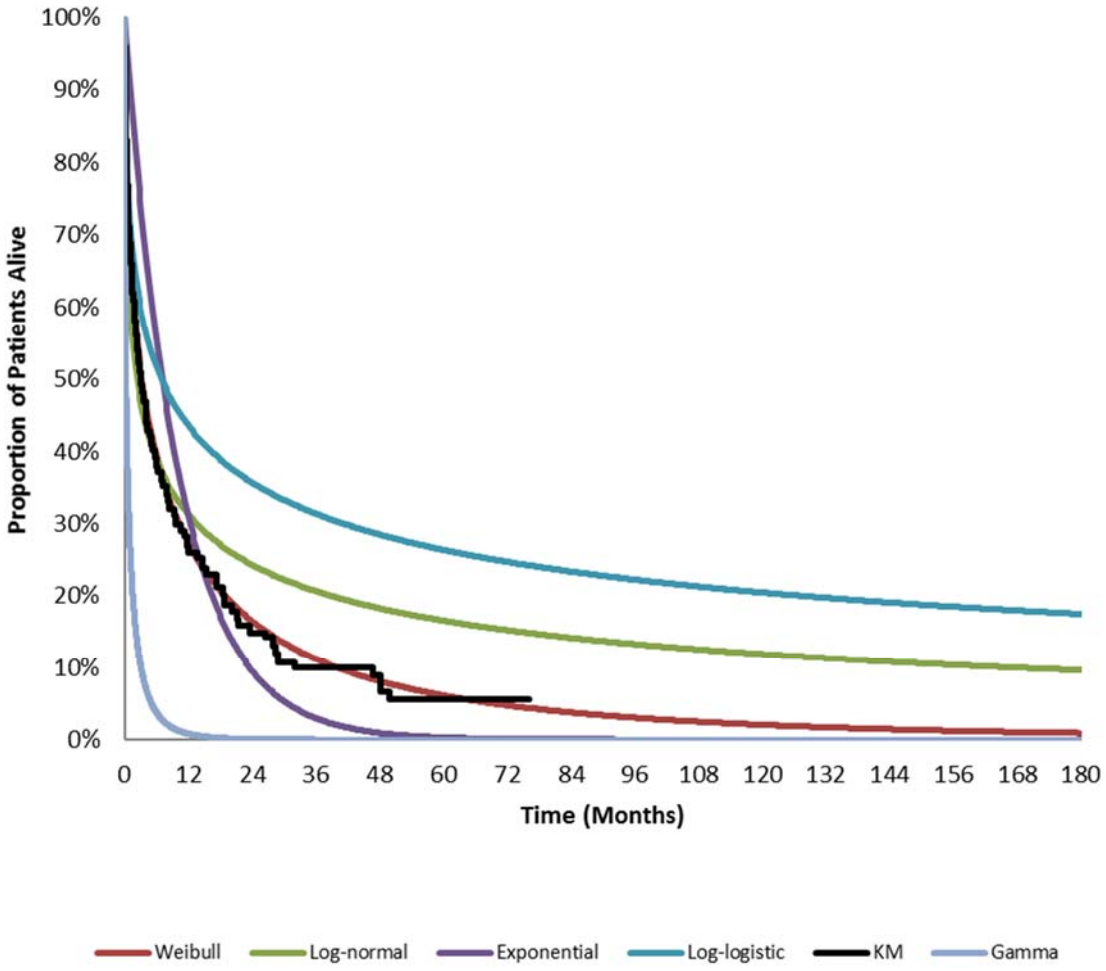
Figure 34: Extrapolation of OS data from Gooding et al. [26]





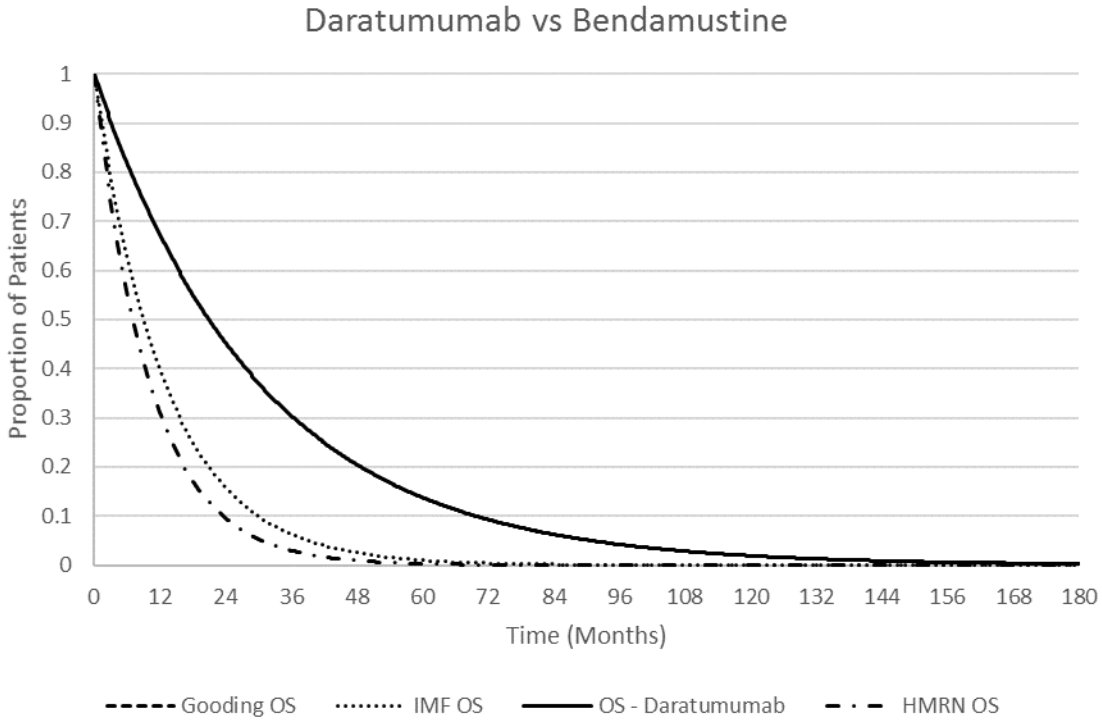
Key: KM, Kaplan–Meier, OS, overall survival.

Figure 35: Extrapolation of OS data from the HMRN data[134]



Key: HMRN**,** Haematological Malignancy Research Network; KM, Kaplan–Meier, OS, overall survival.

Figure 36: Comparison of OS of daratumumab with RWE from the HMRN[134], Gooding et al.[26] and IMF chart review[117, 126]



Key: HMRN**,** Haematological Malignancy Research Network; IMF, International Myeloma Foundation; OS, overall survival, RWE, real world evidence.

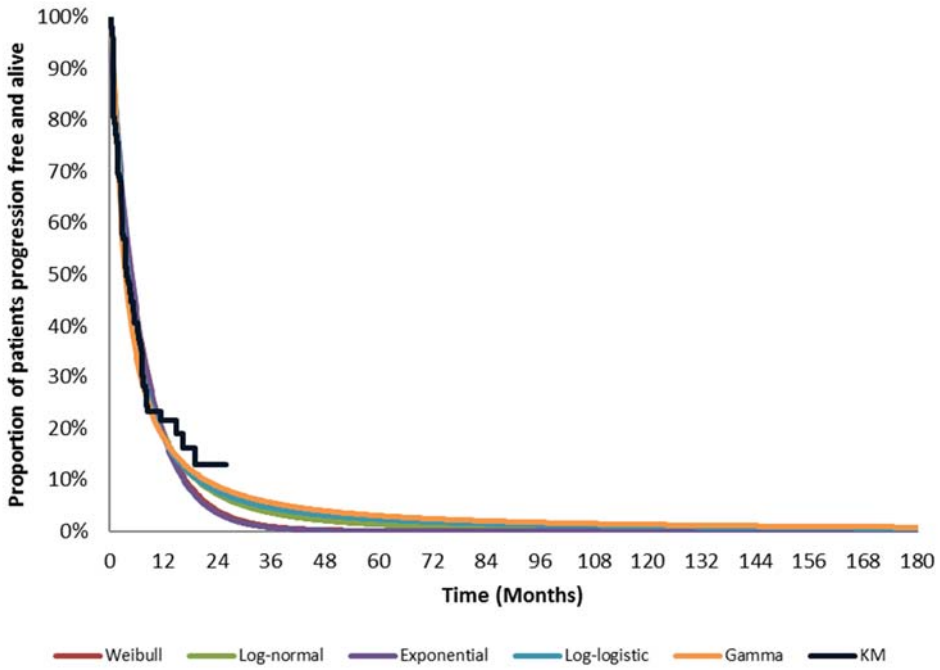
5.3.2 Progression-free survival

5.3.2.1 Daratumumab

The PFS KM data (IRC assessed) are presented in Figure 37 alongside the five parametric curves fitted to these data. AIC and BIC statistics are presented in Table 52. Based on statistical fit and clinical plausibility the log-normal curve was deemed most appropriate for use. This model predicts 2% of patients to be progression-free and alive at five years. Given the completeness of the data (13% of patients were progression-free and alive at the end of the trial period), and that there was a long tail in PFS observed among responders in the integrated daratumumab analysis, the prediction is reasonable and was validated by an NHS Consultant Haematologist.[42] The log-normal curve was therefore selected for use in the base-case analysis and the impact on the ICER of selecting alternative curves was tested in scenario analyses. To test the uncertainty around the method of PFS assessment, an

additional scenario using investigator-assessed PFS has been carried out (see Section 5.8).

Figure 37: Parametric curve fits to PFS data of the integrated MMY2002/ GEN501 cohort



Key: KM, Kaplan–Meier; PFS, progression-free survival.

Table 52: Goodness-of-fit statistics for PFS of daratumumab

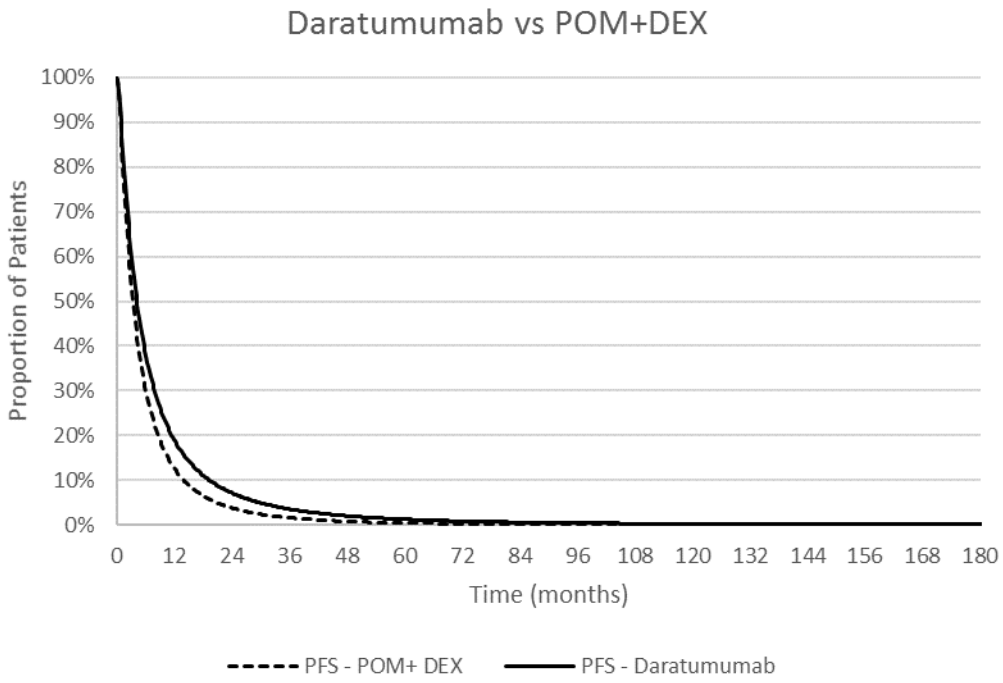
	Log-normal	Log-logistic	Exponential	Weibull	Generalised Gamma
AIC	394.21	399.16	413.61	415.39	388.38
BIC	400.21	405.15	416.61	421.38	397.37
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.					

5.3.2.2 Pomalidomide + dexamethasone

The weighted HR for PFS, derived by the MAIC, when matching to the top 11 characteristics, is 0.806 (95% CI: 0.597, 1.087). To test the uncertainty around the MAIC estimate, results when matching differing numbers of characteristics were utilised in scenario analyses. Figure 38 displays the log-normal curves used in the base-case economic model to predict PFS with daratumumab alongside the curve

used to predict PFS with POM+DEX derived from application of the PFS HR. This shows that patients receiving daratumumab are likely to have an improved PFS than those receiving POM+DEX, after adjusting for the differences across trials.

Figure 38: Log-normal parametric curve fit to PFS of daratumumab monotherapy and resulting OS of POM+DEX



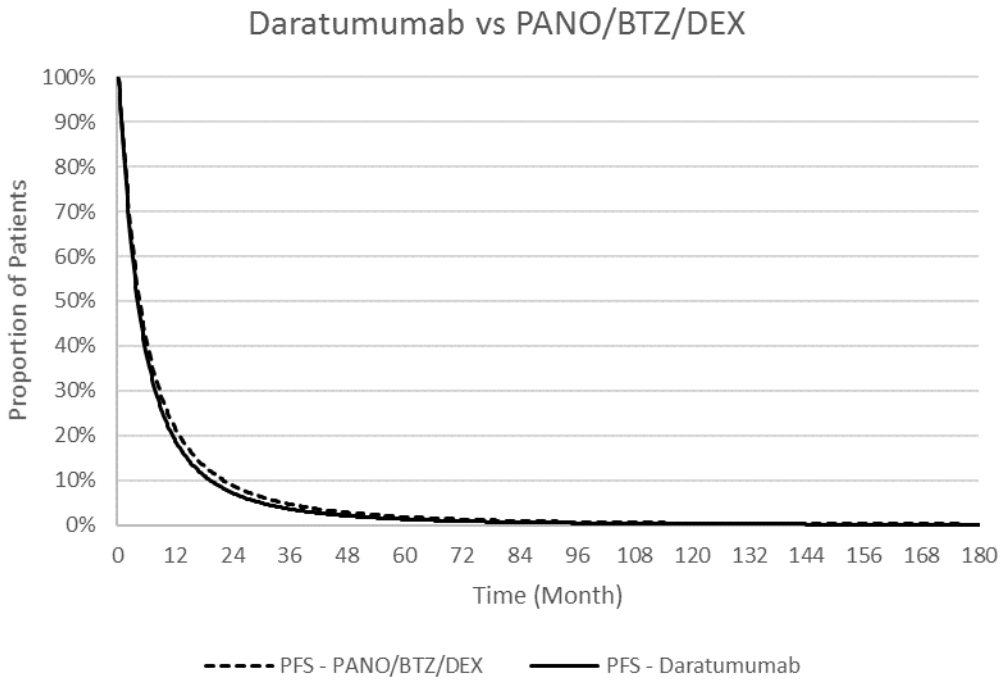
Key: HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.

5.3.2.3 Panobinostat + bortezomib + dexamethasone

The weighted HR for PFS, derived by the MAIC when matching to the top five characteristics (selected using the same method and criteria as described in Section 4.10.3), is 1.087 (95% CI: 0.737, 1.605). Given the analysis against PANO+BORT+DEX is based on small patient numbers (n=55) it is challenging to demonstrate statistical significance. To test the uncertainty around the MAIC estimate, results when matching differing numbers of characteristics were utilised in scenario analyses. Furthermore, as a consequence of data available from PANORAMA 2 it was not possible to adjust for refractory status (other than to bortezomib). The refractory status of patients is a key prognostic factor and given the generally more refractory nature of patients enrolled in MMY2002/GEN501; it is likely

that the lack of adjustment for refractory status would introduce bias against daratumumab. Figure 39 displays the log-normal curves used in the base-case economic model to predict PFS with daratumumab alongside the curve used to predict PFS with PANO+BORT+DEX derived from application of the PFS HR. This shows that PANO+BORT+DEX and daratumumab are exected to provide similar PFS, after adjustment for the differences across trials.

Figure 39: Log-normal parametric curves fit to PFS of daratumumab monotherapy and resulting PFS of PANO+BORT+DEX



Key: BORT, bortezomib; DEX, dexamethasone; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; PANO, panobinostat; PFS, progression-free survival.

5.3.2.4 Bendamustine

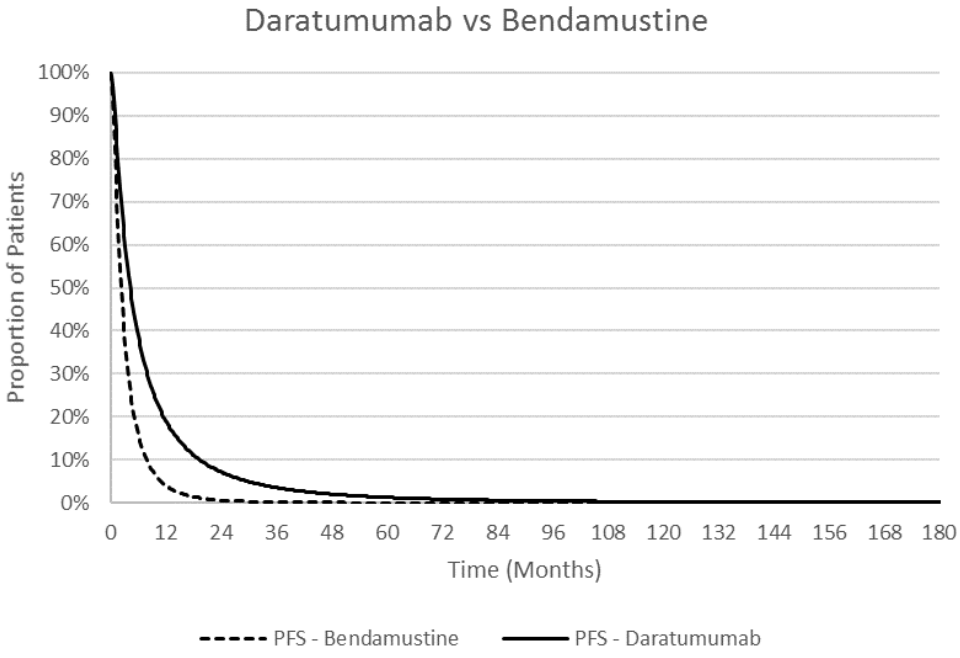
A multivariate regression was conducted to estimate the comparative efficacy of daratumumab versus bendamustine-based therapy using the IMF chart review real-world patient-level data.[117, 126] This derived a HR for PFS of 0.59 (95% CI: 0.43, 0.81).

Figure 40 displays the exponential curves used in the base-case economic model to inform the efficacy of daratumumab alongside the curve used to inform the efficacy of bendamustine-based therapy derived from application of the PFS HR. This shows that patients receiving daratumumab are expected to have a longer, improved PFS period compared with patients receiving off-label treatment with bendamustine-based therapy; this result is statistically significant.

Table 53: HR for PFS of daratumumab vs. bendamustine

	Hazard ratio (95% CI)
Daratumumab vs Bendamustine	0.59 (0.43, 0.81)
Key: CI, confidence interval; IMF, International Myeloma Foundation; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival.	

Figure 40: Log-normal parametric curve fit to PFS of daratumumab monotherapy and resulting PFS of bendamustine-based therapy



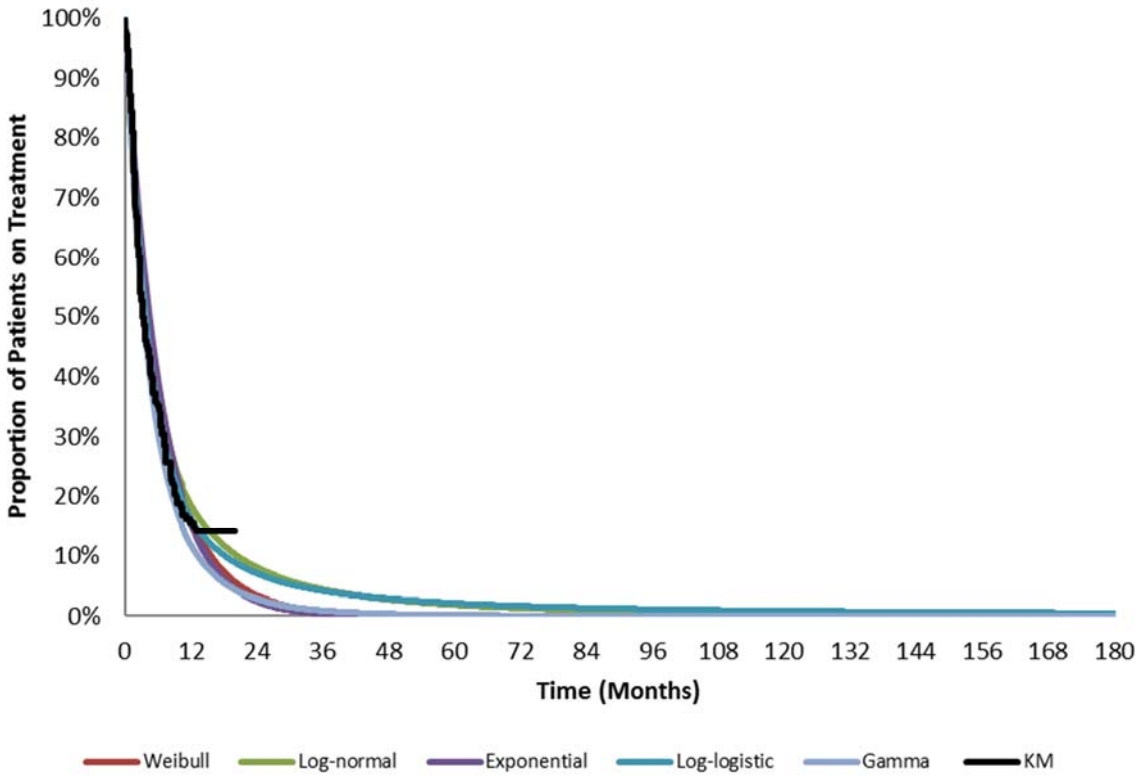
Key: BORT, bortezomib; DEX, dexamethasone; HR, hazard ratio; PANO, panobinostat; PFS, progression-free survival.

5.3.3 Time to treatment discontinuation

In clinical practice, and as observed in MMY2002, GEN501 and MM-003[57], patients may withdraw from active treatment before disease progression. The integrated TTD

data from MMY2002 and GEN501 are presented in Figure 41, alongside the fitted parametric functions. The AIC and BIC statistics indicate that the log-logistic curve has the best statistical fit to the TTD data, as shown in Table 54, and was therefore used in the base-case analysis. A comparison of the PFS and TTD curves for the integrated daratumumab data are thereafter presented in Figure 42.

Figure 41: Parametric curve fits to TTD of the integrated MMY2002/ GEN501 data

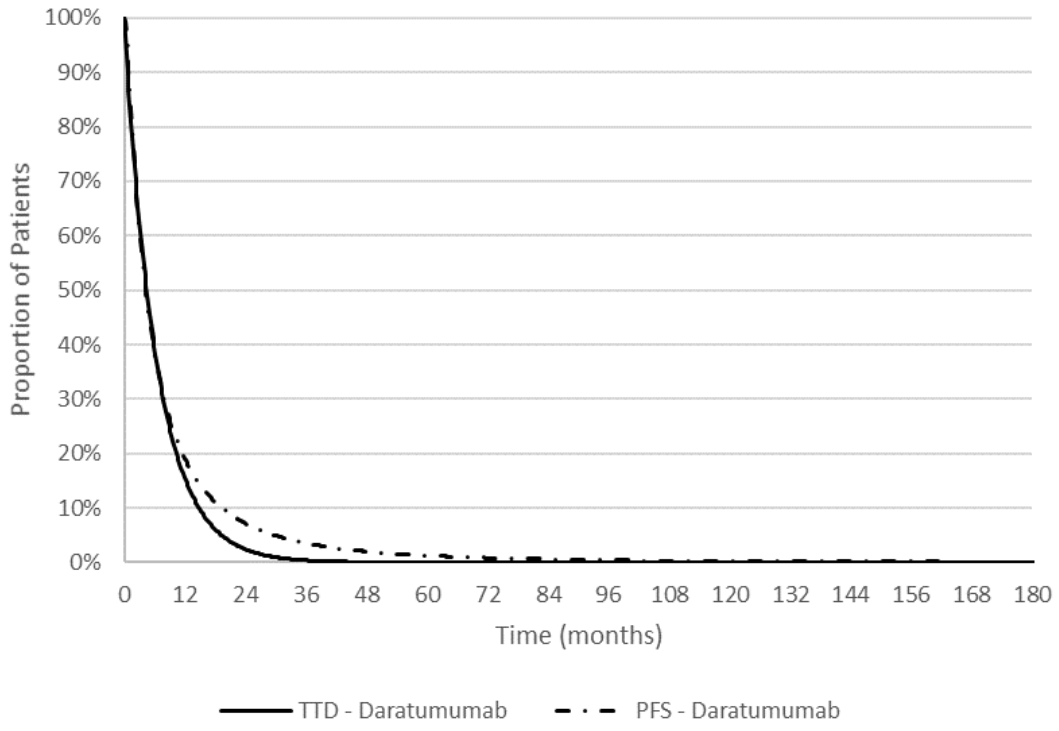


Key: KM, Kaplan–Meier; TTD, time to treatment discontinuation.

Table 54: Goodness-of-fit statistics for TTD

	Log-logistic	Log-normal	Exponential	Weibull	Generalised Gamma
AIC	472.86	483.91	486.74	487.28	481.632
BIC	478.85	489.91	489.74	493.27	490.624
Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; TTD, time to treatment discontinuation.					

Figure 42: Comparison of TTD and PFS data of daratumumab (MMY2002/ GEN501)



Key: TTD, Time to discontinuation; PFS, progression-free survival

5.3.3.1 Pomalidomide + dexamethasone

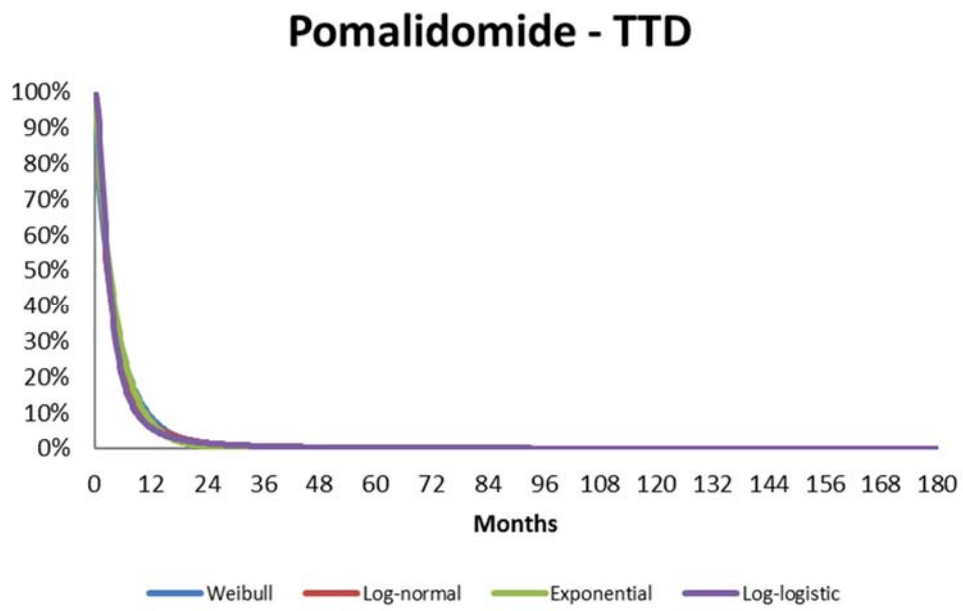
For the POM+DEX arm of MM-003, only mean and median TTD could be obtained from the literature (mean TTD: 4.656; median TTD: 2.854), therefore, the TTD curves for daratumumab were calibrated to match the observed mean and median from MM-003.[57] The parametric curves fit to the POM+DEX data are presented in Figure 43; the log-logistic curve was selected for consistency with daratumumab as shown in Figure 44. This shows that patients were more likely to discontinue treatment with POM+DEX due to disease progression compared with daratumumab. For reference, a comparison of the TTD and PFS data for POM+DEX are presented in

Figure **45.**

As patients cannot receive treatment with daratumumab or POM+DEX beyond progression, if the extrapolated curves resulted in TTD being greater than PFS, TTD

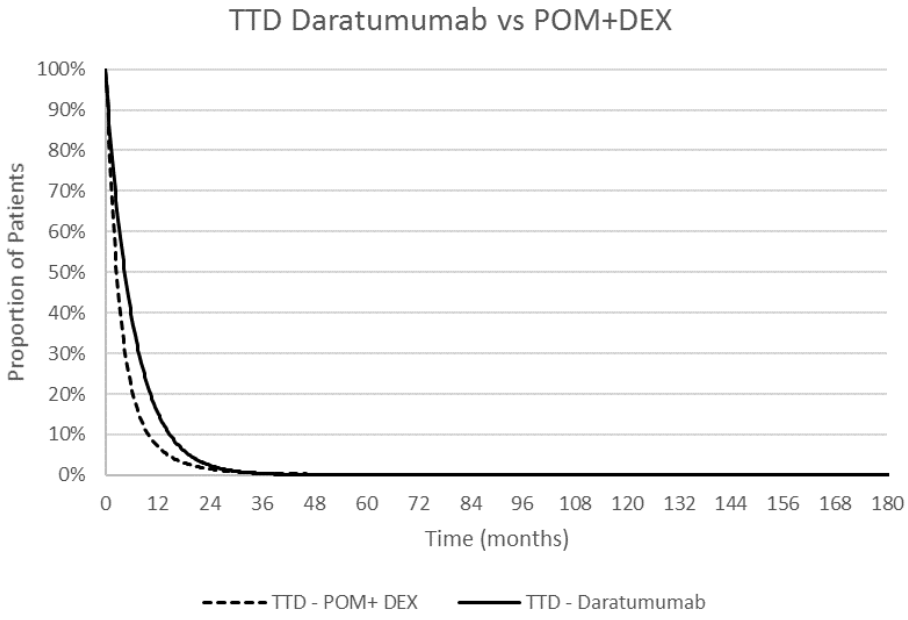
was taken as the minimum of the two values at that time-point for modelling purposes.

Figure 43: Parametric curve fits to TTD of POM+DEX from MM-003[57]



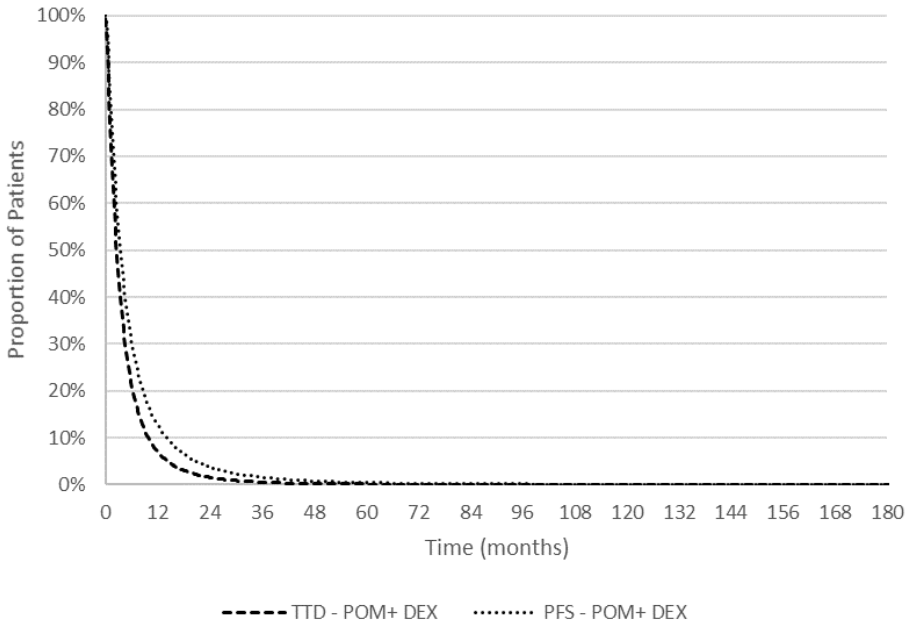
Key: POM+DEX, pomalidomide plus dexamthethasone; TTD, time to treatment discontinuation.

Figure 44: Log-logistic parametric curve for TTD of daratumumab monotherapy and POM+DEX



Key: POM+DEX, pomalidomide plus dexamthethasone; TTD, time to treatment discontinuation.

Figure 45: Comparison of TTD and PFS data of POM+DEX from MM-003



Key: POM+DEX, pomalidomide plus dexamthethasone; TTD, time to treatment discontinuation; PFS, Progression-Free Survival

5.3.3.2 Panobinostat + bortezomib + dexamethasone

There are no TTD data available for patients in the PANORAMA 2 clinical trial[58]. Therefore, in the model, patients receive PANO+BORT+DEX for the maximum number of treatment cycles allowed in the dosing regimen or until progression.[129]

5.3.3.3 Bendamustine

There are no TTD data available for patients in the evidence for bendamustine. In the model, patients receive bendamustine until progression.

5.4 Measurement and valuation of health effects

Patients with poorly managed rrMM have characteristically poor HRQL.[42, 135] The uncontrolled growth of myeloma cells has many consequences, including skeletal destruction, bone marrow failure, suppression of normal immunoglobulin production and renal insufficiency.[136] Symptoms include pain, fatigue and reduced physical function and mobility. There is evidence that patients with myeloma report worse symptoms and problems than those with other haematological cancers.[34]

In addition to the physical symptoms, MM patients can suffer considerably from the fear of disease recurrence and the associated uncertainty about their future due to the incurable and relapsing nature of the disease and limited effectiveness of available treatments. Combined with this uncertainty, patients may also feel a loss of independence and an inability to plan for the future.[135] Cumulative toxicity becomes a substantial problem for patients at fourth line and beyond, in terms of both its symptoms and its consequence for plausible treatment options.

Daratumumab, an effective and well tolerated treatment, has great potential to increase these patients' quality of life through improved tolerability and disease control, as well as prolonged survival. This expectation was made clear through NHS Consultant haematologist review[42], and reflects the HRQL evidence package considered for POM+DEX within the TA338 resubmission Appraisal Committee meeting of 12 October 2016.

As a consequence of the accelerated regulatory approval, daratumumab monotherapy received MA based on a Phase II trial and Phase I/II trial designed for regulatory purposes. Therefore, the clinical trial evidence base for daratumumab monotherapy does not contain HRQL data and so TA338 was used to inform utility estimates for daratumumab.

Unlike TA338, utility data for daratumumab were not disaggregated by response; rather average utility values were used. The use of average utility may underestimate the quality of life associated with the deep and durable response observed with daratumumab. Furthermore, the granularity of EuroQol-5 Dimension (EQ-5D) data may not fully capture patient benefits such as improvement in fatigue.[12]

5.4.1 Health-related quality-of-life data from clinical trials

Although no HRQL measures were included in the Phase II trial programme investigating daratumumab monotherapy in the rrMM population, data are being gathered through an Early Access Programme (EAP).

Based upon data extracted on 23 August 2016, 140 subjects were enrolled in the European component of the EAP and received daratumumab monotherapy; the median age was 65 years and 60% were male. Patients received a median of 1.18 months of therapy (range: 0.03, 5.06), a median of 6 infusions (range: 1, 15) and at a median total dose of 95.56 mg/kg (range: 15.9, 245.7). Discontinuation as a result of progression occurred in 23 patients. Patients from the EAP are of a similar age and gender distribution to the patients in the MMY2002 and GEN501 clinical trials although patients in the daratumumab trials received a greater number of infusions than those in the EAP (GEN501: median total number of infusions= 13.5 [Range: 1, 24]; MMY2002: median total number of infusions= 11 [Range: 1, 16]).

Utility data (EQ-5D-5L) at baseline, treatment cycle two, three and at last assessment from the European component of the EAP are summarised in Table 55. These data indicate a baseline utility of 0.63 (median 0.768), which remains stable up to the third month of treatment. A decrease in mean utility is observed at last assessment, although median utility remains stable. Given the impact of patients discontinuing as a result of progression on the utility at last assessment, it may be concluded that utility remains stable whilst on treatment with daratumumab.

Table 55: EQ-5D-5L data from EAP[137]

	n	Mean utility	Median utility	SD
Baseline	99	0.63	0.68	0.24
Cycle 2, Day 1	39	0.61	0.62	0.32
Cycle 3, Day 1	25	0.60	0.71	0.34
Last Assessment	57	0.58	0.67	0.33
Key: EAP, Early Access Programme; n, number; SD, standard deviation.				

5.4.2 Mapping

No mapping was performed.

5.4.3 Health-related quality-of-life studies

A systematic review was performed in January 2016 to identify HRQL evidence for patients with rrMM or MM. The search aimed to identify studies reporting on the HRQL in patients with MM or rrMM and associated AEs. Further details are provided in Appendix 12. Each reference was first screened for inclusion based on title and abstract. All publications that met entry criteria for the review were obtained as full articles and reassessed against the review criteria. To be included in this systematic review, references had to meet the inclusion criteria (and none of the exclusion criteria) detailed in Table 56.

Table 56: Inclusion and exclusion criteria for HRQL studies

	Inclusion	Exclusion
Study population	Adult patients with MM	No adult MM patients
Intervention	Untreated patients included	None
Outcome	Utility values produced using generic, preference-based measures of patient utility, disease-specific measures or vignettes Instrument responses should be elicited from patients Valuations of utilities should be based on general population preferences	Disease specific and non-preference-based measures not converted to utilities Proxy questionnaire responses
Study types	Quality of life studies Economic evaluations reporting patient utility values	None
Publication types	None	Letters and comment articles
Language	Studies reported in English	Studies not reported in English
Other	Studies must present sufficient detail of the methodology used and provide extractable results	Publications that fail to present sufficient methodological detail or extractable results
Key: MM, multiple myeloma; rrMM, relapsed/refractory multiple myeloma.		

Nineteen studies were included in the final review. Six were cost-effectiveness studies[26, 138-142], six were mapping studies[143-148] and seven were quality of life studies.[149-155] A summary of the studies identified alongside the full Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram are presented in Appendix 12.

Only one study identified in the literature review included utilities at a similar stage of the treatment pathway as patients in MMY2002 and GEN501.[154] This poster detailed the results of patient EQ-5D-3L data from the pivotal study for POM+DEX, MM-003.[57] Results were reported by disease progression and treatment arm. In total, 1,252 observations were reported pre-progression, with a mean utility of 0.61 (standard deviation 0.31), and 154 observations were reported post-progression, with a mean utility of 0.57 (standard deviation 0.3).

The utilities reported in the Palumbo study[154] are broadly consistent with those reported by patients in the European component of the EAP; minor differences are to be expected given the different instruments used (EQ-5D-3L versus EQ-5D-5L), with EQ-5D-5L expected to give more reliable estimates of utility as a consequence of the increased granualirity of this instrument.

Other EQ-5D data in the review varied considerably. Kharroubi et al. reported a utility of 0.52 based on 1,839 patients[144], Proskorovsky et al. reported a utility of 0.7 based on 154 patients[147], and Gooding et al. reported a utility of 0.69 based on 132 patients.[26] However, these studies included patients at earlier lines of therapy to that being considered in this submission; the utility value reported by Kharroubi et al. is from patients with newly diagnosed MM who were not receiving any treatment and consequently is particularly low.[144]

In addition to the literature review described above, utility data and associated assumptions within key previous in rrMM NICE submissions (TA338 and TA380) were reviewed.

The utility data informing TA338 assumptions are the same MM-003 EQ-5D-3L data analysed and reported by Palumbo and colleagues. Yet for the TA338 submission, these data were further analysed by the company, who took a stepwise-regression approach to model the utility data as a function of treatment response, disease progression status, adverse event status, whether the patient was hospitalised, and further baseline demographic factors. This enabled the company to incorporate a utility benefit for POM+DEX versus its comparators, via progressive disease, response rate, adverse event and hospitalisation advantages. The summary of utility estimates by health status in TA338 is shown in Table 57. Analysing the data in this way is advantageous to regimens with good toxicity profiles and response rates such as DARA and POM+DEX, however, the reliability of parameter estimates from a regression of utility data from a medium-sized clinical trial (n=455) upon so many explanatory variables is limited.

The utility values used in TA380 are shown in Table 58. These came from patients from the PANORAMA 1 trial who, as noted throughout this dossier, are at an earlier line of therapy than those in the MMY2002 and GEN501 trials. These estimates are

greater than comparable estimates from MM-003 patients [154] and suggest patients have highest utility when they are pre-progression and off-treatment. This likely reflects the toxicity profiles of the regimens in PANORAMA 1 and during the appraisal process, the evidence review group (ERG) noted that the utilities did not account for AEs experienced by those patients treated with panobinostat and that the utility scores used in the model may not account adequately for the relatively poor safety profile observed in the PANORAMA 1 trial. It is therefore expected that these estimates are optimistic for patients receiving PANO+BORT+DEX.

Table 57: TA338 base-case utility assumptions

Best overall response	Within PD health state?	Hospitalisation or adverse event?	EQ-5D utility
Response	x	X	0.75
Stable disease	x	X	0.65
Progressive disease	x	X	0.61
Stable disease	x	Hospitalisation	0.52
Response	✓	X	0.71
Stable disease	✓	X	0.62
Progressive disease	✓	x	0.57
Stable disease	✓	Hospitalisation	0.48
Key: PD, progressive disease.			

Table 58: TA380 base-case utility assumptions

State	Utility value mean, sd
Pre-progression (PANO+BORT+DEX)	0.706 (0.192)
Pre-progression (BORT+DEX)	0.725 (0.197)
Pre-progression (No Treatment)	0.762 (0.166)
Post progression	0.64 (0.128)
Key: BORT, bortezomib, DEX, dexamethasone; PANO, panobinostat; SD, Standard deviation; TA, technology appraisal.	

Following consideration of the available options, a conservative approach to utility assumptions was taken. Disease-progression-specific utility estimates from MM-003 reported by Palumbo et al (0.61 PFS, 0.57 PPS) are used in the model base-case.

Utility decrements for AEs are applied, but as described in Section 5.4.4, conservative assumptions are made here too. Consultant Haematologist advice is that patients receiving daratumumab would be expected to have a greater on-treatment utility than patients receiving other available options, even POM+DEX. In comparison to PANO+BORT+DEX and bendamustine-based regimens for patients with no other alternative, both DARA and POM+DEX offer tolerability and effectiveness HRQL benefits. Possible toxicity associated with daratumumab is front-loaded due to the dosing schedule, whereas patients receiving more consistent doses of POM+DEX are prone to fatigue which can have a cumulative impact of patient's quality of life.[42]

The base-case utility assumptions should be considered conservative. Exploration of estimates from previous NICE submissions in Section 5.8 illustrates the impact of using alternative utility estimates.

5.4.4 Adverse reactions

All Grade 3 or 4 AEs occurring in ≥5% of subjects, reported in either MMY2002 and GEN501 as related to daratumumab, in PANORAMA 2[58] as related to PANO+ BORT+DEX or in MM-003[57] as related to POM+DEX, are accounted for in the model. Data on adverse events were not available for bendamustine and so, based on clinical opinion[42], adverse event incidence was assumed to be the same as POM+DEX from MM-003. Based on expert clinical advice from a clinical validation meeting held in March 2016[41], nausea, peripheral neuropathy and upper respiratory tract infections were considered to be of particular clinical importance, and were therefore included regardless of severity (grade) and if experienced by ≥1% patients receiving either daratumumab, PANO+BORT+DEX, POM+DEX or bendamustine. All AE incidence data was further validated in October 2016 where it was agreed that the incidence rates reported were reflective of what is seen in clinical practice with the addition that fatigue would be expected to have a high incidence in patients receiving POM+DEX.[42]

A study, identified in the systematic review, by Brown et al.[156] that evaluated LEN+DEX compared with dexamethasone alone in rrMM reported associated AE disutilities. This was used as the primary source of AE disutilities in the base-case analysis as it provided a degree of internal consistency between the AE disutility values. In an effort to maintain consistency, where disutilities were not reported by Brown et al.[156], values were sought from the NICE technology appraisal for lenalidomide (TA171)[157], which drew upon the same trial data. Not all utility decrements were available from either source, and therefore, alternative studies were sought from the literature. All AE disutility estimates are presented in Table 59 with other sources including Lloyd et al.[158], Tolley et al.[159] and Sullivan et al.[160], which have all be used to inform disutility estimates in previous NICE technology appraisals (TA359).[161] Clinical opinion was also sought for dis-utilities which were not reported in the literature and to validate those that were.[42]

Where the utility duration was not reported, a duration of one month (28 days) was assumed for each AE disutility. The disutility and duration were used to estimate the utility decrement over one year, and this QALY decrement was applied in the first model cycle only. Adverse event durations were also validated by a clinican practicing in the NHS in England.[42]

Table 59: AE incidence and utility decrement estimates

AE	Daratumumab AE incidence rate, % Weighted average of MMY2002 and GEN501, Jan 2015 data cut[95]	PANO+BORT+DEX AE incidence rate, % PANORAMA 2	Bendamustine	POM+DEX AE incidence rate, % MM-003[57]	Disutility	Duration (Days)	QALY decrement	Disutility source
Febrile neutropenia	0%	NR	9%	9%	-0.39	28	-0.03	Launois 1996
Neutropenia	10%	15%	48%	48%	-0.15	28	-0.01	Brown 2013[156]/Partial Review TA171[157]
Anaemia	19%	15%	33%	33%	-0.31	180	-0.02	Brown 2013[156]/Partial Review TA171[157]
Thrombocytopenia	17%	64%	22%	22%	-0.31	28	-0.02	Brown 2013[156]/Partial Review TA171[157]
Lymphopenia	6%	NR	NR	NR	-0.07	28	0.00	Assume lowest in range (Partial Review TA171)[157]
Leukopenia	2%	NR	9%	9%	-0.07	28	0.00	Assume lowest in range (Partial Review TA171)[157]
Upper respiratory infection (all grades)	20%	NR	16%	16%	-0.19	7	-0.01	Assume the same as pneumonia
Pneumonia	6%	15%	14%	14%	-0.19	7	-0.01	Brown

AE	Daratumumab AE incidence rate, % Weighted average of MMY2002 and GEN501, Jan 2015 data cut[95]	PANO+BORT+DEX AE incidence rate, % PANORAMA 2	Bendamustine	POM+DEX AE incidence rate, % MM-003[57]	Disutility	Duration (Days)	QALY decrement	Disutility source
								2013[156]/Partial Review TA171[157]
Hypophosphatemia	NR	6%	NR	NR	-0.07	28	0.00	Partial Review TA171[157]
Nausea (all grades)	6%	60%	15%	15%	-0.10	28	-0.01	Lloyd 2006[158]
Diarrhoea	NR	20%	NR	NR	-0.10	28	-0.01	Lloyd 2006[158]
Fatigue	2%	20%	5%	5%	-0.12	28	-0.01	Lloyd 2006[158]
Asthenia	NR	9%	NR	NR	-0.12	28	-0.01	Assumed the same as fatigue
Dyspnoea	0%	NR	5%	5%	-0.12	28	-0.01	Assume the same as fatigue[158]
Back pain	4%	NR	5%	5%	-0.07	28	0.00	Assumed the same as peripheral neuropathy
Peripheral neuropathy (all grades)	NR	NR	2%	2%	-0.10	28	0.01	Clinical Opinion
Flatulence	NR	5.50%	NR	NR	0.00	28	0.00	Assumed
Abdominal Pain	NR	5.50%	NR	NR	-0.05	28	0.00	Sullivan et al.

AE	Daratumumab AE incidence rate, % Weighted average of MMY2002 and GEN501, Jan 2015 data cut[95]	PANO+BORT+DEX AE incidence rate, % PANORAMA 2	Bendamustine	POM+DEX AE incidence rate, % MM-003[57]	Disutility	Duration (Days)	QALY decrement	Disutility source
								2011[160]
Abdominal distention	NR	7.30%	NR	NR	-0.05	28	0.00	Sullivan et al. 2011[160]
Hypokalaemia	NR	7.27%	NR	NR	-0.20	0.02	0.00	Clinical Opinion
Dehydration	NR	5.45%	NR	NR	0.00	28	0.00	Assumed
Hypotension	NR	9.09%	NR	NR	-0.07	0.01	0.00	Clinical Opinion
Septic Shock	NR	5.50%	NR	NR	-0.20	28	0.01	Tolley et al. 2013[159]
Syncope	NR	9.10%	NR	NR	-0.10	28	0.01	Clinical Opinion
Sepsis	NR	9.09%	NR	NR	-0.20	28	0.01	Tolley et al. 2013[159]
Key: AE, adverse event; BORT, bortezomib; DEX, Dexamethasone; NR, not reported; PANO, panobinostat; QALY, quality-adjusted life year.								

5.4.5 Health-related quality-of-life data used in cost-effectiveness analysis

As described in Section 5.4.3, disease-progression-specific utility estimates from MM-003 are used in the model base-case.[154] The approach to capture AE disutility was set out in Section 5.4.4. These utility assumptions are summarised in Table 60. The utility values used may be considered conservative as they do not account for differences in response across treatments and as such will not capture the impact of the superior clinical effectiveness profile of daratumumab on utility. Furthermore, utility estimates are based on EQ-5D which is known to be limited in its ability to capture the impact of fatigue on QoL. Fatigue is a common symptom of myeloma and a side effect that is particularly associated with POM+DEX. This conservative approach to utility is explored to some extent by using alternative health-state utility assumptions from TA338 and TA380. However, whilst utility values from TA338 and TA380 used in scenario analysis are higher than those used in the base case, differences with respect to response across treatments are still not captured.

Table 60: Summary of model utility data

State	**Utility value**	**Confidence interval**	**Source**
Pre-progressive disease	0.61	0.59, 0.63	Palumbo 2013[154]
Progressive disease	0.57	0.55, 0.59	Palumbo 2013[154]
Adverse event	**Utility decrement**	**Confidence interval**	**Source**
Febrile neutropenia	-0.39	-0.24, -0.55	Launois 1996
Neutropenia	-0.15	-0.09, 0.21	Brown 2013[156]/Partial Review TA171[157]
Anaemia	-0.31	-0.20, 0.44	Brown 2013[156]/Partial Review TA171[157]
Thrombocytopenia	-0.31	-0.20, 0.44	Brown 2013[156]/Partial Review TA171[157]
Lymphopenia	-0.07	-0.04, -0.09	Assume lowest in range (Partial Review TA171)[157]
Leukopenia	-0.07	-0.04, -0.09	Assume lowest in range (Partial

			Review TA171)[157]
Upper respiratory infection (all grades)	-0.19	-0.12, -0.27	Assume the same as pneumonia
Pneumonia	-0.19	-0.12, -0.27	Brown 2013[156]/Partial Review TA171[157]
Hypophosphatemia	-0.07	-0.04, -0.09	Partial Review TA171[157]
Nausea (all grades)	-0.10	-0.07, -0.15	Lloyd 2006[158]
Diarrhoea	-0.10	-0.07, -0.15	Lloyd 2006[158]
Fatigue	-0.12	-0.07, -0.16	Lloyd 2006[158]
Asthenia	-0.12	-0.07, -0.16	Assumed the same as fatigue
Dyspnoea	-0.12	-0.07, -0.16	Assume the same as fatigue[158]
Back pain	-0.07	-0.04, -0.09	Assumed the same as peripheral neuropathy
Peripheral neuropathy (all grades)	-0.10		Clinical Opinion
Flatulence	0.00	0,0	Assumed
Abdominal Pain	-0.05	-0.03, -0.07	Sullivan et al. 2011[160]
Abdominal distention	-0.05	-0.03, -0.07	Sullivan et al. 2011[160]
Hypokalaemia	-0.20		Clinical Opinion
Dehydration	0.00	0,0	Assumed
Hypotension	-0.07		Clinical Opinion
Septic Shock	-0.20	-0.12, -0.28	Tolley et al. 2013[159]
Syncope	-0.10		Clinical Opinion
Sepsis	-0.20	-0.12, -0.28	Tolley et al. 2013[159]
Key: AE, adverse event; HS, health state.			

5.5 Cost and healthcare resource use identification, measurement and valuation

Costs used within the model reflect the UK NHS perspective and consisted of four components:

- Drug acquisition costs (including administration costs and concomitant medication)
- Treatment monitoring cost
- Costs for management of adverse events
- Costs of subsequent treatments
- End-of-life care costs

5.5.1 Resource identification, measurement and valuation studies

A systematic review was performed in January 2016 to identify resource use evidence relevant for patients with rrMM or MM treated within the NHS in England. The search strategy, and further details are fully documented in Appendix 13.

To be included in this systematic review, references had to meet the inclusion criteria (and none of the exclusion criteria) detailed in Table 61.

Table 61: Inclusion and exclusion criteria for cost-effectiveness studies

	Inclusion	**Exclusion**
Study population	Adult patients with MM	No adult MM patients
Intervention	No restriction by treatment. Untreated patients included.	None
Outcome	Any outcomes quantifying the costs and/or resource use requirements of advanced melanoma and its management. Any outcomes quantifying the costs and/or resource use associated with disease or treatment related adverse events. Costs should be reported as incurred by the NHS in the UK.	None
Study types	Cost and/or resource use studies and economic evaluations.	None
Publication types	None	Letters and comment articles.
Language	Studies reported in English	Studies not reported in English
Other	Studies must present sufficient detail of the methodology used and provide extractable results.	Publications that fail to present sufficient methodological detail or extractable results.

	Inclusion	Exclusion
Key: MM, multiple myeloma; NHS, National Health Service		

Six studies were identified through systematic database searches[26, 46, 154, 156, 162, 163]. These studies are summarised in Appendix 13. Data from these studies were considered alongside evidence from NICE TA338 and TA380.

Two of the six identified studies disseminate evidence from the NICE appraisal of bortezomib (TA129)[46, 162], which is recommended in England and Wales for a restricted population of progressive MM patients who have relapsed after first-line treatment. The relapsed and refractory patients who stand to benefit from daratumumab are at a later stage of the treatment pathway, and as such are expected to have different resource use requirements. In addition, the key data from these studies is now more than a decade old. These studies are therefore of limited use for the purpose of this appraisal.

Two further included studies relate to the use of lenalidomide in clinical practice. The analysis by Brown et al. of the cost-effectiveness of lenalidomide in England and Wales was based on materials from NICE TA171 (lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy)[156], while Palumbo et al.[154] published a review and recommendations for the clinical management of lenalidomide outside of trial settings.[46, 154, 162]

A further included study comprises a systematic review of bisphosphonates in metastatic disease.[163] Bisphosphonates can be used to prevent skeletal-related events in multiple myeloma, but are thought not to be of direct comparative relevance for the purpose of this appraisal.

The final study in the review is a retrospective analysis of medical resource utilisation (MRU) costs, drug costs and clinical outcomes for 39 UK patients whose multiple myeloma is relapsed and/or refractory to bortezomib and lenalidomide.[26] Gooding et al. report MRU by resource category, reporting frequency and cost estimates for inpatient admissions and other attendances, invasive and radiological procedures, supportive therapy, transfusions and blood tests.[26] It should be noted however that

this study is based on a small number of patients and thus MRU from this study is subject to a degree of uncertainty.

Descriptions of resource use and cost assumptions were identified in the manufacturer submissions to NICE for both TA338 and TA380.

The resource use assumptions in TA380 were taken from the PANORAMA 1 clinical trial. The patients in this trial were in an earlier treatment line than those in MMY2002 and GEN501. Since patients at an earlier treatment line are expected to require different resource use, TA380 was not considered an appropriate source for this submission. Manufacturer assumptions from TA338 however are useful to inform assumptions in the economic model. The TA338 cost and resource use systematic review included only three UK studies.[156, 164, 165] Two were identified by our search[156, 165], although one was excluded as it is a conference abstract reporting limited information.[165] Another was a cost analysis of a bisphosphonate for treated and untreated patients published by Bruce et al. (1999).[164] MRU assumptions in TA338 are reported in Table 62. These were based on the ERG's model in NICE TA228, the appraisal of bortezomib and thalidomide for the first-line treatment of multiple myeloma. These assumptions led to an estimated cost for a lifetime of disease management per POM+DEX-treated patient of £3,965. [50]

In addition to the resources in Table 62, the manufacturer in NICE TA338 included costs associated with red blood count and platelet transfusions, as well as additional monitoring costs for POM+DEX patients in their first eight weeks of treatment, in line with the product's SmPC. Estimated mean per-patient lifetime costs for POM+DEX were £3,263, comparable to the lifetime cost of other resources associated with disease management.[50]

Table 62: NICE TA338 manufacturer resource use assumptions

Disease management, medical resource use item	Rate per year, PFS	Rate per year, PPS
Haematologist clinical visit, on treatment	12	0
Haematologist clinical visit, off treatment	4	4
Full blood count	10.7	20.1
Biochemistry	9.7	17.3
Protein electrophoresis	6.7	9.6

Immunoglobulin	6.4	9.7
Urinary light chain excretion	2.7	4.9
Key: NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; PPS, post-progression survival; TA, technology appraisal.		

5.5.2 Intervention and comparators' costs and resource use

Acquisition costs for daratumumab, POM+DEX, PANO+BORT+DEX, and bendamustine are presented in Table 63. The list price for daratumumab is used. Janssen is aware that both POM+DEX and PANO+BORT+DEX have simple Patient Access Schemes (PAS) however these are confidential and thus all economic modelling is carried out using list prices.

A clinical validation meeting highlighted that in clinical practice bendamustine is rarely given as a therapy on its own and 60% of the time would be given with thalidomide and dexamethasone (THAL+DEX), 30% of the time bendamustine would be given with steroids only and 10% of the time bendamustine would be given alone.

Table 64 details the treatment dosing schedules for daratumumab, POM+DEX, PANO+BORT+ DEX, and bendamustine-based treatment. The doses and treatment schedule for daratumumab are consistent with the EMA European Public Assessment Report (EPAR),[10] doses and treatment schedule for POM+DEX are consistent with the EMA EPAR for pomalidomide,[128] and the doses and treatment schedule for PANO+BORT+ DEX are consistent with the EMA EPAR for panobinostat.[129] The dosing schedule for bendamustine is consistent with the the standard dosing regimen used in clinical practice, as advised by Professor Kwee Yong.[42]

Since daratumumab and POM+DEX are given until disease progression or unacceptable toxicity, TTD analyses are used to capture time until treatment withdrawal in the economic analysis, as described in 5.3.3. Since no TTD is available for PANO+BORT+DEX, it is administered for a maximum of 16 treatment cycles in the economic model; bendamustine is also given until progression. This assumption was considered reasonable as per expert clinical opinion.[42] Administration costs

associated with daratumumab and the comparators are presented in Table 65. A cost for the oral administration is included as a one-off cost in the first model cycle.

To calculate the number of daratumumab vials required per administration for an average patient in the NHS in England, while accounting for wastage, weight data from European patients from the integrated daratumumab cohort (MMY2002/GEN501) were used. Dosing based on method-of-moments weight distribution estimation, using patient weight data, were applied to estimate the mean number of vials required in the base-case. The method assumes a normal distribution for body weight (mean and standard deviation of patient weight 73.91 kg and 15.25 kg) and calculates the proportion of patients requiring each possible number of vials.[166] This calculation is an accurate method of accounting for wastage, assuming that no vial sharing occurs. A similar method has been used in the recent bortezomib NICE appraisal (NICE TA307).[167] Based on the method of moments calculation and the acquisition costs listed in Table 63, the mean treatment acquisition cost per administration of daratumumab (at list price) in the model is £4,437.39.

The method of moments technique described above was also used to calculate the number of vials required per administration for an average patient in the NHS in England while accounting for wastage for bortezomib (when administered as part of PANO+BORT+DEX) and bendamustine using the body surface area (BSA) rather than weight. BSA was calculated from the weight data from European patients from the integrated daratumumab cohort (MMY2002/GEN501) and height data from the whole dataset using the Dubois Formula.[168] It is justified to use weight data from European patients and height data from the whole trial population, as it is not expected that the height distribution would differ by country but it is known that weight distribution does. The cost per administration for bortezomib and bendamustine are reported in Table 63.

Table 63: Treatment formulations and acquisition costs

Drug	Formulation	Cost per vial/pack (at list price)	Vials/tabs per pack	Cost per mg	Cost per administration
Daratumumab	100mg	£360.00	1	£3.60	£4,437.39
	400mg	£1,440.00		£3.60	
Pomalidomide	4mg	£8,884.00	21	£105.76	NA
Dexamethasone	2mg	£78.00	100	£0.39	NA
Panobinostat	10mg	£3,492.00	6	£58.20	NA
	15mg	£3,492.00		£38.80	
	20mg	£4,656.00		£38.80	
Bortezomib	4mg	£217.82	1	£217.82	£762.38
Bendamustine	25mg	£347.26	5	£2.78	£991.33 (150mg/m2) £388.51 (60mg/m2)
	100mg	£1,379.04		£2.76	

Table 64: Treatment dosing schedules

Drug	Dose per administration	Administration method	Dosing cycle	Dosing schedule*	Treatment duration
Daratumumab	16mg/kg	Complex chemotherapy with prolonged infusion	28 days	Days 1, 8, 15 and 22 of each cycle in Cycles 1-2, then Days 1 and 15 of each cycle in Cycles 3-6, then Day 1 of each cycle for subsequent cycles	TTD data from pooled MMY2002 and GEN501
Pomalidomide	4mg	Oral	28 days	Days 1-21 of each cycle	TTD data from MM-003[57]
Dexamethasone (with POM)	40mg	Oral	28 days	Days 1, 8, 15 and 22 of each cycle	TTD data from MM-003[57]
Dexamethasone (with PANO)	20mg	Oral	21 days	Days 1, 2, 4, 5, 8, 9, 11 and 12 for first 8 cycles, Days 1, 2, 8 and 9 for cycles 9 – 16	Maximum of 16 treatment cycles or until progression
Panobinostat	20mg	Oral	21 days	Days 1, 3, 5, 8, 10 and 12 for first 8 cycles, Days 1, 3, 5, 8, 10 and 12 for cycles 8 – 16	Maximum of 16 treatment cycles or until progression
Bortezomib (with PANO)	1.3mg/m²	Injection	21 days	Days 1, 2, 8 and 9 for cycles 8 - 16. Days 1, and 8 for the first 8 cycles	Maximum of 16 treatment cycles or until progression
Bendamustine (alone or with steroids)	150.0mg/m²	Complex chemotherapy	28 days	Bendamustine is administered as an IV treatment on days 1 and 2 of a 28-day cycle	Until progression
Bendamustine (with THAL+DEX)	60mg/m^2	Complex Chemotherapy	28 days	Bendamustine is administered as an IV treatment on days 1 and 8 of a 28-day cycle	Until Progression
Thalidomide (with BENDA)	50mg	Oral	28 days	Daily	Until Progression

Dexamethasone (with BENDA)	40mg	Oral	28 days	Days 1, 8, 15 and 22	Until Progression

Key: EMA, European Medicines Agency; EPAR, European public assessment report; POM, pomalidomide; PANO, panobinostat; BORT, bortezomib; DEX, dexamethasone; SmPC, summary of product characteristics; TTD, Time to treatment discontinuation.
Notes: *Dosing schedules are applied until disease progression or unacceptable toxicity unless stated otherwise. The dosing schedule for daratumumab reflects that in Study MMY2002 and draft EMA product label; the dosing schedule for pomalidomide plus dexamethasone reflects that in the EMA EPAR for pomalidomide.[128] The dosing schedule for PANO + BORT + DEX reflects that in the EMA EPAR for panobinostat.[129] The dosing schedule for bendamustine and chemotherapy are consistent with the corresponding SmPCs.[130]

Table 65: Treatment administration costs

Regimen	Type of administration	Doses applied	Cost	NHS Reference Costs 2014-15 Code
Daratumumab	First complex infusion	1st dose only	£414	SB14Z Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance
	Subsequent complex infusions	All subsequent doses	£362	SB15Z Deliver subsequent elements of a chemotherapy cycle
POM+DEX	Oral drug initiation	1st dose only	£192	SB11Z Deliver Exclusively Oral Chemotherapy
Panobinostat	Oral drug initiation	1st dose only	£192	SB11Z Deliver Exclusively Oral Chemotherapy
Bortezomib	Injection	Per dose	£257	SB12Z Deliver simple Parenteral Chemotherapy at first attendance
Bendamustine	First complex infusion	1st dose only	£414	SB14Z Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance
	Subsequent complex infusions	All subsequent doses	£362	SB15Z Deliver subsequent elements of a chemotherapy cycle
Thalidomide	Oral	1st dose only	£192	SB11Z Deliver Exclusively Oral Chemotherapy

Key: POM; pomalidomide, DEX, dexamethasone; NHS, National Health Service.

5.5.2.1 Concomitant treatment

Prior to each daratumumab administration, corticosteroid, antipyretic and antihistamine treatments are required. To account for the costs of these medicines in the economic analysis, treatment acquisition costs are included as described in Table 66 and Table 67

Anti-coagulation therapy is recommended alongside POM+DEX, unless a patient is contraindicated. Acquisition costs for such therapies are included in the economic analysis, and are reported in Table 66 and Table 67.

All patients receiving bendamustine must be also administered a corticosteroid intravenously.[92] This is reported in Table 66 and Table 67.

Some patients require granulocyte-colony stimulating factor (GCSF) treatment and blood transfusions as part of supportive care. Across MMY2002 and GEN501, 132 RBC transfusions were required by 44 (29.7%) patients (an average of three transfusions per patient over the trial period), 67 platelet transfusions were required by 14 (9.5%) patients (an average of 4.79 transfusions per patient over the trial period), and 12 (8.1%) patients required GCSF (assumed to be administered once per patient).[97] Of the patients receiving POM+DEX, 43% required GCSF, 49% received RBC transfusions and 20% received platelet transfusions.[50] The number of transfusions and GCSF treatments per patient was assumed to be the same as observed in the daratumumab clinical trials as this was considered reflective of clinical practice when validated by a clinician practicing in NHS England.[42] This is shown in Table 68.

No concomitant medication information is reported in the PANORAMA2 trial report.[58] Clinical opinion suggests that 20% of patients receiving PANO+BORT+DEX would require GCSF and 20% would require transfusion. [42] It is assumed that the number of transfusions would be equivalent to that observed in the daratumumab clinical trials.[42] This is shown in Table 68.

Upon Consultant Haematologist review it was advised that it would be reasonable to assume that the proportion and number of GCSF and transfusions required for patients receiving bendamustine would be the same as observed in the daratumumab clinical trials. [42] This is shown in Table 68.

Costs associated with platelet and RBC transfusion were taken from NICE TA338 and updated to the latest costs available. These are reported in Table 68 and, for simplicity, are applied as a one-off cost on the first cycle.

Table 66: Concomitant treatment formulations and acquisition costs

Co-medication	Formulation	Cost per vial/pack*	Vials/tabs per pack	Cost per mg
Corticosteroid (methylprednisolone IV)	125mg	£4.75	1	£0.04
Antipyretic (acetaminophen)	500mg	£0.43	100	£0.00
Antihistamine (cetirizine hydrochloride)	10mg	£0.19	30	£0.00
Acetylsalicylic acid	75mg	£0.47	100	£0.00
Key: IV, intravenous. **Notes:** *Latest Drugs and pharmaceutical electronic market information (eMIT) estimates.[169]				

Table 67: Concomitant treatment doses and cost per treatment administration

Treatment	Co-medication	Dose per administration*	Cost per treatment administration
Daratumumab	Corticosteroid (methylprednisolone IV)	60mg	£2.28
	Antipyretic (acetaminophen)	1000mg	£0.01
	Antihistamine (cetirizine hydrochloride)	10mg	£0.01
POM+DEX	Acetylsalicylic acid	325mg	£0.02
Bendamustine	Corticosteroid (methylprednisolone IV)	60mg	£2.28
PANO+BORT +DEX	None		
Key: BORT, bortezomib; DEX, dexamethasone; IV, intravenous; PANO, panobinostat; POM, pomalidomide. Notes: *Latest Drugs and pharmaceutical electronic market information (eMIT) estimates.[169]			

Table 68: GCSF, RBC Transfusions and Platelet Transfusions, one-off cost used

Treatment	Concomitant drug name	% patients receiving	Number per patient	Unit cost	One-off cost applied
Daratumumab	GCSF	8%	1.00	£52.70	£202.38
	RBC Transfusion	30%	3.00	£121.85[170]	
	Platelet Transfusion	10%	4.79	£196.96[170]	
POM+DEX	GCSF	43%[50]	1.00	£52.70	£390.30
	RBC Transfusion	49%[50]	3.00	£121.85[170]	
	Platelet Transfusion	20%[50]	4.79	£196.96[170]	
PANO+BORT +DEX	GCSF	20%[42]	1.00	£52.70	£272.17
	RBC Transfusion	20%[42]	3.00	£121.85[170]	
	Platelet Transfusion	20%[42]	4.79	£196.96[170]	
Bendamustine	GCSF	8%	1.00	£52.70	£202.38
	RBC Transfusion	30%	3.00	£121.85[170]	
	Platelet Transfusion	10%	4.79	£196.96[170]	

Key: BORT, bortezomib; DEX, dexamethasone; GCSF, granulocyte colony-stimulating factor; POM, pomalidomide; PANO, panobinostat; RBC, red blood cell.

5.5.3 Health-state unit costs and resource use

The MRU and respective unit costs attributed to the management of disease in patients treated with the intervention and the comparators are shown in Table 69 and Table 70. It is assumed that all treatment arms would require the same resource use. Disease management is assumed to comprise haematological physician visits, blood count tests and biochemistry, and to vary by status of disease progression and by treatment. For consistency with previously accepted appraisals, the estimates of MRU were sourced directly from NICE TA338, which considered therapy at a similar

line to that of this submission. These estimates were validated at NHS Consultant Haematologist review as reflective of clinical practice.[42]

Table 69: Resource use associated with model health states, by treatment

Health state	Resource	Frequency per week	Source
PFS (on treatment)	Physician visit	0.23	NICE TA338 [50]
	Complete blood count test	0.21	
	Biochemistry	0.19	
PFS (off treatment)	Physician visit	0.08	
	Complete blood count test	0.21	
	Biochemistry	0.19	
PPS, subsequent active treatment	Physician visit	0.08	
	Complete blood count test	0.39	
	Biochemistry	0.33	
PPS, BSC	Physician visit	0.08	
	Complete blood count test	0.39	
	Biochemistry	0.33	

Key: BSC, best supportive care; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; PPS; post-progression survival; TA, Technology Appraisal.

Table 70: Model health state resource costs

Medical resource	Cost	Source
Physician visit	£162.02	National Schedule of Reference Costs - Year 2014-15 - NHS trusts and NHS foundation trusts – Chemotherapy (Total National Average Costs) Services Code 303: Clinical Haematology
Complete blood count test	£3.01	National Schedule of Reference Costs - Year 2014-15 - NHS trusts and NHS foundation trusts – Chemotherapy (Total National Average Costs) DAPS05: Haematology
Blood chemistry	£1.19	National Schedule of Reference Costs - Year 2014-15 - NHS trusts and NHS foundation trusts – Chemotherapy (Total National Average Costs) DAPS04: Clinical biochemistry

Key: NHS, National Health Service.

5.5.4 Adverse reaction unit costs and resource use

The costs associated with each AE included in the economic model (described in Section 5.4) were sourced from the 2014/2015 NHS Reference Cost database[171]; these costs and associated disease codes are summarised in Table 71.

Table 71: Adverse event costs

Adverse event	Treatment cost	NHS Reference Costs 2014-15[171] Code
Febrile neutropenia	£6,697.31	PA45Z (NHS 2011/2012) Febrile Neutropenia with Malignancy
Neutropenia	£1,096.05	Weighted average of the codes: SA08G, SA08H, SA08J for Other Haematological or Splenic Disorders
Anaemia	£788.00	Weighted average of the codes: SA04G, SA04H, SA04I, SA04J, SA04K, SA04L for Iron Deficiency Anaemia
Thrombocytopenia	£617.55	Weighted average of the code: SA12G, SA12H, SA12J, SA12J, SA12K for Thrombocytopenia
Lymphopenia	£1,096.05	Weighted average of the codes: SA08G, SA08H, SA08J for Other Haematological or Splenic Disorders
Leukopenia	£1,096.05	Weighted average of the codes: SA08G, SA08H, SA08J for Other Haematological or Splenic Disorders
Upper respiratory infection (all grades)	£759.21	Weighted average of the codes: DZ19D, DZ19E, DZ19F, DZ19G for Other Respiratory Disorders
Pneumonia	£1,965.45	Weighted average of the codes: DZ11D, DZ11E, DZ11F, DZ11G, DZ11H, DZ11J for Lobar, Atypical or Viral Pneumonia and DZ23D, DZ23E, DZ23F, DZ23G for Bronchopneumonia
Hypophosphatemia	£1,249	Weighted average of the codes: KC05G, KC05H, KC05J, KC05K, KC05L, KC05M, KC05N for Fluid or Electrolyte Disorders, without Interventions
Diarrhoea	£1,165	Weighted average of the codes: FZ91J, FZ91K, FZ91L, FZ91M for Non-Malignant Gastrointestinal Tract Disorders without Interventions
Nausea (all grades)	£727.55	WA21Z: Other Procedures or Health Care Problems
Vomiting	£727.55	WA21Z: Other Procedures or Health Care Problems
Fatigue	£727.55	WA21Z: Other Procedures or Health Care Problems
Asthenia	£727.55	WA21Z: Other Procedures or Health Care Problems
Dyspnoea	£216.66	DZ46Z: Respiratory Muscle Strength Studies. Service code 258
Back pain	£863.18	Weighted average of the codes: HC32D, HC32E, HC32F

Adverse event	Treatment cost	NHS Reference Costs 2014-15[171] Code
		for Low Back Pain
Peripheral neuropathy (all grades)	£643.85	AB10Z: Unspecified Pain Procedures
Flatulence	£0	Assumed
Abdominal Pain	£2,410	FZ90A: Abdominal Pain with intervention
Abdominal distention	£2,410	FZ90A: Abdominal Pain with intervention
Hypokalaemia	£1,249	Weighted average of the codes: KC05G, KC05H, KC05J, KC05K, KC05L, KC05M, KC05N for Fluid or Electrolyte Disorders, without Interventions
Dehydration	£0	Assumed
Hypotension	£1,096	Weighted average of the codes: SA08G, SA08H, SA08J for Other Haematological or Splenic Disorders
Septic Shock	£2,973	WH07D: Infections or Other Complications of Procedures, with Single Intervention, with CC
Syncope	£0	Assumed
Sepsis	£2,973	WH07D: Infections or Other Complications of Procedures, with Single Intervention, with CC
Key: CC, complications and comorbidity; NHS, National Health Service.		

5.5.5 Miscellaneous unit costs and resource use

5.5.5.1 Subsequent treatment costs

Similar to routine practice, rrMM patients in the daratumumab Phase II studies went on to receive subsequent active therapy. Across the integrated dataset, 72% of patients received subsequent active treatment following discontinuation of daratumumab; the distribution of subsequent therapies is shown in Table 72. Clinical opinion suggested that although this figure is high compared to what is seen in clinical practice, patients receiving daratumumab are more likely to go on to receive subsequent therapy due to its mechanism of action.[42]. Clinical opinion also suggests the proportion of patients who receive subsequent therapy after daratumumab is 55%, which is similar to the proportion report in MMY2002.[42] The proportion and distribution of patients who receive subsequent therapy to POM+DEX (39.4%) is sourced from NICE TA338 (Table 72).[50] Clinical opinion suggests that the proportion

of bendamustine patients who would go on to receive subsequent treatment would be similar to that of POM+DEX but that PANO+BORT+DEX would be greater than this as PANO+BORT+DEX is generally used in less refractory patients.

It is assumed that the subsequent treatments received in clinical practice would reflect those received by patients in the respective daratumumab and POM+DEX trials. Given the predominant equity in treatments available to patients in the daratumumab and POM+DEX trials along with the immunomodulatory benefits and tolerability of daratumumab, it is inferred that the higher level of subsequent treatment seen following daratumumab is a result of the improved health status of patients.

Table 72 displays the distribution of subsequent treatment. For daratumumab this has been sourced from the integrated MMY2002/GEN501 and some changes made based on clinical opinion. For POM+DEX, this has been sourced from MM-003 and it is assumed that PANO+BORT+DEX and bendamustine follow the same distribution.[79]

To account for the cost of subsequent therapy in the economic analysis, a cost was included upon treatment progression. Table 73 shows weekly acquisition costs for the treatments in Table 72.

To understand the average duration of treatment for fifth-line patients, HMRN data (2004-2013) were consulted.[42] The mean duration of treatment for patients receiving 5th line treatment in the HMRN dataset was 94 days[172] and thus duration of subsequent treatment was assumed to be 94 days in the economic model.

Table 72: Distribution of subsequent treatments

Subsequent treatment	Proportion of MMY2002 patients	Proportion of PANORAMA 2[58] patients	Bendamustine[42]	Proportion of MM003 patients[50]
Dexamethasone	44%	25%	25%	25%
Pomalidomide	0%	0%	0%	0%
Cyclophosphamide	24%	17%	17%	17%
Carfilzomib	0%	0%	0%	0%
Bortezomib	0%	15%	15%	15%
Melphalan	17%	0%	0%	0%
Etoposide	11%	0%	0%	0%
Bendamustine	0%	10%	10%	10%

Table 73: Drug formulation, dose, administration, proportion of doses received and total drug acquisition cost per week, subsequent treatments

Subsequent treatment	Formulation	Cost per vial/pack	Vials/tabs per pack	Dose per administration	Doses per week	Drug Cost per week	Admin cost per week	Source
Dexamethasone	2mg	£50.31	100	40mg	3.00	£30.19	£192*	
Pomalidomide	4mg	£8,884.00	21	4mg	5.25	£2,221.00	£192*	
Cyclophosphamide	500mg	£9.00	1	450mg/m²	1.00	£8.10	£192*	DoH, eMIT[169]
Carfilzomib	60mg	£1,056.00	1	20mg/m²	1.50	£528.00	£1,542	MIMS[b]
Bortezomib	4mg	£762.38	1	1mg/m²	1.33	£377.56	£1,028	MIMS[c]
Melphalan	2mg	£45.38	25	150mg/m²	0.67	£90.76	£192*	MIMS[d]
Etoposide	100mg	£12.15	1	100mg/m²	1.25	£15.19	£1,285	MIMS[e]
Bendamustine	100 mg	£1,379.04	5	100 mg/m²	0.50	£137.90	£514	MIMS[f]

Key: DoH, Department of Health; eMIT, electronic Market Information Tool; MIMS, Monthly Index of Medical Specialities; tabs, tablets.
Notes: a One-off oral chemotherapy admin cost, not induced weekly; b (antineoplastics – Kyprolis); c (antineoplastics – Velcade); d (antineoplastics – melphalan); e (antineoplastics – etoposide); f antineoplastics – bendamustine).

5.5.5.2 End-of-life care costs

In TA338, expert opinion was used to inform resource use assumptions around terminal care. Terminal care was assumed to be distributed across hospital services (20%), hospice services (40%) and home services (40%), and daily costs were obtained from the National Audit Office. These terminal care costs were assumed to be incurred in the last week of life. Inflating to 2012/13 costs using the Personal Social Services Research Unit (PSSRU) inflation indices, the mean end-of-life cost was £853.58.[50] To ensure consistency across appraisals, the same end-of-life cost assumptions have been applied in this economic appraisal.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of base-case de novo analysis inputs

A summary of all the variables used in the economic model is provided in Appendix 14.

5.6.2 Assumptions

Key assumptions in the model are summarised in Table 74.

Table 74: Key assumptions in the economic base-case and their justification

Assumption	Justification
Mortality risk is applied exclusively from the trial. No distinction is made between mortality related to MM or unrelated to MM	Given the short life expectancy of patients with rrMM, only trial data were used to model the OS of patients, i.e. no general population mortality was considered additionally
The model structure accurately reflects the disease and is sufficient to address the decision problem	Informed by systematic review and validated at Consultant Haematologist review
Assumptions required to compare single-arm trial data outcomes for daratumumab to comparator trial data	Key assumptions justified and tested thoroughly wherever possible
Health-state specific utility estimates are assumed to be the same for all treatment arms	Conservative assumption based on available data
Health-state specific resource use is	Validated at Consultant Haematologist

Assumption	Justification
assumed to be the same for all treatment arms	review and consistent with TA338
Proportional hazards assumption holds	Alternative non-PH methods were explored to test sensitivity of model results to structural assumption
The important prognostic factors selected for MAIC are applicable to both OS and PFS	Patient demographics that have an impact on survival are also expected to impact PFS
There are no unmeasured confounders	Cannot adjust for unmeasured confounders. The impact of this is expected to be minimal versus POM+DEX as it was possible to adjust for all prognostic factors considered important by expert clinicians. However, it was not possible to adjust for refractrory status (other than to bortezomib) versus PANO+BORT+DEX and this is likely to have introduced bias against daratumumab.
Bortezomib as part of PANO+BORT+DEX and BORT+DEX is assumed to be administered subcutaneously	Reflective of clinical practice
Key: BORT, bortezomib; DEX, dexamethasone; OS, overall survival, PANO, panobinostat; PH, proportional hazards; PFS, progression-free survival; rrMM, relapsed/refractory multiple myeloma.	

5.7 Base-case results

5.7.1 Base-case cost-effectiveness analysis results

The base-case results for daratumumab versus POM+DEX, PANO+BORT+DEX and bendamustine, based on the list-price for all interventions, are presented in Table 75 Due to the nature of the MAIC analyses, it is not appropriate to collate results into a fully incremental analysis. This is because the MAIC adjusts the daratumumab IPD to match the characteristics of patients in the comparator clinical trial (i.e., MM-003 and PANORAMA 2). The comparative efficacy is then calculated between the comparator and this adjusted daratumumab efficacy data. As such, the effective population of daratumumab patients varies between the two comparisons versus POM+DEX and PANO+BOR+DEX; in effect, the MAIC produces matched pairwise comparisons. Furthermore, comparing comparative effectiveness estimates derived using MAIC directly with those derived utilsing a multivariate regression analysis

(such as in the case against bendamustine-based therapy) is also inappropriate. Base-case pairwise deterministic ICERs show that, albeit an end-of-life indication, daratumumab monotherapy is cost-effective against PANO+BORT+DEX at standard WTP thresholds. At list price, daratumumab is associated with 0.19 incremental QALYs at an incremental cost of £4,541 to derive an ICER of £24,109 per QALY gained.

However, it is important to acknowledge that the most important and relevant comparison in the decision problem is that of daratumumab monotherapy versus POM+DEX. POM+DEX is the most likely intervention to be displaced in NHS England with the introduction of daratumumab, whereas both PANO+BORT+DEX and bendamustine have lower, more restricted use, as evidenced by market share figures. In comparison to POM+DEX, daratumumab monotherapy generates 0.54 incremental QALYs, at an incremental cost of £29,150. Hence, deriving an ICER of £53,804 per QALY gained (at list price), slightly higher than the applicable end-of-life WTP threshold.

When comparing with bendamustine-based therapy, daratumumab monotherapy shows clear incremental benefit through 0.74 QALYs at an incremental cost of £40,744 (at list price). These results derive an ICER of £55,161 per QALY gained, also slightly above end-of-life WTP thresholds.

Table 75: Pairwise base-case results

	Total			Incremental			ICER (Dara vs comparator) at list prices
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Daratumumab	£79,071	1.36	2.54				
POM+DEX	£49,921	0.81	1.46	£29,150	0.54	1.07	£53,804
PANO+BORT +DEX	£74,530	1.17	2.14	£4,541	0.19	0.39	£24,109
Bendamustine-based therapy	£38,327	0.62	1.10	£40,744	0.74	1.44	£55,161
Key: BORT, bortezomib; DEX, dexamethasone; Dara, daratumumab; year; ICER, incremental cost-effectiveness ratio; LY, life year; PANO, panobinostat; POM, pomalidomide; QALY, quality-adjusted life.							

5.7.2 Clinical outcomes from the model

Table 76 compares the median estimates of key clinical outcomes from the integrated MMY2002/GEN501 analysis with model predictions of the same outcomes; results show consistency between the clinical trial and model results.

Table 76: Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
PFS – daratumumab	Median 4.0 months	Median 4.4 months
OS – daratumumab	Median 20.1 months	Median 20.9 months
Key: PFS, progression-free survival; OS, overall survival.		

As a consequence of applying HRs (derived from the MAICs) to the results from the integrated daratumumab cohort, the model predicts outcomes as if patients enrolled in MMY2002/GEN501 had received treatment with POM+DEX or PANO+BORT+DEX. Therefore, it is important to note that as a result, it is not appropriate to directly compare the modelled results for POM+DEX to the results from MM-003 [57] or the modelled results for PANO+BORT+DEX to the results from PANORAMA2.[58]

5.7.3 Disaggregated results of the base-case incremental cost-effectiveness analysis

The disaggregated costs are presented in Table 77 and Table 78.

The disaggregated QALYs by health state are presented in Table 79, and disaggregated life years in Table 80.

Table 77: Disaggregated costs

		POM+DEX				PANO+BORT+DEX				Bendamustine-based therapy			
	Daratumumab	POM+DEX	Incremental	Absolute Increment	% Increment	PANO+BORT+DEX	Incremental	Absolute Increment	% Increment	Bendamustine-based therapy	Incremental	Absolute Increment	% Increment
Drug costs (at list price)	£68,862	£44,590	£24,271	£24,271	74%	£60,532	£8,329	£8,329	65%	£30,853	£38,009	£38,009	87%
Admin costs	£5,670	£191	£5,479	£5,479	17%	£7,398	-£1,728	£1,728	14%	£2,742	£2,928	£2,928	7%
Co-medication costs	£238	£392	-£154	£154	0%	£272	-£34	£34	0%	£223	£15	£15	0%
Adverse events	£801	£2,236	-£1,434	£1,434	4%	£2,835	-£2,033	£2,033	16%	£2,248	-£1,447	£1,447	3%
Pre-progression monitoring costs on treatment	£1,272	£741	£531	£531	2%	£1,490	-£218	£218	2%	£704	£569	£569	1%
Pre-progression monitoring costs off treatment	£35	£104	-£68	£68	0%	£18	£18	£18	0%	£0	£35	£35	0%

		POM+DEX				PANO+BORT+DEX				Bendamustine-based therapy			
	Daratumumab	POM+DEX	Incremental	Absolute Increment	% Increment	PANO+BORT+DEX	Incremental	Absolute Increment	% Increment	Bendamustine-based therapy	Incremental	Absolute Increment	% Increment
Subsequent treatment costs	£9	£43	-£34	£34	0%	£60	-£52	£52	0%	£45	-£37	£37	0%
Subsequent treatment admin costs	£162	£151	£12	£12	0%	£211	-£48	£48	0%	£159	£4	£4	0%
Post-progression monitoring	£1,239	£661	£578	£578	2%	£920	£319	£319	2%	£532	£707	£707	2%
Terminal care	£782	£812	-£30	£30	0%	£793	-£11	£11	0%	£822	-£40	£40	0%
Total	**£79,071**	**£49,921**	**£29,150**	**£29,150**	**100%**	**£74,530**	**£4,541**	**£4,541**	**100%**	**£38,327**	**£40,744**	**£40,744**	**100%**
Key: POM, pomalidomide; DEX, dexamethasone; PANO, panobinostat; BORT, bortezomib.													

Table 78: Disaggregated costs by health state

		POM+DEX				PANO+BORT+DEX				Bendamustine-based therapy			
	Daratumumab	POM+DEX	Incremental	Absolute Increment	% Increment	PANO+BORT+DEX	Incremental	Absolute Increment	% Increment	Bendamustine-based therapy	Incremental	Absolute Increment	% Increment
Pre-progression on treatment	£76,843	£48,151	£28,693	£28,693	98%	£72,527	£4,316	£4,316	95%	£36,769	£40,074	£40,074	98%
Pre-progression off treatment	£35	£104	-£68	£68	0%	£18	£18	£18	0%	£0	£35	£35	0%
Post-progression	£1,410	£855	£555	£555	2%	£1,191	£219	£219	5%	£736	£674	£674	2%
Terminal costs	£782	£812	-£30	£30	0%	£793	-£11	£11	0%	£822	-£40	£40	0%
Total	**£79,071**	**£49,921**	**£29,150**	**£29,346**	**100%**	**£61,438**	**£17,632**	**£17,632**	**100 %**	**£38,327**	**£40,744**	**£40,823**	**100 %**
Key: POM, pomalidomide; DEX, dexamethasone; PANO, panobinostat; BORT, bortezomib													

Table 79: Disaggregated QALYs

		POM+DEX				PANO+BORT+DEX				Bendamustine-based therapy			
	Daratumumab	POM+DEX	Incremental	Absolute Increment	% Increment	PANO+BORT+DEX	Incremental	Absolute Increment	% Increment	Bendamustine-based therapy	Incremental	Absolute Increment	% Increment
Pre-progression on treatment	0.39	0.23	0.16	0.16	25%	0.46	-0.07	0.07	21%	0.22	0.18	0.18	24%
Pre-progression off treatment	0.03	0.09	-0.06	0.06	9%	0.02	0.01	0.01	5%	0.00	0.03	0.03	4%
Post-progression	0.93	0.50	0.44	0.44	66%	0.69	0.24	0.24	75%	0.40	0.53	0.53	72%
AE	0.00	0.00	0.00	0.00	0%	0.00	0.00	0.00	0%	0.00	0.00	0.00	0%
Total	**1.36**	**0.81**	**0.54**	**0.66**	**100%**	**1.17**	**0.19**	**0.32**	**100%**	**0.62**	**0.74**	**0.74**	**100%**
Key: POM, pomalidomide; DEX, dexamethasone; PANO, panobinostat; BORT, bortezomib; QALY, quality-adjusted life-year; AE, Adverse event													

Table 80: Disaggregated life-years

		POM+DEX				PANO+BORT+DEX				Bendamustine-based therapy			
	Daratumumab	POM+DEX	Incremental	Absolute Increment	% Increment	PANO+BORT+DEX	Incremental	Absolute Increment	% Increment	Bendamustine-based therapy	Incremental	Absolute Increment	% Increment
Pre-progression on treatment	0.67	0.38	0.29	0.29	23%	0.78	-0.11	0.11	18%	0.36	0.31	0.31	22%
Pre-progression off treatment	0.05	0.15	-0.10	0.10	8%	0.03	0.02	0.02	3%	0.00	0.05	0.05	4%
Post-progression	1.82	0.93	0.88	0.88	69%	1.33	0.49	0.49	79%	0.74	1.08	1.08	75%
Total	**2.54**	**1.46**	**1.07**	**1.28**	**100%**	**2.14**	**0.39**	**0.61**	**100%**	**1.10**	**1.44**	**1.44**	**100%**
Key: POM, pomalidomide; DEX, dexamethasone; PANO, panobinostat; BORT, bortezomib													

5.8 Sensitivity analyses

The economic model has numerous parameters that are integral to provide the model outcomes. Sensitivity analyses were used to investigate how sensitive the model is to changes in the deterministic input parameter values. Uncertainty margins were applied to each parameter of interest based on corresponding margins provided in the literature or based on assumptions if this information was unavailable.

The cost-effectiveness model accommodated three different ways of assessing the impact of input parameter uncertainty on the model outcomes. These included deterministic (or one-way) sensitivity analyses, probabilistic sensitivity analyses, and scenario analyses:

- One-way sensitivity analyses were used to determine the drivers of the model outcomes;
- Probabilistic sensitivity analyses were used to display how the combined uncertainty of all input parameters translates into the overall uncertainty of the model outcomes;
- Scenario analyses were used to assess the impact of certain model settings on the results that were not subject to the deterministic sensitivity analyses (e.g. time horizon of the model, alternative input parameter choices).

The deterministic (or one-way) sensitivity analyses and probabilistic sensitivity analyses were pre-programmed using Microsoft® Visual Basic for Applications (VBA) with their inputs defined in the input parameter worksheets.

5.8.1 Probabilistic sensitivity analysis

A total of 8,000 iterations were used to inform the final PSA analysis because utilising this number generated stable mean results. The outputs of the stabilisation analyses are presented in Appendix 15.

Mean PSA results are presented in Table 81. PSA scatterplots and cost-effectiveness acceptability curves (CEAC) for each pairwise comparison are presented across Figure 46 to Figure 51. Differences between deterministic and mean PSA results are driven by non-normally distributed comparative effectiveness parameters affecting both health and cost outcomes, as illustrated by PSA scatterplots. Mean PSA ICERs were slightly lower than the deterministic ICERs and the CEACs suggest that the likelhihood of daratumumab monotherapy being cost-effective at list-price, utilising an end-of-life threshold of £50,000 per QALY, is 43% versus POM +DEX, 63% versus PANO+BORT+DEX and 39% versus bendamustine-based therapy. Of note, the spread of the CE scatterplots is an inevitable consequence of the availbale clinical data in an orphan, end-of-life setting.

Table 81: Probabilistic results

	Total			Incremental			ICER (Dara vs Comparator)
	Costs	**QALYs**	**LYs**	**Costs**	**QALYs**	**LYs**	
Daratumumab	£77,953	1.36	2.55				
POM+DEX	£49,655	0.83	1.50	£28,298	0.53	1.05	£53,167
PANO+BORT +DEX	£74,313	1.20	2.22	£3,640	0.16	0.33	£22,654
Bendamustine-based therapy	£39,472	0.63	1.13	£38,481	0.73	1.42	£52,734

Key: POM, pomalidomide; DEX, dexamethasone; PANO, panobinostat; BORT, bortezomib; QALY, quality-adjusted life year; LY, life year; ICER, incremental cost-effectiveness ratio.

Figure 46: CE plane daratumumab vs POM+DEX

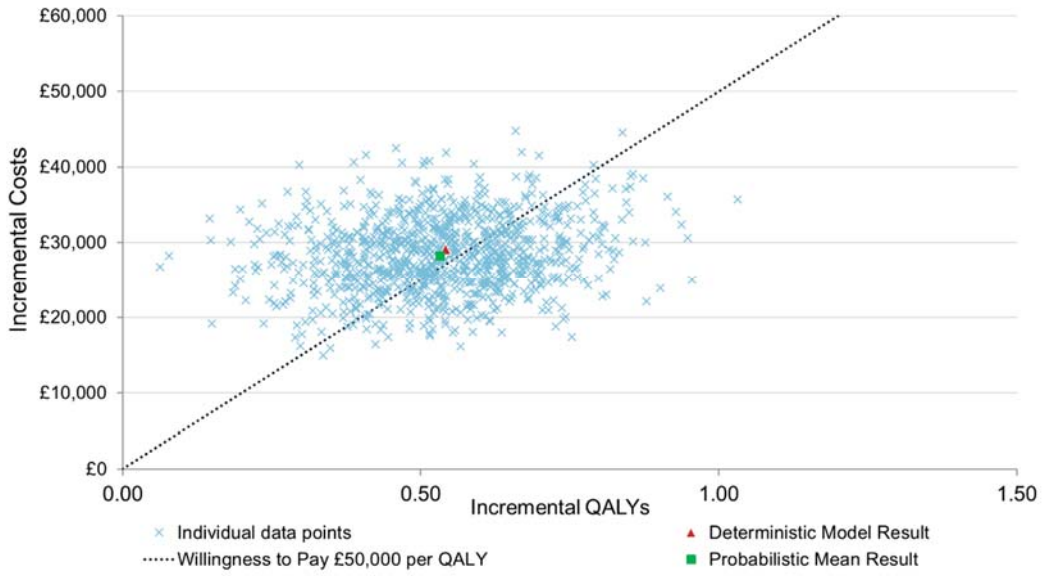


Figure 47: CEAC daratumumab vs POM+DEX

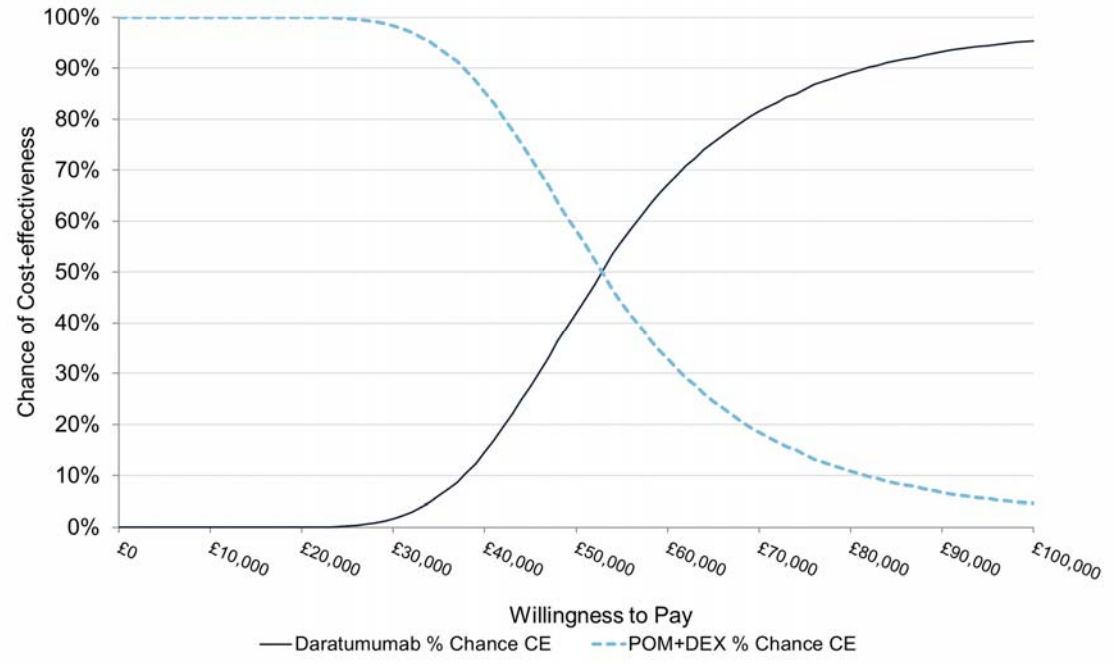


Figure 48: CE Plane for daratumumab vs PANO+BORT+DEX

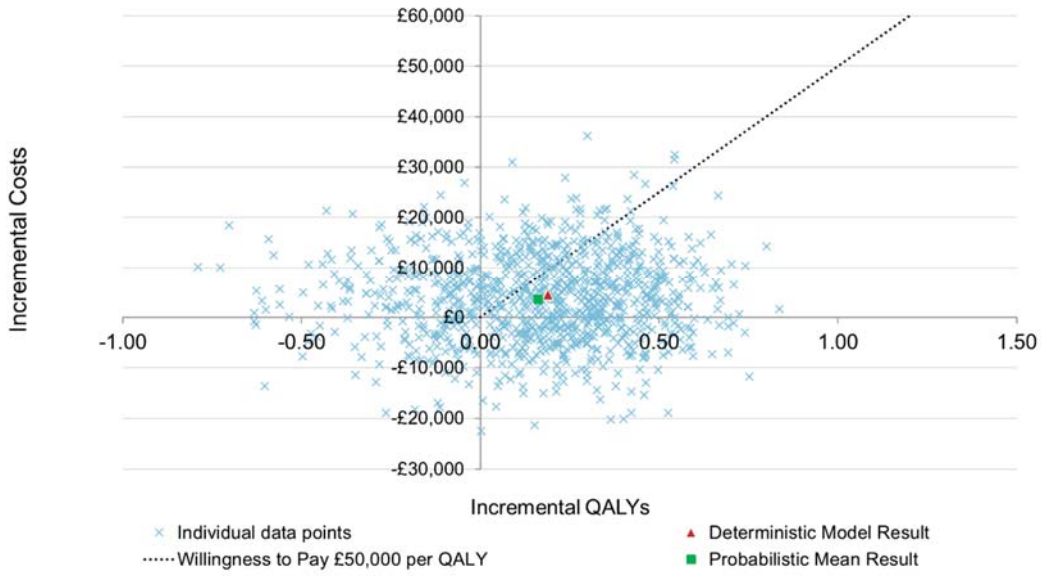


Figure 49: CEAC for daratumumab vs PANO+BORT+DEX

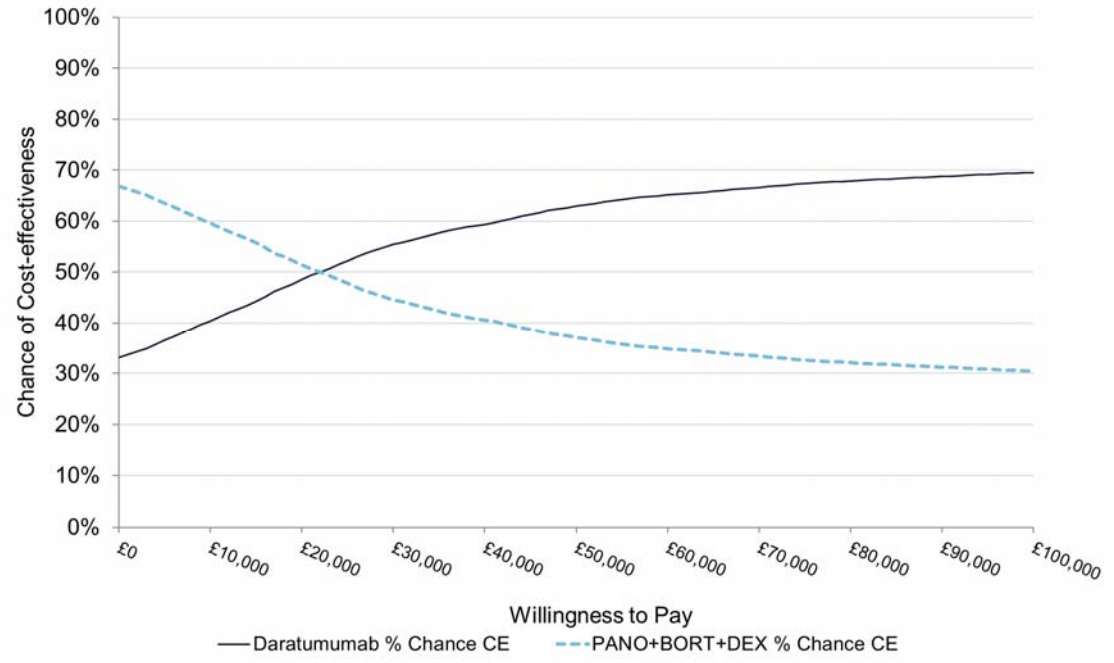


Figure 50: CE plane for daratumumab vs bendamustine-based therapy

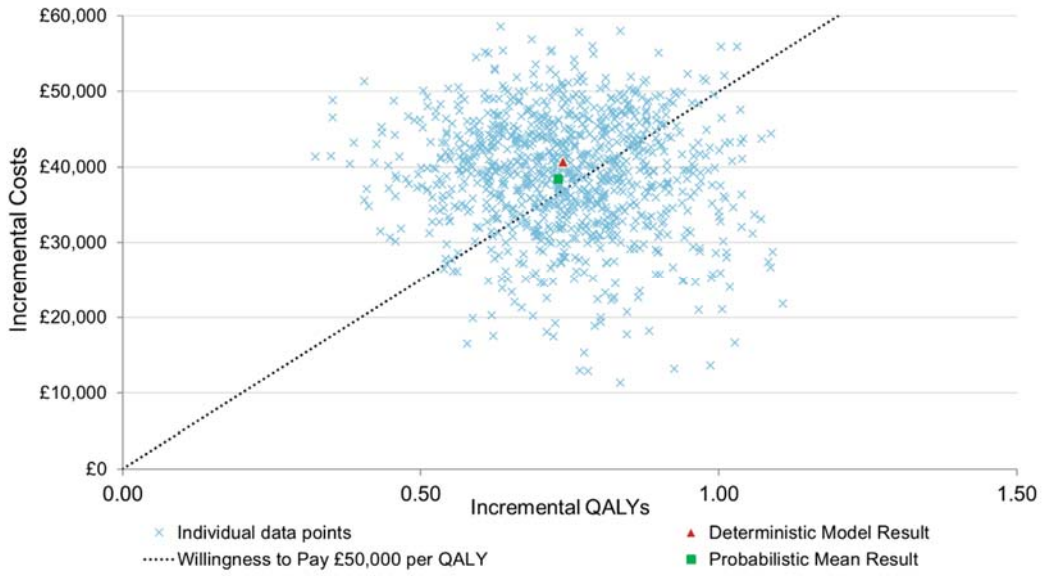
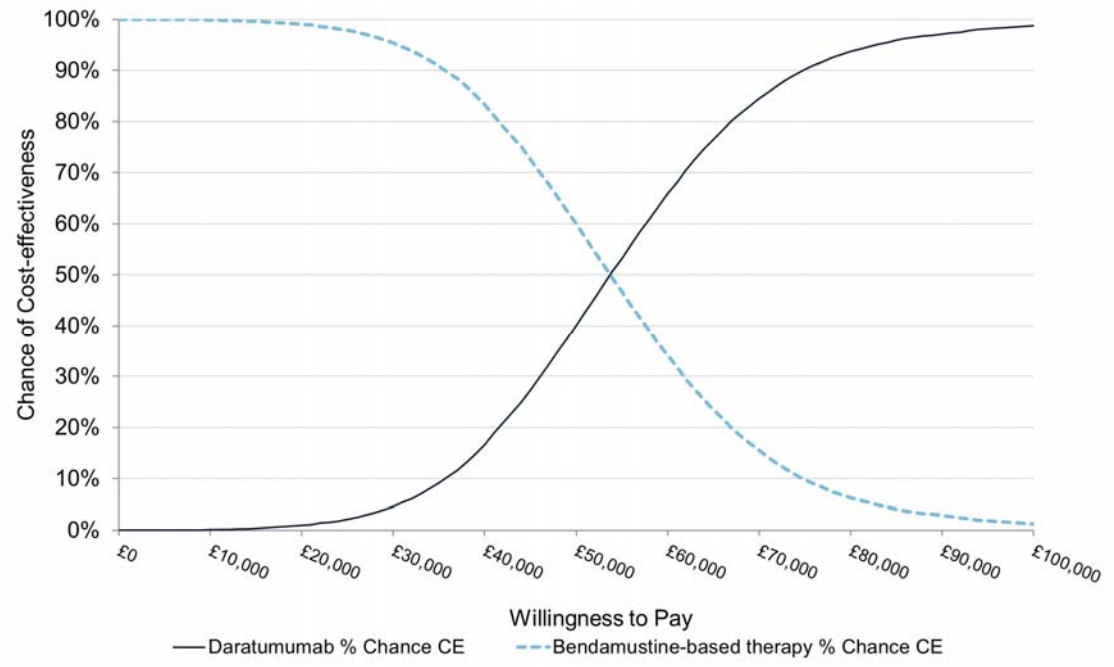


Figure 51: CEAC for daratumumab vs bendamustine-based therapy

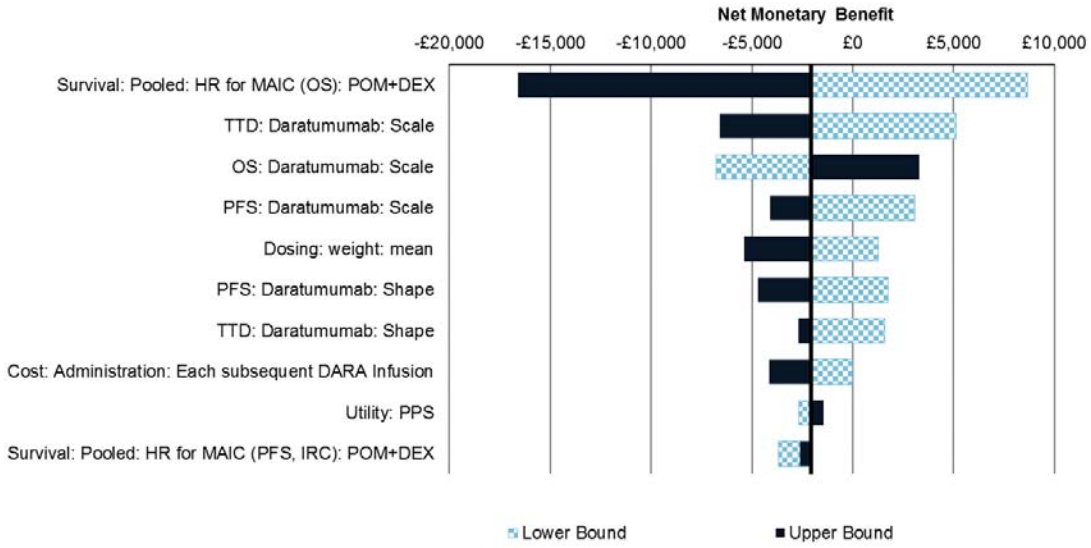


5.8.2 Deterministic sensitivity analysis

One-way sensitivity analyses (OWSA) were run using the upper and lower bounds of the 95% CI of each input parameter at a time. The end-of-life WTP threshold of £50,000 per QALY gained was used to calculate estimated net monetary benefit (NMB). Tornado diagrams illustrating key OWSA results versus each comparator are presented in Figure 52, Figure 53 and Figure 54.

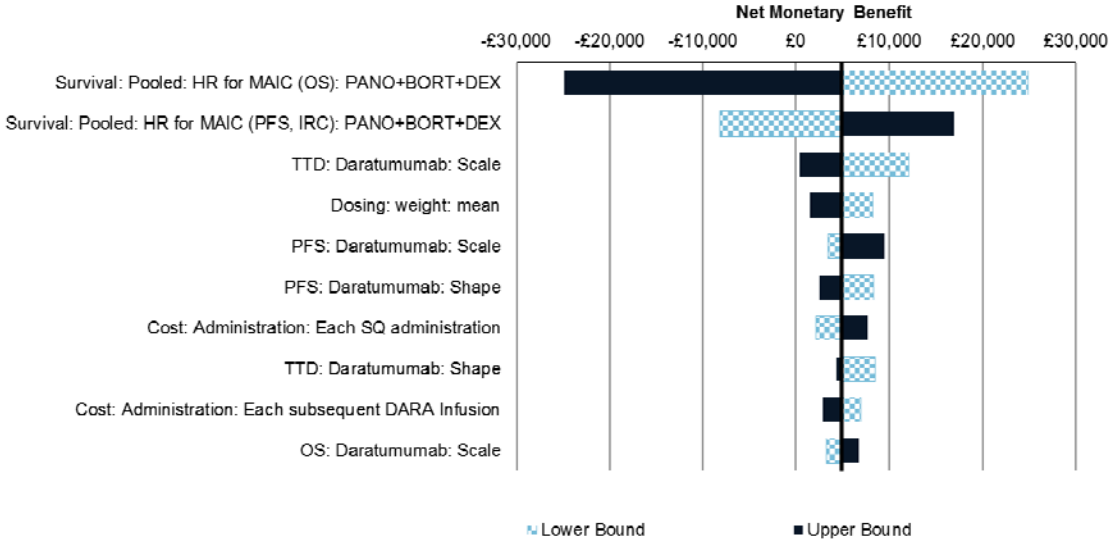
Uncertainty around relative effectiveness parameters are shown to be primary drivers of the ICER for each comparison. This is reflective of the nature of the evidence base, particularly in relation to the clinical effectiveness data for PANO+BORT+DEX and bendamustine-based therapy. Such uncertainty is expected given previously acknowledged limitations in the comparator evidence base in this fourth-line setting; Janssen can do little to alleviate this uncertainty as it is related to the poor evidence base of the comparators. Furthermore, the uncertainty inherent to these parameters is unlikely to be alleviated from further data in clinical practice. Uncertainty around post-progression utility assumptions and daratumumab administration cost assumptions were also shown to be important for estimated results because of the long period of post-progression survival with daratumumab and the required dosing schedule of daratumumab, respectively.

Figure 52: Tornado diagram for daratumumab vs POM+DEX



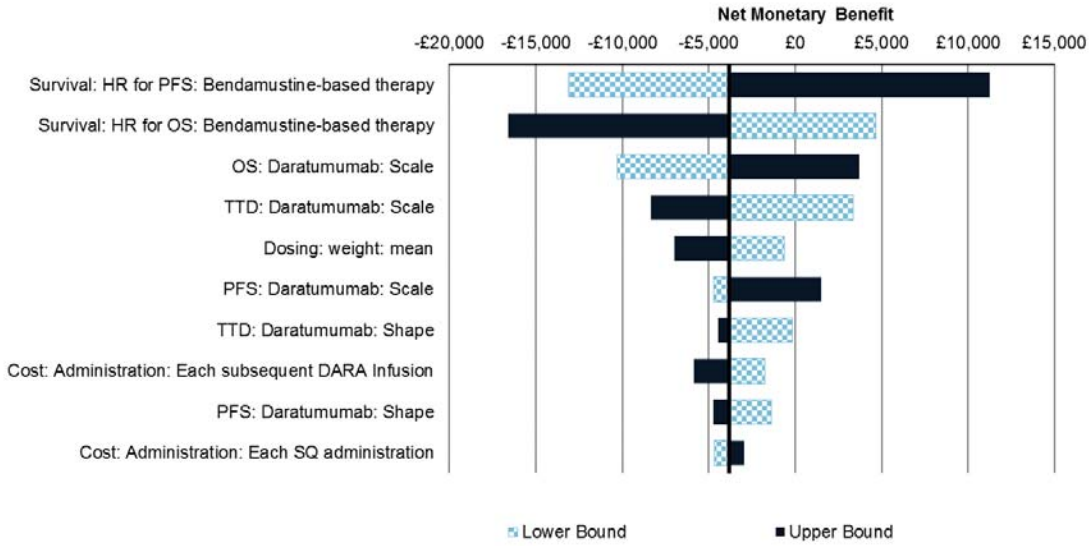
Key: AE, adverse event; DEX, dexamethasone; HR, hazard ratio; IRC, independent review committee; MAIC, matching-adjusted indirect comparison; OS, overall survival; POM, pomalidomide; PFS, progression-free survival.

Figure 53: Tornado diagram for daratumumab vs PANO+BORT+DEX



Key: AE, adverse event; BORT, bortezomib; DARA, daratumumab; DEX, dexamethasone; HR, hazard ratio; IRC, independent review committee; MAIC, matching-adjusted indirect comparison; OS, overall survival; PANO, panobinostat; PFS, progression-free survival.

Figure 54: Tornado diagram for daratumumab vs bendamustine-based therapy



Key: DARA, daratumumab; SubsTx, subsequent treatment.

5.8.3 Scenario analysis

The scenarios included in the analysis and their justification are presented in Table 82. Scenario analysis results are shown in Table 83.

Results of scenario analyses show that the economic model is fairly robust with respect to different parametic distributions for TTD, PFS and OS. The variation that is seen in comparisons with PANO+BORT+BEX and bendamustine-based therapy is not unexpected given the paucity of evidence available for these comparators.

When matching for all 18 characteristics in the MAIC versus POM+DEX, the ICER decreases by approximately £3K, however, doing so reduces the effective sample size. In order to balance the adjustment for prognostic factors with reduction in effective sample size, only the 11 most important factors were adjusted for in the base-case. As such, the base-case ICER may be considered conservative.

The IMF chart review data also provided IPD for POM+DEX and could therefore inform a multivariate regression analysis with daratumumab. Using clinical effectiveness estimates from this analysis resulted in an ICER of £39,512, a

reduction of over £14K. This analyses indicates that the MAIC used in the base case is likely to be conservative.

The scenario analyses using independent curve fits to address the proportional hazards assumption had miminal impact on the the ICER and thus supports the appropriateness of the base-case for comparisons against POM+DEX and PANO+BORT+DEX.

Table 82: Scenario analyses conducted and Justification

Parameter	Base-case	Scenario	Justification
Time horizon	15 years	5 years, 10 years	Time horizon may be shorter in practice
Discounting	3.5%	0%, 6%	NICE guidelines
Patient population used in the MAIC	Integrated MMY2002/GEN501	MMY2002	MMY2002 increases the number of characteristics on which to match but reduces reliability as a consequence of reduced sample size
Subsequent treatment costs	Included	Excluded	To test the impact of included costs of subsequent treatment, considering the long post-progression survival seen with daratumumab
PFS measure	IRC	INV	To assess the impact of investigator assessed PFS on model results
Utility value source	Palumbo et al.[154] PFS 0.6 PPS 0.57	TA 380 (PFS 0.71, PPS 0.64) TA338 (PFS 0.65, PPS 0.57)	Average utilities from Palumbo et al. may underestimate utility in daratumumab treated patients[154]
OS parametric curve;	Exponential	Weibull, log-logistic, log-normal, gamma	Follow NICE TSD guidelines
PFS parametric curve	Log-logistic	Weibull, exponential, log-normal, gamma	Follow NICE TSD guidelines
TTD parametric curve;	Log-logistic	Weibull, log-logistic, log-normal,	Follow NICE TSD guidelines

Parameter	Base-case	Scenario	Justification
		gamma	
MAIC vs POM+DEX	11 criteria	3 criteria, 5 criteria, 18 criteria, only POM-naïve patients	To test uncertainty around MAIC estimates.
MAIC vs PANO+BORT+DEX	5 criteria	2 criteria, 12 criteria	To test uncertainty around MAIC estimates
Comparative efficacy	MAIC HR applied	Independent curve fits to data post MAIC vs POM+DEX Multivariate regression of IMF data	To test sensitivity to proportional hazards assumption To assess generalizability of MAIC results
Comparative efficacy	MAIC HR applied	Independent curve fits to data post MAIC vs PANO+BORT+DEX	To test sensitivity to proportional hazards assumption

Key: BORT, bortezomib; DEX, dexamethasone; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; PANO, panobinostat; PFS, progession-free survival, POM, pomalidomide; TSD, Technical Support Document; TTD, time to treatment discontinuation.

Table 83: Scenario analyses results

Parameter	Base case	Scenario analysis	ICER (DARA vs POM+DEX)	ICER (DARA vs PANO+BORT+DEX)	ICER (DARA vs Bendamustine-based therapy)
Basecase			**£53,804**	**£24,109**	**£55,161**
Time horizon	15 years	5 years	£66,679	£21,481	£65,691
Time horizon	15 years	10 years	£54,795	£23,616	£55,937
Discount rate (costs and QALYs)	3.50%	0%	£49,214	£26,376	£50,805
Discount rate (costs and QALYs)	3.50%	6%	£57,356	£22,235	£58,492
Utilities	Palumbo: PFS 0.6, PPS 0.57	TA 380 (PFS 0.71, PPS 0.64)	£48,964	£20,842	£50,667
Utilities	Palumbo: PFS 0.6, PPS 0.57	TA338 (PFS 0.65, PPS 0.57)	£53,125	£24,554	£54,174
Daratumumab TTD curve fits	Log-logistic	Log-normal	£55,178	£28,059	£56,168
Daratumumab TTD curve fits	Log-logistic	Exponential	£42,635	Daratumumab Dominates	£46,969
Daratumumab TTD curve fits	Log-logistic	Weibull	£42,985	Daratumumab Dominates	£47,225
Daratumumab TTD curve fits	Log-logistic	Gamma	£59,061	£39,229	£59,017
Daratumumab PFS curve fits	Log-normal	Exponential	£42,695	Daratumumab	£45,374

Parameter	Base case	Scenario analysis	ICER	ICER (DARA vs	ICER (DARA vs
				Dominates	
Daratumumab PFS curve fits	Log-normal	Log-logistic	£60,393	£49,344	£60,262
Daratumumab PFS curve fits	Log-normal	Gamma	£58,782	£40,341	£53,948
Daratumumab PFS curve fits	Log-normal	Weibull	£43,299	Daratumumab Dominates	£46,228
Daratumumab OS curve fits	Exponential	Weibull	£58,717	£26,359	£59,886
Daratumumab OS curve fits	Exponential	Log-logistic	£36,472	£16,285	£38,216
Daratumumab OS curve fits	Exponential	Log-normal	£34,555	£15,642	£36,004
Daratumumab OS curve fits	Exponential	Gamma	£55,818	£25,411	£56,210
Daratumumab PFS	IRC	INV	£51,612	£32,756	£56,202
MAIC population	Daratumumab patient population used is integrated GEN501/MMY2002	Daratumumab patient population used is MMY2002	£51,433	Daratumumab Dominates	£57,502
MAIC vs POM+DEX	11 Matched Criteria	3 Matched Criteria	£59,260	NA	NA
MAIC vs POM+DEX	11 Matched Criteria	5 Matched Criteria	£57,759	NA	NA
MAIC vs POM+DEX	11 Matched Criteria	18 Matched Criteria	£50,870	NA	NA
MAIC vs POM+DEX	Patient pre-treated with pomalidomide included	Patient pre-treated with pomalidomide excluded	£59,097	NA	NA
MAIC vs POM+DEX	Proportional Hazards assumed	Independent curve fits	£54,735	NA	NA

Parameter	Base case	Scenario analysis	ICER	ICER (DARA vs	ICER (DARA vs
Comparative efficacy, POM+DEX	MAIC	Multivariate regression analyses using IMF	£39,512	NA	NA
MAIC vs PANO+BORT+DEX	5 Matched Criteria	2 Matched Criteria	NA	£12,508	NA
MAIC vs PANO+BORT+DEX	5 Matched Criteria	12 Matched Criteria	NA	£29,771	NA
MAIC vs PANO+BORT+DEX	Proportional Hazards assumed	Independent curve fits	NA	£23,271	NA

5.8.4 Summary of sensitivity analyses results

Comprehensive sensitivity analyses were conducted around model inputs and assumptions through PSA, OWSA and numerous scenario analysis.

The PSA derived ICERs which were slightly lower than the deterministic ICERs although, differences were not clinically or economically meaningful. The spread of the PSA scatterplots is driven by the non-normally distributed estimates of comparative effectiveness, which effect health benefits and cost outcomes to a similar magnitude.

The OWSA showed that the main driver of the ICER for each comparison was comparative effectiveness. Such uncertainty is not unexpected given previously acknowledged limitations in the comparator evidence base in this heavily pre-treated and highly refractory fourth-line setting. Janssen can do little to alleviate the type of uncertainty inherent to these analyses as it attributed to the poor evidence base of the comparators, specifically in relation to PANO+BORT+DEX and bendamustine.

The assumption around post-progression utility was also shown to be influential because of the long period of post-progression survival with daratumumab. This is driven by the observed post-progression survival with daratumumab, accredited to its multifactorial and unique MoA.

Numerous scenario analyses have explored uncertainty in the model results and resulting ICERs against all comparators are shown to both increase and decrease around the base-case. ICERs are shown to range between £34-60K/QALY versus POM+DEX, £12-49K/QALY versus PANO+BORT+DEX, and £36-60K/QALY versus bendamustine-based therapy.

In conclusion, comprehensive sensitivity analyses have extensively tested the uncertainty inherent to the decision-problem. Notwithstanding limitations in the available data, these sensitivity analyses demonstrate the results are generally robust, particular with respect to POM+DEX, the key comparator of interest.

5.9 Subgroup analysis

There are no subgroups considered in this analysis.

5.10 Validation of de novo cost-effectiveness analysis

5.10.1 Clinician advice

Clinical validation of the approach and key assumptions was carried out in two stages; first at an advisory board attended by NHS Consultant Haematologists with extensive and ongoing experience of treating rrMM patients; then prior to submission to validate and finalise model assumptions during a web-linked meeting with a Consultant Haematologists.

In consideration of the appropriateness of the key clinical data for the decision problem, patients enrolled in the MMY2002 and GEN501 studies were considered representative of patients whose prior therapy included a PI and an IMiD and who have demonstrated disease progression on the last therapy.

However, as discussed in Section 4, these patients, and those enrolled in the MMY2002 trial in particular, are heavily pre-treated and highly refractory. If approved for use in the NHS in England in line with available clinical data, daratumumab is to be used at fourth-line. In clinical practice, it is expected that many patients would not have such an extensive treatment history as those observed in the key daratumumab trials. Therefore, while patients are representative of those with aggressive disease and poor prognosis, the severity of the key trial population means ORR and OS results may be considered conservative estimates of response and survival to that which may be achieved in a less heavily pre-treated population in clinical practice, and the economic analysis results reflect this.

5.10.2 Internal validity

The model was quality-assured by internal processes at the company who built the economic model, independent of Janssen. In these processes, an economist not involved in the model's construction reviewed the model for coding errors, inconsistencies and the plausibility of inputs. The model was also put through a checklist of known modelling errors, and the assumptions were questioned.

5.11 Interpretation and conclusions of economic evidence

The economic analysis optimises the use of available data in this heavily treated and highly refractory rrMM patient population, while fully accounting for the clinically and economically relevant parameters in the decision problem.

The economic model predicts comparable clinical outcomes to those observed in the integrated daratumumab trial data (MMY2002/GEN501) and this demonstrates that the model is accurate at simulating disease progression in rrMM. Model assumptions and associated predictions were further validated by Consultant Haematologists practicing in the NHS to ensure that key parameters, such as parametric survival extrapolations, were clinically plausible. This was vital given the paucity of evidence available for comparator treatments.

In the absence of head-to-head data, indirect estimates of comparative efficacy were synthesised from the wider evidence base. As a consequence of utilising HRs derived from MAIC for POM+DEX and PANO+BORT+DEX, it is inappropriate to directly compare the modelled results for these comparators to their respective published trial data (i.e. MM-003 and PANORAMA 2). Similarly, given the restrictions in place on the use of bendamustine and the fact that bendamustine is likely to be used at fifth line or later within the IMF, it is inappropriate to compare the modelled results to these real-world data.

Results of the economic analysis demonstrate that daratumumab is an effective, life-extending treatment for patients with rrMM and predict daratumumab to provide 2.54 life years. This exceeds the life years expected for POM+DEX, PANO+BORT+DEX and bendamustine-based therapy by 12.8 months, 4.7 months and 17.3 months, respectively. These incremental survival gains of >3 months further support end-of-life criteria and ICERs derived using list-prices for all interventions are in with the region of NICE's WTP threshold for end-of-life, orphan treatments.

Comprehensive sensitivity analyses have extensively tested the uncertainty inherent to the decision-problem. Notwithstanding limitations in the available data, these sensitivity analyses demonstrate the results are generally robust, particularly with respect to POM+DEX, the key comparator of interest. Comparative effectiveness is

the key uncertainty inherent to this decision problem, yet such uncertainty is not unexpected given the limitations in the comparator evidence base.

In consideration of the available evidence and comprehensive economic analysis, daratumumab is cost-effective and represents a clinically and economically viable use of NHS resources in the fourth-line setting. Daratumumab monotherapy fufills the high current unmet need for effective and well tolerated treatments in rrMM.

6 Assessment of factors relevant to the NHS and other parties

The number of incident patients was estimated using incidence statistics from Cancer Research UK.[44] The incidence rate per 100,000 were used with the population estimates to estimate the incident population. It has been assumed that there is no growth in incidence statistics.

In 2013, 4,703 people were diagnosed with MM in England [44] and an estimated 15% of patients with rrMM receive four or more lines of therapy in clinical practice.[45] Applying these percentages to the incidence of MM in England, an estimated 705 patients would be eligible for daratumumab monotherapy in the fourth-line setting.

Market share data from IMS Harmony indicate that currently (May 2016), the market share of POM+DEX, PANO+BORT+DEX and bendamustine are 46%, 14% and 14%, respectively. However, it is important to note that POM+DEX ceased to be available through the CDF from September 2015. Therefore, current market share estimates are not reflective of the decision problem. As such, market share data for pomalidomide (64%) were taken from September 2015. As bendamustine-based therapy is considered a proxy for patients who are not able to receive PANO+BORT+DEX or POM+DEX, it has been assumed that the bendamustine-based therapy arm in this model would be remainder of the market share.

Table 84: Current market share estimates

PANO+BORT+DEX		POM+DEX		Bendamustine	
Proportion	**N**	**Proportion**	**N**	**Proportion**	**N**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: BORT, bortezomib; DEX, dexamethasone; PANO, panobinostat; POM, pomalidomide.					

It is anticipated that daratumumab will reach a peak market share of 67% at 12 months. It has been assumed that this is split equally across displacing POM+DEX, PANO+BORT+DEX and bendamustine (used as a proxy for for patients who are not able to receive PANO+BORT+DEX or POM+DEX).

Table 85 sets out the expected market share, including daratumumab, for the next five years.

Table 85: Market share with daratumumab

PANO+BORT+DEX		POM+DEX		Bendamustine		Daratumumab	
Proportion	**N**	**Proportion**	**N**	**Proportion**	**N**	**Proportion**	**N**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: BORT, bortezomib; DEX, dexamethasone; PANO, panobinostat; POM, pomalidomide.							

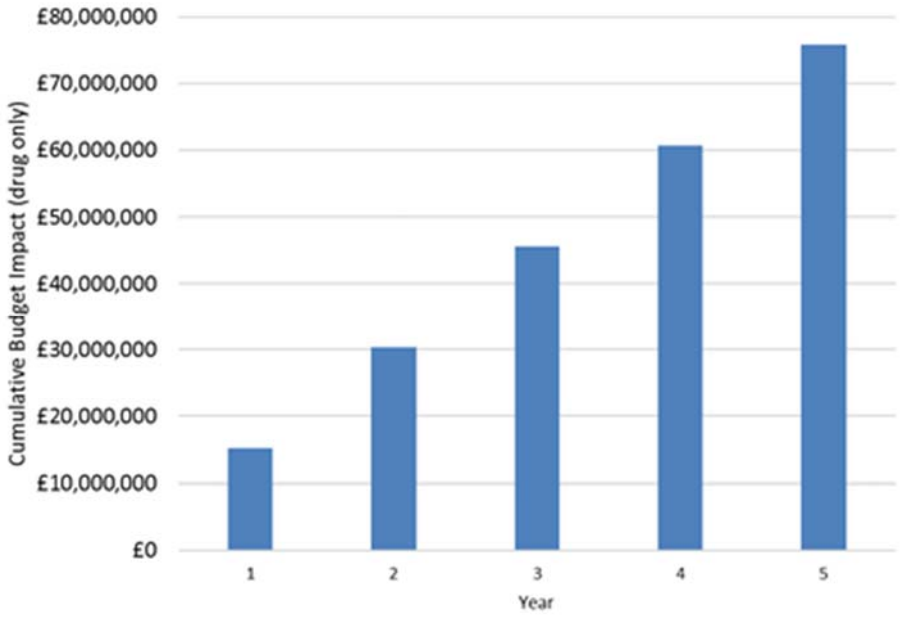
6.1 Budget Impact

Cost-effectiveness model per-patient costs were extracted to inform the likely budget impact, given the above patient numbers. The market shares were also taken into consideration. The budget impact of daratumumab is reported in Table 86.

Table 86: Budget impact

Year	Annual budget Impact		Cumulative	
	Total cost	**Cost (drug only)**	**Total cost**	**Cost (drug only)**
1	£17,497,938	£15,178,158	£17,497,938	£15,178,158
2	£17,497,938	£15,178,158	£34,995,876	£30,356,315
3	£17,497,938	£15,178,158	£52,493,814	£45,534,473
4	£17,497,938	£15,178,158	£69,991,752	£60,712,631
5	£17,497,938	£15,178,158	£87,489,690	£75,890,789

Figure 55: Cumulative budget impact



7 References

1. Khagi Y and Mark TM. Potential role of daratumumab in the treatment of multiple myeloma. *Journal of OncoTargets and Therapy*. 2014; 7:1095-100.

2. Lin P, Owens R, Tricot G and Wilson CS. Flow Cytometric Immunophenotypic Analysis of 306 Cases of Multiple Myeloma. *Am J Clin Pathol*. 2004; 121(4):482-8.

3. Santonocito AM, Consoli U, Bagnato S, et al. Flow cytometric detection of aneuploid CD38++ plasmacells and CD19+ B-lymphocytes in bone marrow, peripheral blood and PBSC harvest in multiple myeloma patients. *Leukemia Res*. 2004; 28(5):469-77.

4. Krejcik J, Casneuf T, Nijhof I, et al. Immunomodulatory Effects and Adaptive Immune Response to Daratumumab in Multiple Myeloma. American Society of Hematology. Orlando, Florida, USA. 2015.

5. de Weers M, Tai Y-T, van der Veer MS, et al. Daratumumab, a Novel Therapeutic Human CD38 Monoclonal Antibody, Induces Killing of Multiple Myeloma and Other Hematological Tumors. *J Immunol*. 2011; 186(3):1840-8.

6. Marco JH, Boross P, Overdijk MB, et al. Daratumumab, a Human CD38 Antibody Induces Apoptosis of Myeloma Tumor Cells Via Fc Receptor-Mediated Crosslinking. 54th American Society of Heamatology (ASH) Annual Meeting and Exposition Atlanta, GA., USA. 8-11 December 2012. 2974.

7. Overdijk MB, Verploegen S, Bögels M, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. *mAbs*. 2015; 7(2):311-20.

8. Krejcik J, Casneuf T, Nijhof IS, et al. Daratumumab depletes CD38+ immune-regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. *Blood*. 2016.

9. Usmani S, Weiss BM, Bahlis N, et al. Clinical Efficacy of Daratumumab Monotherapy in Patients With Heavily Pretreated Relapsed or Refractory Multiple Myeloma. American Society of Hematology Orlando, Florida, USA. 2015.

10. European Medicines Agency. EPAR Assessment Report, Darzalex (Daratumumab). 2016. (Updated: 20 June 2016) Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004077/WC500207295.pdf. Accessed: 1 September 2016.

11. European Medicines Agency. Committee for Orphan Medicinal Products (COMP): Minutes for the meeting on 19-21 April. 2016. Accessed: 18 October 2016.

12. Wailoo A, Davis S, Tosh J and School of Health and Related Research UoS. The incorporation of health benefits in cost utility analysis using the EQ-5D. 2010. Available at: http://www.nicedsu.org.uk/PDFs%20of%20reports/DSU%20EQ5D%20final%20report%20-%20submitted.pdf. Accessed: 24 October 2016.

13. Kyle RA and Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukemia*. 2009; 23(1):3-9.

14. Cancer Research UK. Myeloma 2016. (Updated: 17 February 2016) Available at: http://www.cancerresearchuk.org/about-cancer/type/myeloma/. Accessed: 26 August 2016.

15. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc*. 2003; 78(1):21-33.

16. Moreau P, San Miguel J, Ludwig H, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annal Oncol*. 2013; 24(suppl 6):vi133-vi7.

17. Bianchi G and Anderson KC. Understanding biology to tackle the disease: Multiple myeloma from bench to bedside, and back. *CA Cancer J Clin*. 2014; 64(6):422-44.

18. Prideaux SM, Conway O'Brien E and Chevassut TJ. The Genetic Architecture of Multiple Myeloma. *Adv Hematol*. 2014; 2014:16.

19. Palumbo A and Anderson K. Multiple myeloma. *N Engl J Med*. 2011; 364(11):1046-60.

20. Barlogie B, Mitchell A, van Rhee F, et al. Curing myeloma at last: defining criteria and providing the evidence. *Blood*. 2014; 124(20):3043-51.

21. Bird J, Owen R, D'Sa S, et al. Guidelines for the diagnosis and management of multiple myeloma. 2014. Available at:

http://www.bcshguidelines.com/documents/MYELOMA_GUIDELINE_Feb_2014_for_BCSH.pdf. Accessed: 1 April 2016.

22. Brenner H, Gondos A and Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. *Blood*. 2008; 111(5):2521-6.

23. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008; 111(5):2516-20.

24. Usmani S, Ahmad T, Ng Y, et al. Analyses of Real World Data on Overall Survival in Multiple Myeloma Patients with at Least 3 Prior Lines of Therapy Including a PI and an IMiD, or Double Refractory to a PI and an IMiD. American Society of Hematology. Orlando, Florida, USA. 2015.

25. Usmani S, Desai A, Ahmadi T, et al. Analysis of overall survvial in multiple myeloma patients with ≥3 Lines of Therapy Including a PI and an IMiD, or Double Refractory to a PI and an IMiD Using Real-world Data. European Haematology Association. Vienna, Austria. 2015.

26. Gooding S, Lau IJ, Sheikh M, et al. Double Relapsed and/or Refractory Multiple Myeloma: Clinical Outcomes and Real World Healthcare Costs. *PLoS ONE*. 2015; 10(9):e0136207.

27. Kumar SK, Lee JH, Lahuerta JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. *Leukemia*. 2012; 26(1):149-57.

28. Tarant JL, Ashcroft J, Feyler S, et al. Treatment patterns & survival in multiple myeloma patients sequentially exposed to thalidomide, bortezomib & lenalidomide in a UK single centre. *Blood*. 2013; 122.

29. Streetly MJ, Kazmi M, Campbell T and Schey SA. Clinical review of overall survival for myeloma patients progressing after both bortezomib and lenalidomide based therapy. *Br J Haematol*. 2014; 165:68.

30. Wang TF, Ahluwalia R, Fiala MA, et al. The characteristics and outcomes of patients with multiple myeloma dual refractory or intolerant to bortezomib and lenalidomide in the era of carfilzomib and pomalidomide. *Leuk Lymphoma*. 2014; 55(2):337-41.

31. Usmani S, Ahmadi T, Ng Y, et al. Analysis of Real-World Data on Overall Survival in Multiple Myeloma Patients With >/=3 Prior Lines of Therapy Including a Proteasome Inhibitor (PI) and an Immunomodulatory Drug (IMiD), or Double Refractory to a PI and an IMiD. *Oncologist*. 2016.

32. Silbermann R and Roodman GD. Myeloma bone disease: Pathophysiology and management. *J Bone Oncol*. 2013; 2(2):59-69.

33. Mols F, Oerlemans S, Vos AH, et al. Health-related quality of life and disease-specific complaints among multiple myeloma patients up to 10 yr after diagnosis: results from a population-based study using the PROFILES registry. *Eur J Haematol*. 2012; 89(4):311-9.

34. Johnsen AT, Tholstrup D, Petersen MA, et al. Health related quality of life in a nationally representative sample of haematological patients. *Eur J Haematol*. 2009; 83(2):139-48.

35. Jordan K, Proskorovsky I, Lewis P, et al. Effect of general symptom level, specific adverse events, treatment patterns, and patient characteristics on health-related quality of life in patients with multiple myeloma: results of a European, multicenter cohort study. *Support Care Cancer*. 2014; 22(2):417-26.

36. Baz R, Lin HM, Hui AM, et al. Development of a conceptual model to illustrate the impact of multiple myeloma and its treatment on health-related quality of life. *Support Care Cancer*. 2015; 23(9):2789-97.

37. Rizzo M, Xu Y, Panjabi S and Iheanacho I. A Systematic Literature Review of the Economic Burden in Multiple Myeloma. ISPOR 17th Annual European Congress. Amsterdam, The Netherlands. 2014.

38. Rha SY, Park Y, Song SK, et al. Caregiving burden and the quality of life of family caregivers of cancer patients: the relationship and correlates. *Eur J Oncol Nurs*. 2015; 19(4):376-82.

39. Scottish Medicines Consortium (SMC). 972/14: pomalidomide 1mg, 2mg, 3mg and 4mg hard capsules (Imnovid®). 2014. Available at: https://www.scottishmedicines.org.uk/SMC_Advice/Advice/972_14_pomalidomide_Imnovid/pomalidomide_Imnovid_Resubmission. Accessed: 20 October 2016.

40. All Wales Medicine Strategy Group (AWMSG). Pomalidomide (Imnovid®) 1 mg, 2 mg, 3 mg and 4 mg hard capsules 2015. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/2590. Accessed: 20 October 2016.

41. Janssen Research & Development. Daratumumab Advisory Board. 2 March 2016. Data on File.

42. Janssen Research & Development. Clinical validation meeting for daratumumab. 11 October 2016. Data on File.

43. Richardson P, Schlossman RL, Alsina M, et al. Time to event analyses in PANORAMA 2: A Phase 2 study of panobinostat, bortezomib, and dexamethasone in patients with relapsed and bortezomib-refractory multiple myeloma. *Blood*. 2013; 122(21):1970.

44. Cancer Research UK. Myeloma incidence statistics. 2016. (Updated: 17 February 2016) Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence#heading-Zero. Accessed: 26 August 2016.

45. Yong K, Delforge M, Driessen C, et al. Multiple myeloma: patient outcomes in real-world practice. *Br J Haematol*. 2016; [Epub ahead of print].

46. National Institute for Health and Care Excellence (NICE). TA129: Bortezomib monotherapy for relapsed multiple myeloma. 2007. Available at: https://www.nice.org.uk/guidance/ta129. Accessed: 11 December 2015.

47. National institute for Health and Care Excellence (NICE). TA171: Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. 2013. Available at: https://www.nice.org.uk/guidance/ta171. Accessed: 11 December 2015.

48. National Institute for Health and Care Excellence (NICE). TA228: Bortezomib and thalidomide for the first-line treatment of multiple myeloma. 2011. Available at: https://www.nice.org.uk/guidance/ta228. Accessed: 11 December 2015.

49. National Institute for Health and Care Excellence (NICE). TA311: Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation. 2014. (Updated: 23 April 2014) Available at: https://www.nice.org.uk/guidance/ta311?unlid=6968294322015117195156. Accessed: 31 August 2016.

50. National Institute for Health and Care Excellence (NICE). TA338: Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib. 2015. Available at: https://www.nice.org.uk/guidance/ta338. Accessed: 11 December 2015.

51. National Institute for Health and Care Excellence (NICE). TA380: Panobinostat for treating multiple myeloma after at least 2 previous treatments. 2016. Available at: https://www.nice.org.uk/guidance/TA380/chapter/1-Recommendations. Accessed: 26 May 2016.

52. Pratt G, Bowcock S, Lai M, et al. United Kingdom Myeloma Forum (UKMF) position statement on the use of bendamustine in myeloma. 2013. Available at: http://www.ukmf.org.uk/wp-content/uploads/2014/01/ijlh.pdf. Accessed: 31 August 2013.

53. Palumbo A, Rajkumar SV, San Miguel JF, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. *J Clin Oncol*. 2014; 32(6):587-600.

54. National Institute for Health and Care Excellence (NICE). NG35: Myeloma: diagnosis and management. 2016. (Updated: February 2016) Available at: https://www.nice.org.uk/guidance/ng35/chapter/Recommendations. Accessed: 31 August 2016.

55. National Institute for Health and Care Excellence (NICE). NICE Pathways: Myeloma Overview. 2016. Available at: http://pathways.nice.org.uk/pathways/myeloma. Accessed: 31 August 2016.

56. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Multiple myeloma Version 3.2016. 2016. Available at: www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf. Accessed: 1 April 2016.

57. San Miguel J, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2013; 14(11):1055-66.

58. Richardson PG, Schlossman RL, Alsina M, et al. PANORAMA 2: Panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. *Blood*. 2013; 122:2331-7.

59. San-Miguel JF, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. *Lancet Oncol*. 2014; 15(11):1195-206.

60. Novartis Pharmaceuticals UK Ltd. Panobinostat for treating multiple myeloma in people who have received at least one prior therapy (ID663). Company evidence submission. 2015. (Updated: 20 May 2015) Available at: https://www.nice.org.uk/guidance/TA380/documents/multiple-myeloma-panobinostat-post-1-prior-therapy-id663-committee-papers2. Accessed: 1 September 2016.

61. He Y, Wheatley K, Clark O, et al. Early versus deferred treatment for early stage multiple myeloma. *Cochrane Database Syst Rev*. 2003; (1):CD004023.

62. Naumann-Winter F, Greb A, Borchmann P, et al. First-line tandem high-dose chemotherapy and autologous stem cell transplantation versus single high-dose chemotherapy and autologous stem cell transplantation in multiple myeloma, a systematic review of controlled studies. *Cochrane Database Syst Rev*. 2012; 10:CD004626.

63. Tan Y, Xu S, Li X, et al. Allogeneic stem cell transplantation with matched sibling donor versus autologous stem cell transplantation for newly diagnosed Multiple Myeloma. *Cochrane Database Syst Rev*. 2013; (4).

64. Clinical trials website. Available at: www.clinicaltrials.gov. Accessed: 11 December 2015.

65. National Cancer Drugs Fund List v6.0. Available at: https://www.england.nhs.uk/wp-content/uploads/.../ncdf-list-nov-15.pdf. Accessed: 11 December 2015.

66. National Institute for Health and Care Excellence (NICE) website. Available at: https://www.nice.org.uk/. Accessed: 11 December 2015.

67. Scottish Medicines Consortium (SMC) website. Available at: https://www.scottishmedicines.org.uk. Accessed: 11 December 2015.

68. McKibbon KA, Wilczynski NL, Haynes RB and Hedges T. Retrieving randomized controlled trials from medline: a comparison of 38 published search filters. *Health Info Libr J*. 2009; 26(3):187-202.

69. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. *N Engl J Med*. 2015; 373(13):1207-19.

70. Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet*. 2016.

71. Usmani SZ, Weiss BM, Plesner T, et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma *Blood*. 2016; 128(1):37-44.

72. Voorhees PM, Mulkey F, Hassoun H, et al. Alliance A061202. A phase I/II study of pomalidomide, dexamethasone and ixazomib versus pomalidomide and dexamethasone for patients with multiple myeloma refractory to lenalidomide and proteasome inhibitor based therapy: Phase I results. *Blood*. 2015; 126(23):375.

73. Leleu X, Attal M, Arnulf B, et al. Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: Intergroupe Francophone du Myélome 2009-02. *Blood*. 2013; 121:1968-75.

74. Richardson PG, Siegel DS, Vij R, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: A randomized phase 2 study. *Blood*. 2014; 123:1826-32.

75. Matsue K, Iwasaki H, Chou T, et al. Pomalidomide alone or in combination with dexamethasone in Japanese patients with refractory or relapsed and refractory multiple myeloma. *Cancer Science*. 2015; 106:1561-7.

76. Sonneveld P, Heyne N, Kueenburg E, et al. MM-013: An ongoing phase 2 trial of pomalidomide and low-dose dexamethasone (POM + LoDEX) in relapsed/refractory multiple myeloma (RRMM) with moderate or severe renal impairment (RI) including patients (pts) undergoing hemodialysis. *J Clin Oncol*. 2014; 32.

77. DiCapua Siegel DS, Agajanian R, Gaur R, et al. MM-014: A phase 2 trial evaluating efficacy, safety, and biomarkers of pomalidomide plus low-dose dexamethasone (POM + LoDEX) in relapsed/refractory multiple myeloma (RRMM) following second-line lenalidomide plus dexamethasone (LEN + DEX). *J Clin Oncol*. 2014; 32.

78. Lacy MQ, Allred JB, Gertz MA, et al. Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: Comparison of 2 dosing strategies in dual-refractory disease. *Blood*. 2011; 118:2970-5.

79. San Miguel J, Raab MS, Goldschmidt H, et al. A randomized phase 2 study of pomalidomide/dexamethasone with or without elotuzumab in patients with relapsed/refractory multiple myeloma. ASCO Annual Meeting. 2016.

80. Baz R, Martin TG, Alsina M, et al. Pomalidomide, cyclophosphamide, and dexamethasone is superior to pomalidomide and dexamethasone in relapsed and refractory myeloma: Results of a multicenter randomized phase II study. *Blood*. 2014; 124.

81. Dechow T, Aladoud A, Hurtz H, et al. Overall response rate of patients wtih refractory multiple myeloma treated wtih pomalidomide and low dose dexamethasone after lenalidomide failure: interim results of the POSEIDON study. European Haematology Association. 2016.

82. Dimopoulos MA, Palumbo A, Weisel K, et al. Safety and efficacy in the stratus (MM-010) trial, a single-arm phase 3b study evaluating pomalidomide + low-dose dexamethasone in patients with refractory or relapsed and refractory multiple myeloma. *Blood*. 2014; 124.

83. Miles O and Wells M. Efficacy of pomalidomide after progression following lenalidomide and bortezomib-a multicenter retrospective study. *Clin Lymphoma Myel*. 2015; 15:e302.

84. Montes-Gaisan C, Cuesta A, Bermúdez A, et al. Pomalidomide in refractory multiple myeloma (MMRR): A single center experience. *Clin Lymphoma Myel*. 2015; 15:e311.

85. Sriskandarajah P, Pawlun C, Boyle E, et al. Retrospective observational study of patients with relapsed/refractory myeloma treated with pomalidomide – the UK Experience. British Society of Haematology. Edinburgh, United Kingdom. 20-22 April 2015.

86. Caers J, Vekemans MC, Van De Broek I, et al. Responding patients show durable responses to bendamustine in double refractory multiple myeloma patients. *Haematologica*. 2014; 99:643-4.

87. Kim SJ, Kim K, Eom HS, et al. Bendamustine-based salvage therapy in heavily pretreated refractory myeloma patients: KMM125 study. *Clin Lymphoma Myel*. 2013; 13:S142-S3.

88. Grey-Davies E, Bosworth JL, Boyd KD, et al. Bendamustine, thalidomide and dexamethasone is an effective salvage regimen for advanced stage multiple myeloma. *Brit J Haematol*. 2012; 156:552-5.

89. Lau IJ, Smith D, Aitchison R, et al. Bendamustine in combination with thalidomide and dexamethasone is a viable salvage option in myeloma relapsed and/or refractory to bortezomib and lenalidomide. *Ann Hematol*. 2015; 94:643-9.

90. Mian M, Pescosta N, Luminari S, et al. Phase II trial to investigate efficacy and safety of bendamustine, dexamethasone and thalidomide in relapsed or refractory multiple myeloma patients after treatment with lenalidomide and bortezomib. *Haematologica*. 2014; 99:382-3.

91. Musto P, Fraticelli VL, Mansueto G, et al. Bendamustine in relapsed/refractory multiple myeloma: the "real-life" side of the moon. *Leuk Lymphoma*. 2015; 56(5):1510-3.

92. Stohr E, Schmeel FC, Schmeel LC, et al. Bendamustine in heavily pre-treated patients with relapsed or refractory multiple myeloma. *J Cancer Res Clin Oncol*. 2015; 141(12):2205-12.

93. Jagannath S, Roy A, Kish J, et al. Real-world treatment patterns and associated progression-free survival in relapsed/refractory multiple myeloma among US community oncology practices. *Expert Rev Hematol*. 2016:1-11.

94. Kistler KD, Rajangam K, Faich G and Lanes S. Cardiac event rates in patients with newly diagnosed and relapsed multiple myeloma in us clinical practice. *Blood*. 2012; 120.

95. Janssen Research & Development. An Open-label, Multicenter, Phase 2 Trial Investigating the Efficacy and Safety of Daratumumab in Subjects With Multiple Myeloma Who Have Received at Least 3 Prior Lines of Therapy (Including a Proteasome Inhibitor and IMiD) or are Double Refractory to a Proteasome Inhibitor and an IMiD. (Clinical study report) 12 May 2015.

96. Janssen Research & Development. Daratumumab (HuMax-CD38) Safety Study in Multiple Myeloma – Open-label, Dose-Escalation Followed by Open-Label, Single-Arm Study. (Clinical study report) 14 May 2015.

97. Janssen Research & Development. MMY2002/GEN501: 18-month integrated efficacy analysis. 2016. Data on file.

98. Janssen Research & Development. Addendum 1: An Open-label, Multicenter, Phase 2 Trial Investigating the Efficacy and Safety of Daratumumab in Subjects With Multiple Myeloma Who Have Received at Least 3 Prior Lines of Therapy (Including a Proteasome Inhibitor and IMiD) or are Double Refractory to a Proteasome Inhibitor and an IMiD. (Clinical study report) 26 August 2015.

99. Janssen Research & Development. Addendum 1: Daratumumab (HuMax-CD38) Safety Study in Multiple Myeloma – Open label, Dose Escalation Followed by Open Label, Single-Arm Study. (Clinical study report) 26 August 2015.

100. Chapuy CI, Nicholson RT, Aguad MD, et al. Resolving the daratumumab interference with blood compatibility testing. *Transfusion*. 2015; 55(6 Pt 2):1545-54.

101. Oostendorp M, Lammerts van Bueren JJ, Doshi P, et al. When blood transfusion medicine becomes complicated due to interference by monoclonal antibody therapy. *Transfusion*. 2015; 55(6 Pt 2):1555-62.

102. Schey S, Brown SR, Tillotson AL, et al. Bendamustine, thalidomide and dexamethasone combination therapy for relapsed/refractory myeloma patients: results of the MUKone randomized dose selection trial. *Brit J Haematol*. 2015; 170(3):336-48.

103. [redacted]

104. [redacted]

105. Signorovitch JE, Sikirica V, Erder MH, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. *Value Health*. 2012; 15(6):940-7.

106. Signorovitch JE, Wu EQ, Yu AP, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to

psoriasis treatment with adalimumab or etanercept. *Pharmacoeconomics*. 2010; 28(10):935-45.

107. National Institute for Health and Care Excellence (NICE). TA251: Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia. 2012. (Updated: 25 April 2012) Available at: https://www.nice.org.uk/guidance/ta251. Accessed: January 2012.

108. Kirson NY, Rao S, Birnbaum HG, et al. Matching-adjusted indirect comparison of adalimumab vs etanercept and infliximab for the treatment of psoriatic arthritis. *J Med Econ*. 2013; 16(4):479-89.

109. Novartis Pharmaceuticals UK Ltd. Benefit Assessment Dossier in accordance with § 35a of the German Social Code - Book V (SGB V). 2013. Available at: https://www.g-ba.de/downloads/92-975-1151/2015-09-25_Modul4A_Panobinostat.pdf. Accessed: 24 October 2016.

110. Rajkumar SV and Buadi F. Multiple myeloma: new staging systems for diagnosis, prognosis and response evaluation. *Best Pract Res Clin Haematol*. 2007; 20(4):665-80.

111. Guyot P, Ades AE, Ouwens MJ and Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol*. 2012; 12:9.

112. Wei LJ, Lin DY and Weissfeld L. Regression Analysis of Multivariate Incomplete Failure Time Data by Modeling Marginal Distributions. *Amer Statist Assoc*. 1989; 84(408):1065-73.

113. Hajek R, Masszi T, Petrucci MT, et al. A randomized phase III study of carfilzomib vs low-dose corticosteroids with optional cyclophosphamide in relapsed and refractory multiple myeloma (FOCUS). *Leukemia*. 2016.

114. National Institute for Health and Care Excellence (NICE). NICE DSU technical support document 17: The use of observational data to inform estimates of treatment effectiveness in technology appraisal: Methods for comparative individual patient data. 2015. (Updated: May 2015) Available at: http://www.nicedsu.org.uk/TSD17%20-%20DSU%20Observational%20data%20FINAL.pdf. Accessed: 21 September 2016.

115. Lin DY and Wei LJ. The robust inference for the proportional hazards model. *J Am Stat Assoc*. 1989; 84:1074-8.

116. Therneau TM and Grambsch P. *Modeling survival data: extending the Cox model*. 2000.

117. Janssen Research & Development. Outcomes of the multivariate regression analysis utilising IMF chart review data. 2016. Data on file.

118. Usmani S, Waheed S, Szymonifka J, et al. Pomalidomide (Pom) in relapsed and refractory multiple myeloma (RRMM) - TheUARK compassionate use protocol. *Blood*. 2011; 118.

119. Zepeda VHJ, Duggan P, Neri PE and Bahlis NJ. Pomalidomide and dexamethasone is an effective regimen for advanced-stage relapsed/refractory multiple myeloma: Experience of a single center. *Blood*. 2014; 124.

120. Krieger O, Machherndl-Spandl S, Binder M, et al. Bendamustin - A novel therapeutic option in relapsed/refractory multiple myeloma. *Onkologie*. 2010; 33:251-2.

121. Gentilini F, Brunetti GA, Finsinger P, et al. Bendamustine and dexamethasone is an effective salvage regimen for patient with advanced multiple myeloma in a home care unit program. *Blood*. 2014; 124.

122. Ramasamy K, Lau IJ, Smith D, et al. Bendamustine combination therapy in patients relapsed and/ or refractory to bortezomib and lenalidomide. *Clin Lymphoma Myeloma Leuk*. 2013; 13:S189.

123. Lokhorst H, Laubach JP, Nahi H, et al. Dose-dependent efficacy of daratumumab (DARA) as monotherapy in patients with relapsed or refractory multiple myeloma (RR MM). ASCO Chicago, IL., US. 30 May-3 June 2014. 8513.

124. Lonial S and Anderson KC. Association of response endpoints with survival outcomes in multiple myeloma. *Leukemia*. 2014; 28(2):258-68.

125. Morgan G, San Miguel JF, Dhanasiri S, et al. Overall survival of patients with relapsed and refractory multiple myeloma: Adjusting for crossover in the MM-003 trial for pomalidomide plus low-dose dexamethasone vs. High-dose dexamethasone. *Haematologica*. 2014; 99:365-6.

126. International Myeloma Foundation. Daratumumab Monotherapy Compared With Real-world Historical Control Data in Heavily Pretreated Patients With Highly Refractory Multiple Myeloma: An Adjusted Treatment Comparison. 2016. Data on file.

127. National Institute for Health and Care Excellence (NICE). Guide to the Methods of Technology Appraisal. 2013. Available at: https://www.nice.org.uk/process/pmg9/chapter/foreword. Accessed: 1 September 2016.

128. European Medicines Agency. EPAR summary for the public, Imnovid (pomalidomide). 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002682/WC500147720.pdf. Accessed: 1 September 2016.

129. European Medicines Agency. EPAR Assessment Report, Farydak (panobinostat). 2016. (Updated: 13/04/2016) Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003725/WC500193298.pdf. Accessed: 1 August 2016.

130. electronic Medicines Compendium (eMC). Summary of product characteristics: Levact 2.5 mg/ml powder for concentrate for solution for infusion. 2015. (Updated: 18-Feb-2015) Available at: https://www.medicines.org.uk/emc/medicine/23469/SPC/Levact+2.5+mg+ml+powder+for+concentrate+for+solution+for+infusion/. Accessed: August 2016.

131. National Health Service. Bendamustine, Thalidomide and Dexamethasone (BTD) 2013. Available at: http://stlukescanceralliance.co.uk/wp-content/uploads/2015/10/Benda-Thal-Dex-BDT-V1-8.13.pdf. Accessed: 1 October 2016.

132. National Institute for Health and Care Excellence (NICE). NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2013. Available at: http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis.updated%20March%202013.v2.pdf. Accessed: 19 January 2015.

133. Janssen Research & Development. Scottish clinician consultation for daratumumab for the treatment of multiple myeloma. 13 April 2016. Data on file.

134. Haematological Malignancy Research Network. Clinical management and outcomes in relapsed/refractory myeloma. 15 February 2016. Data on File.

135. Osborne TR, Ramsenthaler C, Siegert RJ, et al. What issues matter most to people with multiple myeloma and how well are we measuring them? A systematic review of quality of life tools. *Eur J Haematol*. 2012; 89(6):437-57.

136. Ludwig H, Beksac M, Blade J, et al. Current multiple myeloma treatment strategies with novel agents: a European perspective. *Oncologist*. 2010; 15(1):6-25.

137. Janssen Research & Development. Daratumumab Early Access Programme (NCT02477891; MMY3010), Analysis of EQ-5D-5L data. 2016. Data on File.

138. Delea TE, El Ouagari K, Rotter J, et al. Cost-effectiveness of zoledronic acid compared with clodronate in multiple myeloma. *Curr Oncol*. 2012; 19(6):e392-403.

139. van Agthoven M, Segeren CM, Buijt I, et al. A cost-utility analysis comparing intensive chemotherapy alone to intensive chemotherapy followed by myeloablative chemotherapy with autologous stem-cell rescue in newly diagnosed patients with stage II/III multiple myeloma; a prospective randomised phase III study. *Eur J Cancer*. 2004; 40(8):1159-69.

140. Fragoulakis V, Kastritis E, Psaltopoulou T and Maniadakis N. Economic evaluation of therapies for patients suffering from relapsed-refractory multiple myeloma in Greece. *Cancer Manag Res*. 2013; 5:37-48.

141. Moller J, Nicklasson L and Murthy A. Cost-effectiveness of novel relapsed-refractory multiple myeloma therapies in Norway: lenalidomide plus dexamethasone vs bortezomib. *J Med Econ*. 2011; 14(6):690-7.

142. Usmani SZ, Cavenagh JD, Belch AR, et al. Cost-effectiveness of lenalidomide plus dexamethasone vs bortezomib plus melphalan and prednisone in transplant-ineligible US patients with newly-diagnosed multiple myeloma. *J Med Econ*. 2016; 19(3):243-58.

143. Crott R, Versteegh M and Uyl-de Groot CA. An assessment of the external validity of mapping QLQ-C30 to EQ-5D preferences. *Quali Life Res*. 2013; 22:1045-54.

144. Kharroubi SA, Edlin R, Meads D, et al. Use of Bayesian Markov chain Monte Carlo methods to estimate EQ-5D utility scores from EORTC QLQ data in myeloma for use in cost-effectiveness analysis. *Med Decis Making*. 2015; 35(3):351-60.

145. Rowen D, Young T, Brazier J and Gaugris S. Comparison of generic, condition-specific, and mapped health state utility values for multiple myeloma cancer. *Value Health*. 2012; 15(8):1059-68.

146. Quinn C, Hirji I, Shingler SL and Davis C. Mapping Health State Utility Values From Eortc Data Collected From A Clinical Trial Population With Relapsed/Refractory Multiple Myeloma. *Value Health*. 2015; 18(7):A468.

147. Proskorovsky I, Lewis P, Williams CD, et al. Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. *Health Qual Life Outcomes*. 2014; 12.

148. Ashaye AO, Altincatal A, Bender RH, et al. Estimating Eortc-8d Health State Utility Values From Eortc Qlq-C30 Scores In Relapsed Multiple Myeloma. *Value Health*. 2015; 18(7):A468.

149. Uyl-de Groot CA, Buijt I, Gloudemans IJM, et al. Health related quality of life in patients with multiple myeloma undergoing a double transplantation. *Eur J Haematol*. 2005; 74:136-43.

150. Acaster S, Gaugris S, Velikova G, et al. Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: a UK cross-sectional survey. *Support Care Cancer*. 2013; 21(2):599-607.

151. Naik H, Howell D, Qiu X, et al. Canadian cancer site-specific health utility values: Creating the basis for measuring value and costs of therapy. *J Clin Oncol*. 2014; 32((suppl 30; abstr 7)).

152. Delforge M, Minuk L, Eisenmann JC, et al. Health-related quality-of-life in patients with newly diagnosed multiple myeloma in the FIRST trial: lenalidomide plus low-dose dexamethasone versus melphalan, prednisone, thalidomide. *Haematologica*. 2015; 100(6):826-33.

153. Cella D, Moreau P, Kuter D, et al. An ongoing multinational observational study in multiple myeloma (preamble): a preliminary report of disease impact on quality of life. Haematologica. Vienna, Austria. 11 June 2015. S148.

154. Palumbo A, Davies F, Lee D, et al. Quality of Life Weights (Utilities) in Refractory or Relapsed and Refractory Multiple Myeloma (RRMM) Patients Using EORTC-8D and EQ-5D. Lymphoma and Myeloma. New York, US. 24-26th October 2013. P-03.

155. Ashaye AO, Zhang J, Bender RH, et al. Mapping Utility Scores from European organization for Treatment of Cancer Core-30 Questionnaire Scores (Eortc Qlq-C30) In Relapsed Multiple Myeloma. *Value Health*. 2015; 18(3):A208.

156. Brown RE, Stern S, Dhanasiri S and Schey S. Lenalidomide for multiple myeloma: Cost-effectiveness in patients with one prior therapy in England and Wales. *Eur J Health Econ*. 2013; 14:507-14.

157. National Institute of Health and Care Excellence (NICE). Single Technology Appraisal (STA) of lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy with bortezomib (partial review of TA171). 2013. Available at: https://www.nice.org.uk/guidance/GID-TAG452/documents/multiple-myeloma-lenalidomide-post-bortezomib-part-rev-ta171-evaluation-report2. Accessed: 18 April 2016.

158. Lloyd A, Nafees B, Narewska J, et al. Health state utilities for metastatic breast cancer. *Br J Cancer*. 2006; 95(6):683-90.

159. Tolley K, Goad C, Yi Y, et al. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. *Eur J Health Econ*. 2013; 14(5):749-59.

160. Sullivan PW, Slejko JF, Sculpher MJ and Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making*. 2011; 31(6):800-4.

161. National Institute for Health and Care Excellence (NICE). TA359 Manufacturers Submission: Idelalisib for treating chronic lymphocytic leukaemia [ID764]. 2015. Available at: https://www.nice.org.uk/guidance/TA359/documents/leukaemia-chronic-lymphocytic-previously-treated-idelalisib-id764-committee-papers2. Accessed: 1 September 2016.

162. Green C, Bryant J, Takeda A, et al. Bortezomib for the treatment of multiple myeloma patients. *Health Technol Assess*. 2009; 13 Suppl 1:29-33.

163. Ross JR, Saunders Y, Edmonds PM, et al. A systematic review of the role of bisphosphonates in metastatic disease. *Health Technol Assess*. 2004; 8(4):1-176.

164. Bruce N, McCloskey E, Kanis J and Guest J. Economic impact of using clodronate in the management of patients with multiple myeloma. *Brit J Haematol*. 1999; 104(2):358-64.

165. Popat R, Dickson J, Khan I, et al. An alternate day dosing strategy for lenalidomide in multiple myeloma improves cost-effectiveness whilst maintaining efficacy. *Blood*. 2011; 118.

166. Hatswell AJ, Porter J, Lee D, et al. The Cost of Costing Treatments Incorrectly: Errors in the Application of Drug Prices in Economic Evaluation Due to Failing to Account for the Distribution of Patient Weight. *Value Health*. 2016.

167. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal: Lymphoma (mantle cell, untreated) –bortezomib [ID724]. 2015. Available at: https://www.nice.org.uk/guidance/TA370/documents/committee-papers. Accessed: 3 May 2016.

168. DuBois D and DuBois E. A Formula To Estimate The Approximate Surface Area If Height And Weight Be Known *Arch Intern Med (Chic)*. 1916; 17:863-71.

169. Department of Health. Guidance, Drugs and pharmaceutical electronic market information (eMit). 2015. (Updated: 27 November 2015) Available at: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Accessed: 25 April 2016.

170. National Health Service (NHS). Blood and DTS pricing proposals for 2015/16. 2014. Available at: http://www.nhsbt.nhs.uk/download/board_papers/sept14/m14_99.pdf. Accessed: 20 May 2016.

171. Department of Health. NHS Reference Costs. 2015. (Updated: 27 November 2015) Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015. Accessed: 21 June 2015.

172. Janssen Research & Development. Haematological Malignancy Research Network: Clinical management and outcomes in relapsed/refractory myeloma. 22 January 2016. Data on File.

8 Appendices

Appendix 1: Summary of product characteristics (SmPC) and European public assessment report (EPAR) (section 2.2)

Appendix 2: Search strategies for clinical effectiveness and adverse events studies (section 4.1 and 4.12)

Appendix 3: Secondary data sources (Section 4.1)

Appendix 4: Methodology and quality assessment of MMY2002 and GEN501 (Section 4.3)

Appendix 5: Subgroup analysis of MMY2002 and GEN501 (Section 4.8)

Appendix 6: Investigator assessed PFS (Section 4.9)

Appendix 7: Trials identified for potential inclusion in an indirect treatment comparison (Section 4.10)

Appendix 8: Methodology and quality assessment of PANORAMA 2, MM-003 and IMF dataset (Section 4.10)

Appendix 9: Indirect treatment comparison (Section 4.10)

Appendix 10: Search strategy for cost-effectiveness studies (section 5.1.1)

Appendix 11: Testing of proportional hazard assumption

Appendix 12: Search strategy for measurement and valuation of health effects (section 5.4.3)

Appendix 13: Cost and healthcare resource identification, measurement and valuation (section 5.5.2)

Appendix 14: Summary of variables applied in the economic model

Appendix 15: PSA stabiliation analysis

Appendix 16: Safety data from individual MMY2002 and GEN501 trials

Appendix H: Checklist of confidential information

Daratumumab for treating relapsed and refractory multiple myeloma [ID933]

Addendum to company evidence submission

21 December 2016

Dear Jeremy,

Following minor errors identified by the ERG in clarification questions B22 and B26, the model has been corrected and the base case ICERs have changed slightly.

Please accept our apologies for the minor errors identified. Correcting for these two errors leads to revised base case ICERs of £55,766 versus pomalidomide plus dexamethasone (POM+DEX), £32,593 versus panobinostat plus bortezomib plus dexamethasone (PANO+BORT+DEX) and £56,574 versus bendamustine-based therapy.

The model changes made are outlined in the clarification response document and are reiterated here for clarity. Following this, results from the corrected model are presented as requested.

Yours,

Nicola

1 Issues identified in clarification questions

- Clarification question B22. The equation used to estimate the proportion of patients assumed to experience nausea (all grades) in the model ('Adverse events'! E31) is as follows = ((4%*124)+ (12.5%*32))/ (124+32). Please clarify where the 4% for the MMY2002 was obtained from, as according to Table 28 on page 96 of the MMY2002 CSR this value should be 28.2%.

The 4% estimate has been taken from "Transfusion related reactions" data. This is an error and should have been taken from "Treatment-emergent adverse events" data. This has been corrected in the model to 28.2%

- Clarification question B26. Please clarify why the utility decrements in the model for hypotension, septic shock, syncope, peripheral neuropathy, flatulence, abdominal distention and hypokalaemia are positive while those for the remaining adverse events are negative. This question refers to 'Utility'! G57: G61 and 63:G66.

This was an error in the model. This has been corrected in Cells P361: 366 on the "Parameters" sheets to transform values back into negative values as has been done for the other adverse events.

2 Base case and sensitivity analysis results from the corrected model

Base case results from the corrected model are reported in Table 1. Table 2 to Table 5 show disaggregated base case results, and are updates of the tables in Section 5.7.3 of the company submission.

Table 6 and Figure 1 to Figure 6 show results from probabilistic sensitivity analysis of the corrected model, and are updates of the table and figures in Section 5.8.1 of the company submission.

Figure 7 to Figure 9 show deterministic sensitivity analysis results from the corrected model, in the form of tornado diagrams for each pairwise comparison with

daratumumab, and are updates of the figures in Section 5.8.2 of the company submission.

Table 7 shows scenario analysis results from the corrected model, and is an update of Table 83 from Section 5.8.3 of the company submission.

Table 1: Pairwise base-case results from the corrected model (update of Table 75 of CS)

	Total			Incremental			ICER (Dara vs comparator) at list prices
	Costs	**QALYs**	**LYs**	**Costs**	**QALYs**	**LYs**	
Daratumumab	£81,422	1.31	2.54				
POM+DEX	£49,921	0.75	1.46	£31,501	0.56	1.07	£55,766
PANO+BORT+DEX	£74,530	1.10	2.14	£6,892	0.21	0.39	£32,593
Bendamustine-based therapy	£38,327	0.55	1.10	£43,095	0.76	1.44	£56,574

Key: BORT, bortezomib; DEX, dexamethasone; CS, company submission; Dara, daratumumab; year; ICER, incremental cost-effectiveness ratio; LY, life year; PANO, panobinostat; POM, pomalidomide; QALY, quality-adjusted life.

Table 2: Disaggregated costs from the corrected model (update of Table 77 of CS)

		POM+DEX				PANO+BORT+DEX				Bendamustine-based therapy			
	Daratumumab	POM+DEX	Incremental	Absolute Increment	% Increment	PANO+BORT+DEX	Incremental	Absolute Increment	% Increment	Bendamustine-based therapy	Incremental	Absolute Increment	% Increment
Drug costs	£70,905	£44,590	£26,315	£26,315	76%	£60,532	£10,373	£10,373	71%	£30,853	£40,052	£40,052	87%
Admin Costs	£5,836	£191	£5,645	£5,645	16%	£7,398	-£1,561	£1,561	11%	£2,742	£3,094	£3,094	7%
Co-medication costs	£239	£392	-£153	£153	0%	£272	-£33	£33	0%	£223	£16	£16	0%
Adverse Events	£941	£2,236	-£1,294	£1,294	4%	£2,835	-£1,894	£1,894	13%	£2,248	-£1,307	£1,307	3%
Pre-progression Monitoring costs on treatment	£1,272	£741	£531	£531	2%	£1,490	-£218	£218	1%	£704	£569	£569	1%
Pre-progression Monitoring costs off treatment	£35	£104	-£68	£68	0%	£18	£18	£18	0%	£0	£35	£35	0%
Subsequent treatment	£9	£43	-£34	£34	0%	£60	-£52	£52	0%	£45	-£37	£37	0%

		POM+DEX				PANO+BORT+DEX				Bendamustine-based therapy			
	Daratumumab	POM+DEX	Incremental	Absolute Increment	% Increment	PANO+BORT+DEX	Incremental	Absolute Increment	% Increment	Bendamustine-based therapy	Incremental	Absolute Increment	% Increment
costs													
Subsequent treatment Admin costs	£162	£151	£12	£12	0%	£211	-£48	£48	0%	£159	£4	£4	0%
Post-progression Monitoring	£1,239	£661	£578	£578	2%	£920	£319	£319	2%	£532	£707	£707	2%
Terminal Care	£782	£812	-£30	£30	0%	£793	-£11	£11	0%	£822	-£40	£40	0%
Total	**£81,422**	**£49,921**	**£31,501**	**£31,501**	**100%**	**£74,530**	**£6,892**	**£6,892**	**100%**	**£38,327**	**£43,095**	**£43,095**	**100%**
Key: CS, company submission; POM, pomalidomide; DEX, dexamethasone; PANO, panobinostat; BORT, bortezomib													

Table 3: Disaggregated costs, by health state, from the corrected model (update of Table 78 of CS)

		POM+DEX				PANO+BORT+DEX				Bendamustine-based therapy			
	Daratumumab	POM+DEX	Incremental	Absolute Increment	% Increment	PANO+BORT+DEX	Incremental	Absolute Increment	% Increment	Bendamustine-based therapy	Incremental	Absolute Increment	% Increment
Pre-Progression On Treatment	£79,194	£48,151	£31,044	£31,044	98%	£72,527	£6,667	£6,667	96%	£36,769	£42,425	£42,425	98%
Pre-Progression Off Treatment	£35	£104	-£68	£68	0%	£18	£18	£18	0%	£0	£35	£35	0%
Post-Progression	£1,410	£855	£555	£555	2%	£1,191	£219	£219	3%	£736	£674	£674	2%
Terminal Costs	£782	£812	-£30	£30	0%	£793	-£11	£11	0%	£822	-£40	£40	0%
Total	**£81,422**	**£49,921**	**£31,501**	**£31,697**	**100%**	**£61,438**	**£19,983**	**£19,983**	**100%**	**£38,327**	**£43,095**	**£43,174**	**100%**
Key: CS, company submission; POM, pomalidomide; DEX, dexamethasome; PANO, panobinostat; BORT, bortezomib													

Table 4: Disaggregated QALYs from the corrected model (update of Table 79 of CS)

		POM+DEX				PANO+BORT+DEX				Bendamustine-based therapy			
	Daratumumab	POM+DEX	Incremental	Absolute Increment	% Increment	PANO+BORT+DEX	Incremental	Absolute Increment	% Increment	Bendamustine-based therapy	Incremental	Absolute Increment	% Increment
Pre-Progression On Treatment	0.39	0.23	0.16	0.16	24%	0.46	-0.07	0.07	19%	0.22	0.18	0.18	23%
Pre-Progression Off Treatment	0.03	0.09	-0.06	0.06	8%	0.02	0.01	0.01	4%	0.00	0.03	0.03	4%
Post-Progression	0.93	0.50	0.44	0.44	64%	0.69	0.24	0.24	70%	0.40	0.53	0.53	70%
AE	-0.04	-0.07	0.02	0.02	3%	-0.07	0.02	0.02	7%	-0.07	0.02	0.02	3%
Total	**1.31**	**0.75**	**0.56**	**0.68**	**100%**	**1.10**	**0.21**	**0.35**	**100%**	**0.55**	**0.76**	**0.76**	**100%**
Key: CS, company submission; POM, pomalidomide; DEX, dexamethasome; PANO, panobinostat; BORT, bortezomib; AE, adverse event													

Table 5: Disaggregated life years from the corrected model (update of Table 80 of CS)

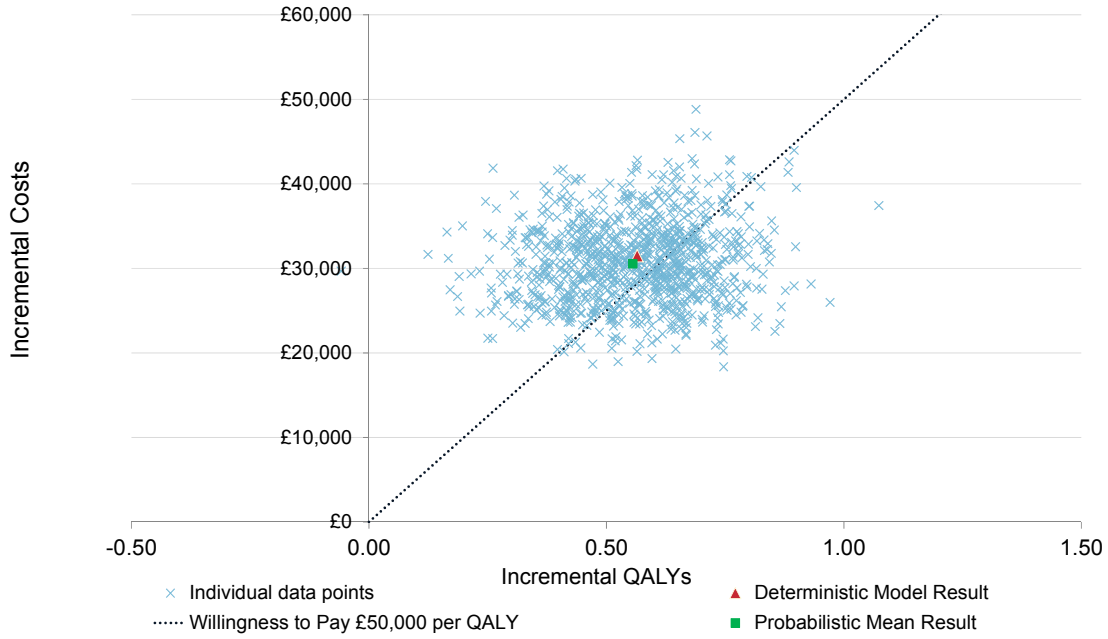
		POM+DEX				PANO+BORT+DEX				Bendamustine-based therapy			
	Daratumumab	POM+DEX	Incremental	Absolute Increment	% Increment	PANO+BORT+DEX	Incremental	Absolute Increment	% Increment	Bendamustine-based therapy	Incremental	Absolute Increment	% Increment
Pre-Progression On Treatment	0.67	0.38	0.29	0.29	23%	0.78	-0.11	0.11	18%	0.36	0.31	0.31	22%
Pre-Progression Off Treatment	0.05	0.15	-0.10	0.10	8%	0.03	0.02	0.02	3%	0.00	0.05	0.05	4%
Post-Progression	1.82	0.93	0.88	0.88	69%	1.33	0.49	0.49	79%	0.74	1.08	1.08	75%
Total	**2.54**	**1.46**	**1.07**	**1.28**	**100%**	**2.14**	**0.39**	**0.61**	**100%**	**1.10**	**1.44**	**1.44**	**100%**
Key: CS, company submission; POM, pomalidomide; DEX, dexamethasome; PANO, panobinostat; BORT, bortezomib													

Table 6: Mean PSA results from the corrected model (update of Table 81 of CS)

	Total			Incremental			ICER (Dara vs Comparator)
	Costs	**QALYs**	**LYs**	**Costs**	**QALYs**	**LYs**	
Daratumumab	£80,197	1.32	2.55				
POM+DEX	£49,653	0.76	1.50	£30,544	0.56	1.06	£54,987
PANO+BORT+DEX	£74,516	1.14	2.22	£5,681	0.18	0.33	£31,079
Bendamustine-based therapy	£39,313	0.56	1.13	£40,884	0.76	1.43	£54,149

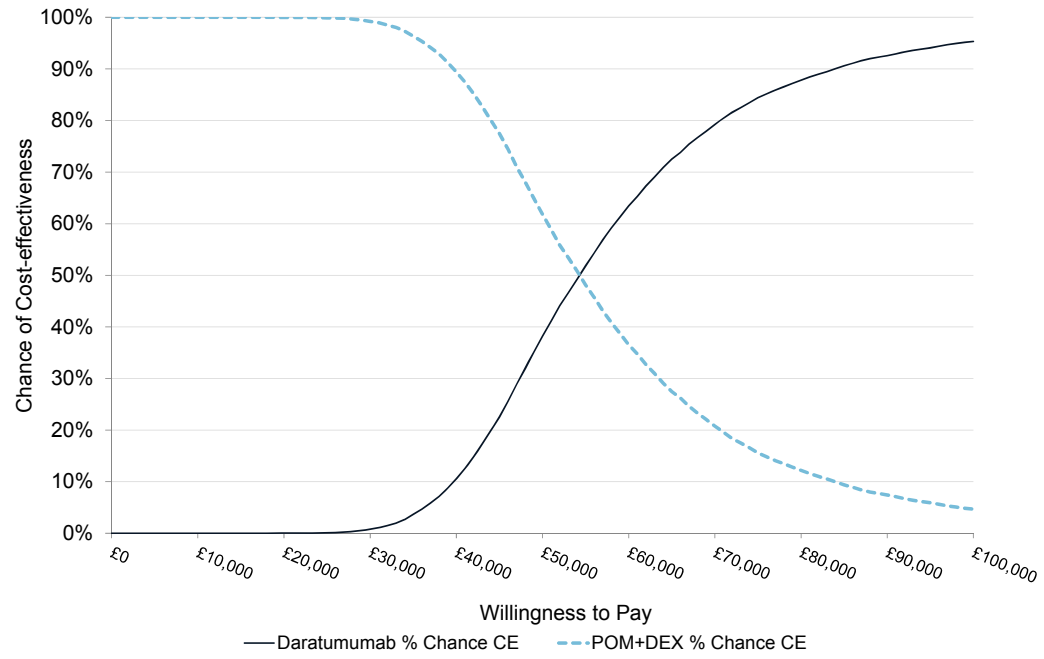
Key: CS, company submission; POM, pomalidomide; DEX, dexamethasome; PANO, panobinostat; BORT, bortezomib; LY, life years; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; DARA, daratumumab

Figure 1: PSA scatterplot - Daratumumab vs POM+DEX, from the corrected model (update of Figure 46 of CS)



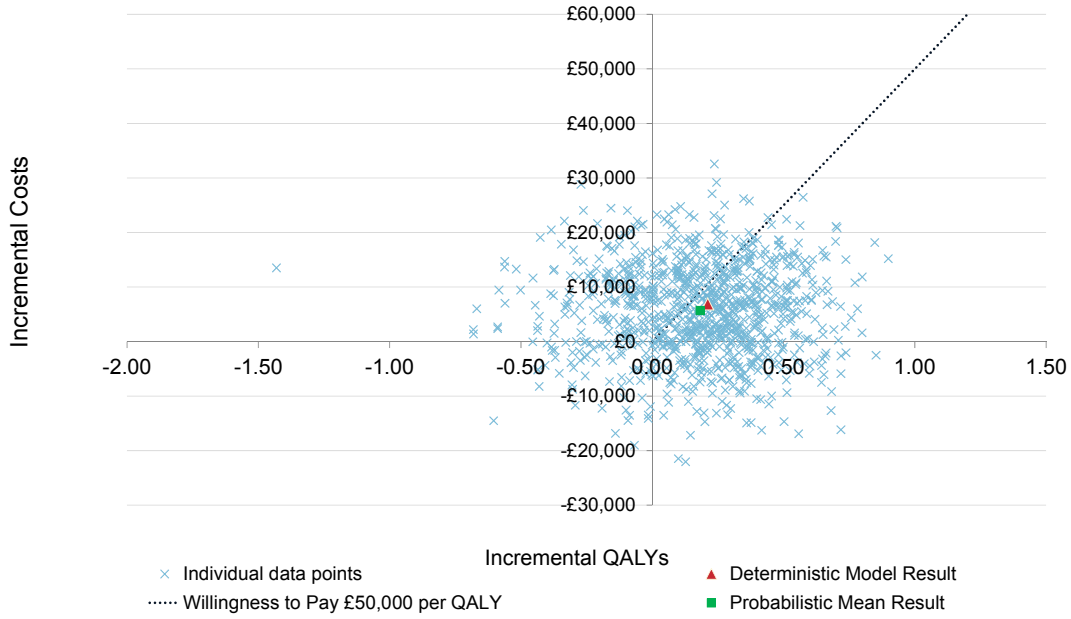
Key: CS, company submission; QALY, quality adjusted life year; POM, pomalidomide; DEX, dexamethasone

Figure 2: CEAC - Daratumumab vs POM+DEX, from the corrected model (update of Figure 47 of CS)



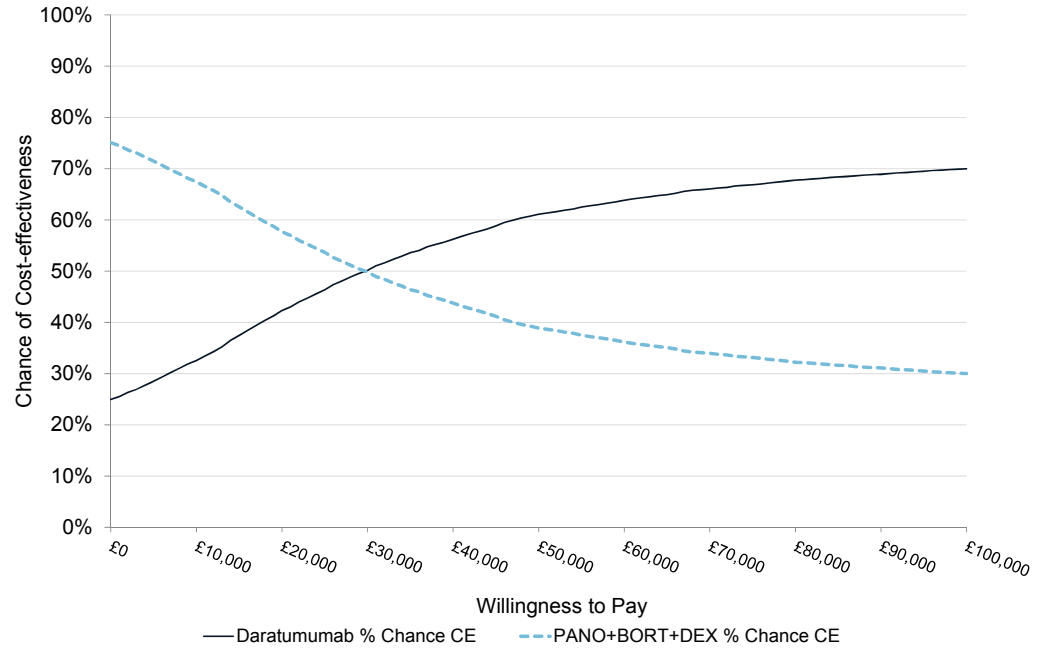
Key: CE, cost-effective; CS, company submission; POM, pomalidomide; DEX, dexamethasone

Figure 3: PSA scatterplot - Daratumumab vs PANO+BORT+DEX, from the corrected model (update of Figure 48 of CS)



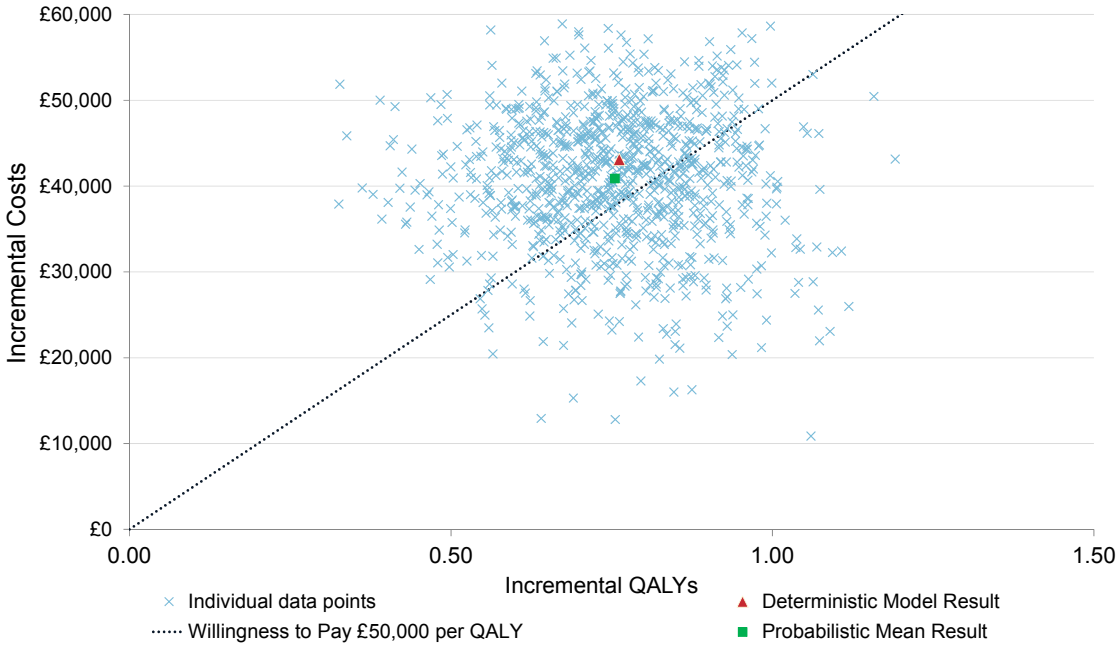
Key: CS, company submission QALY, quality adjusted life years; PANO, panobinostat; BORT, bortezomib; DEX, dexamethasone

Figure 4: CEAC - Daratumumab vs PANO+BORT+DEX, from the corrected model (update of Figure 49 of CS)



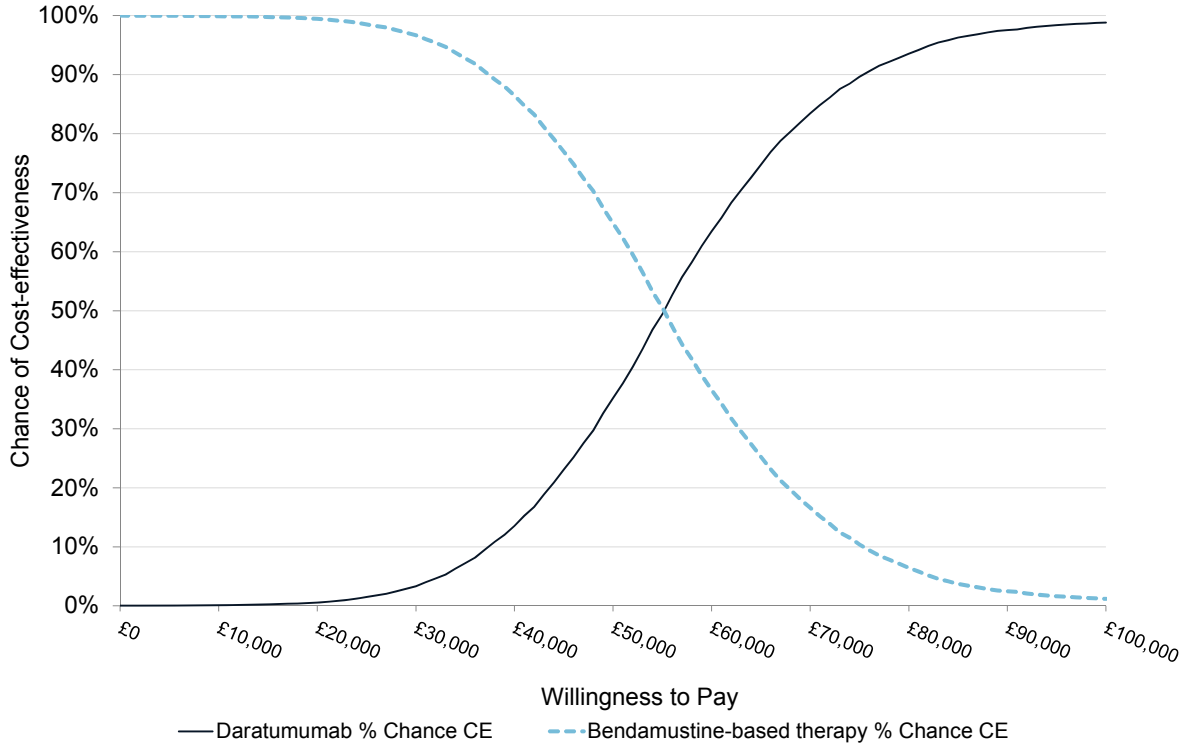
Key: CE, cost-effective; CS, company submission; PANO, panobinostat; BORT, bortezomib; DEX, dexamethasone

Figure 5: PSA scatterplot - Daratumumab vs bendamustine-based therapy, from the corrected model (update of Figure 50 of CS)



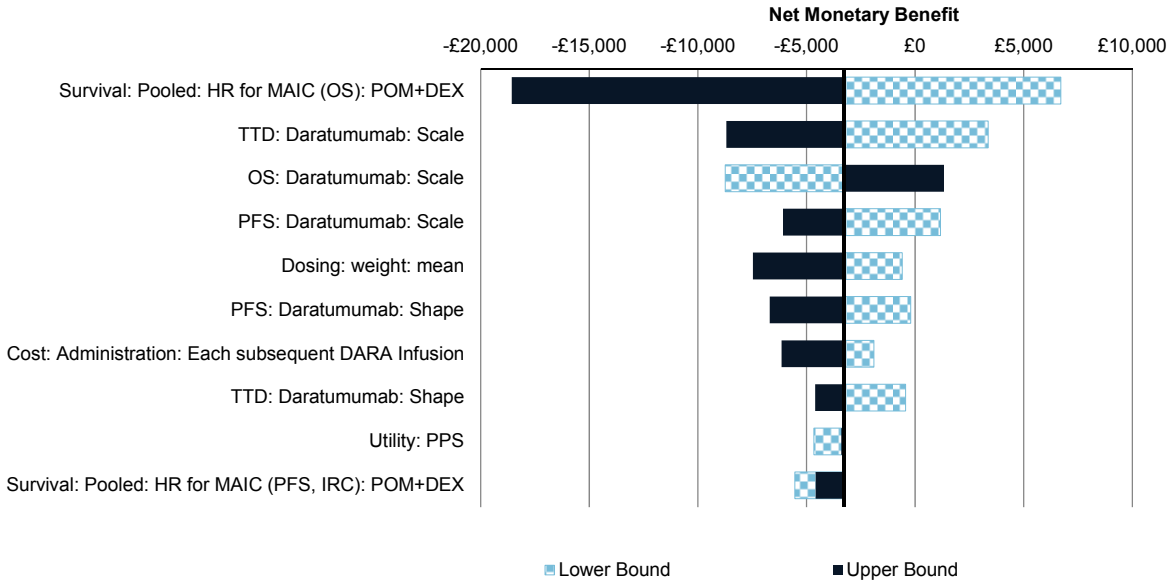
Key: CS, company submission; QALY, quality adjusted life year

Figure 6: CEAC - Daratumumab vs bendamustine based therapy, from the corrected model (update of Figure 51 of CS)



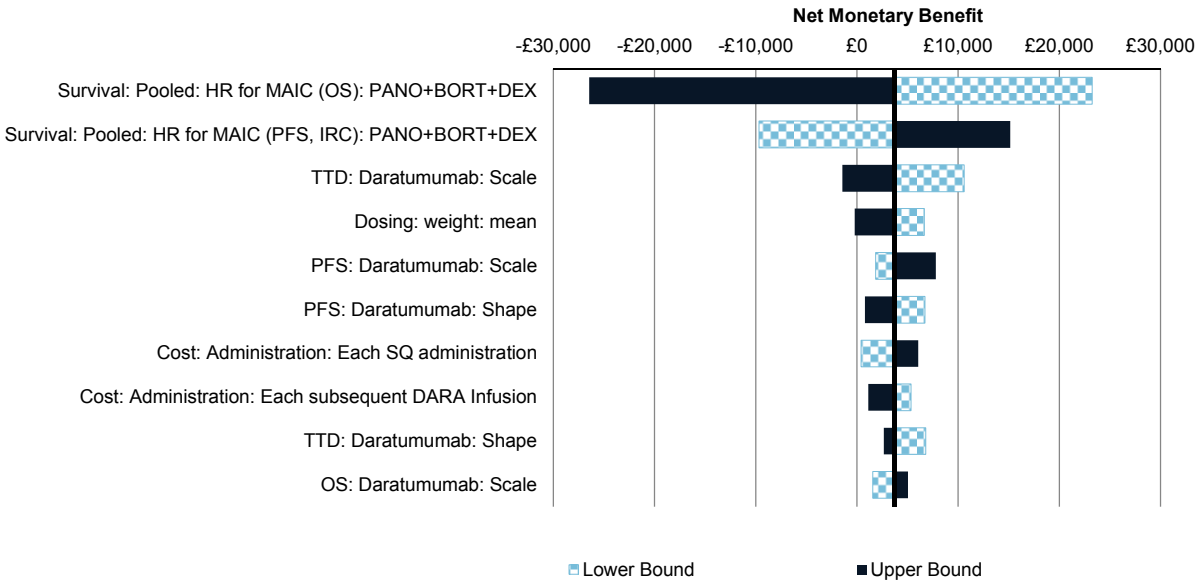
Key: CE, cost-effective; CS, company submission

Figure 7: Tornado Diagram - Daratumumab vs POM+DEX, from the corrected model (update of Figure 52 of CS)



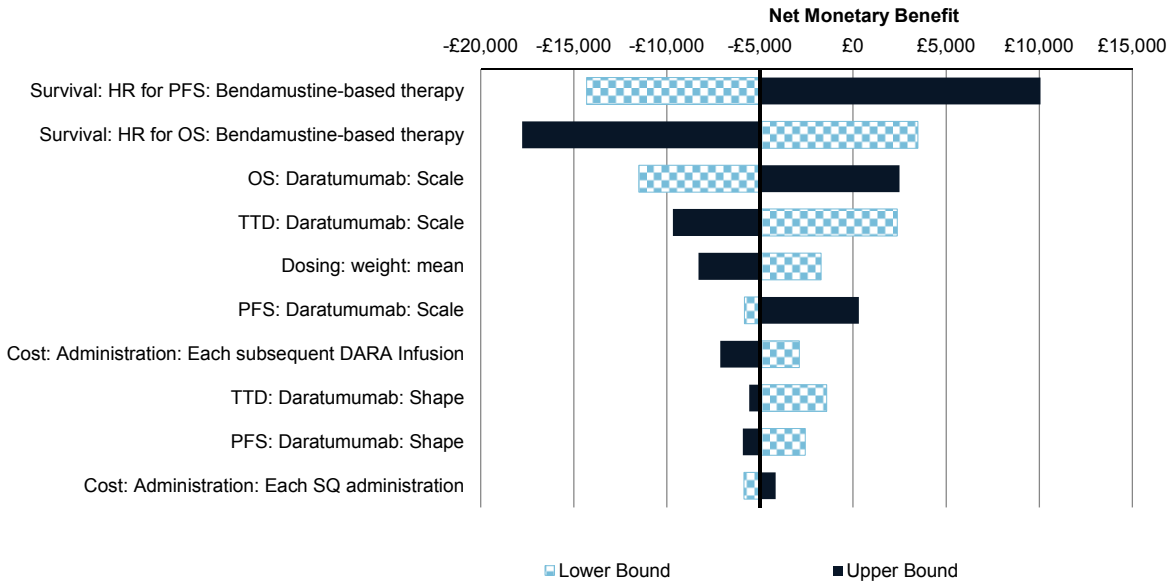
Key: CS, company submission; HR, hazard ratio; PFS, progression-free survival; TTD, time to treatment discontinuation; DARA, daratumumab; POM, pomalidomide; DEX, dexamethasone; MAIC, match adjusted indirect comparison

Figure 8: Tornado Diagram - Daratumumab vs PANO+BORT+DEX, from the corrected model (update of Figure 53 of CS)



Key: CS, company submission; HR, hazard ratio; PFS, progression-free survival; TTD, time to treatment discontinuation; DARA, daratumumab; PANO, panobinostat; DEX, dexamethasone; BORT, bortezomib; MAIC, match adjusted indirect comparison

Figure 9: Tornado Diagram - Daratumumab vs bendamustine-based therapy, from the corrected model (update of Figure 54 of CS)



Key: CS, company submission; HR, hazard ratio; PFS, progression-free survival; TTD, time to treatment discontinuation; DARA, daratumumab

Table 7: Scenario analyses results, from the corrected model (update of Table 83 of CS)

Parameter	Base case	Scenario Analysis	ICER (DARA vs POM+DEX)	ICER (DARA vs PANO+BORT+DEX)	ICER (DARA vs Bendamustine-based therapy)
Basecase			£55,766	£32,593	£56,574
Time horizon	15 years	5 years	£56,772	£32,536	£57,358
Time horizon	15 years	10 years	£56,772	£32,536	£57,358
Discount rate (costs and QALYs)	3.50%	0%	£51,130	£33,606	£52,198
Discount rate (costs and QALYs)	3.50%	6%	£59,318	£31,734	£59,900
Utilities	Palumbo: PFS 0.6, PPS 0.57	TA 380 (PFS 0.71, PPS 0.64)	£49,603	£29,606	£50,137
Utilities	Palumbo: PFS 0.6, PPS 0.57	TA338 (PFS 0.65, PPS 0.57)	£55,090	£33,127	£55,593
Daratumumab TTD curve fits	Log-logistic	Log-normal	£57,002	£35,894	£57,491
Daratumumab TTD curve fits	Log-logistic	Exponential	£45,261	£4,530	£48,784
Daratumumab TTD curve fits	Log-logistic	Weibull	£45,477	£5,109	£48,945
Daratumumab TTD curve fits	Log-logistic	Gamma	£50,419	£18,310	£52,610
Daratumumab PFS	Log-normal	Exponential	£45,120	Daratumumab Dominates	£47,092

curve fits					
Daratumumab PFS curve fits	Log-normal	Log-logistic	£62,082	£55,084	£61,518
Daratumumab PFS curve fits	Log-normal	Gamma	£61,262	£55,656	£53,787
Daratumumab PFS curve fits	Log-normal	Weibull	£45,700	Daratumumab Dominates	£47,921
Daratumumab OS curve fits	Exponential	Weibull	£60,635	£35,337	£61,265
Daratumumab OS curve fits	Exponential	Log-logistic	£38,288	£22,696	£39,552
Daratumumab OS curve fits	Exponential	Log-normal	£36,325	£21,837	£37,305
Daratumumab OS curve fits	Exponential	Gamma	£46,809	£27,229	£48,144
Daratumumab PFS	IRC	INV	£53,677	£40,246	£57,585
MAIC	Daratumumab patient population used is integrated GEN501/MMY2002	Daratumumab patient population used is MMY2002	£54,045	Daratumumab Dominates	£58,876
MAIC vs POM+DEX	11 Matched Criteria	3 Matched Criteria	£61,170	NA	NA
MAIC vs POM+DEX	11 Matched Criteria	5 Matched Criteria	£59,688	NA	NA
MAIC vs POM+DEX	11 Matched Criteria	18 Matched Criteria	£52,840	NA	NA

MAIC vs POM+DEX	Patient pre-treated with pomalidomide included	Patient pre-treated with pomalidomide excluded	£61,009	NA	NA
MAIC vs POM+DEX	Proportional Hazards assumed	Independent curve fits	£56,692	NA	NA
Comparative efficacy, POM+DEX	MAIC	Multivariate regression analyses using IMF	£39,627	NA	NA
MAIC vs PANO+BORT+DEX	5 Matched Criteria	2 Matched Criteria	NA	£28,842	NA
MAIC vs PANO+BORT+DEX	5 Matched Criteria	12 Matched Criteria	NA	£34,870	NA
MAIC vs PANO+BORT+DEX	Proportional Hazards assumed	Independent curve fits	NA	£32,271	NA
Key: CS, company submission; NA, not applicable; PANO, panobinostat; DEX, dexamethasone; BORT, bortezomib; POM, pomalidomide; MAIC, matched adjusted indirect comparison; PFS, progression-free survival; OS, overall survival; TTD, time to treatment discontinuation; PPS, post-progression survival; DARA, dartumumab; QALYs, quality adjusted life years; ICER, incremental cost -effectiveness ratio					

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Single technology appraisal

Daratumumab for treating relapsed and refractory multiple myeloma [ID933]

Dear [redacted],

The Evidence Review Group, BMJ Technology Assessment Group (BMJ-TAG), and the technical team at NICE have looked at the submission received on 15 November 2016 from Janssen. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **6pm on 16 December 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Thomas Palmer, Technical Lead (thomas.palmer@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (jeremy.powell@nice.org.uk).

Yours sincerely

Melinda Goodall
Associate Director – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Section A: Clarification on effectiveness data

A1. **Priority question**: Please clarify which characteristics have been matched/adjusted for each estimate in Tables 40-42 in the company submission and Tables 21-22 in the appendices.

A2. **Priority question**: Please provide results for all outcomes reported in the matching-adjusted indirect comparison (MAIC) sensitivity analyses using data only from the GEN501 trial (as presented for MMY2002 in Tables 21 and 22 in the appendices). Also, please provide for each outcome details of any patient characteristics that were matched/adjusted to estimate relative effects.

A3. **Priority question**: Please provide a more detailed rationale for the selection and the ranking of the risk factors adjusted for in the MAIC. In particular, please explain the rationale around the order of variables in Tables 36 and 37 of the company submission (pages 123 and 124 respectively). Additionally, please outline the company's view on the impact of not incorporating important clinically relevant risk factors (e.g. cytogenetics and ISS staging) on the MAIC.

A4. **Priority Question:** Please provide the weights attributed to the different patient characteristics adjusted for in the pomalidomide plus dexamethasone, and in the panobinostat plus bortezomib plus dexamethasone MAIC analyses for the:

a) integrated daratumumab data

b) MMY2002

c) GEN501.

A5. **Priority question**: Please provide the effect estimates for the outcomes listed below in patients from MMY2002 who did not receive pomalidomide as a previous therapy:

a. overall response rate (ORR)

b. best ORR (with accompanying breakdown of number of events in each categorisation of response)

c. overall survival (OS)

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

d. progression-free survival (PFS)

e. time to response (TTR)

f. duration of response

g. time to discontinuation (TTD).

A6. **Priority question**: For the analyses and populations listed below, please provide estimates of OS, and number of patients included in the analysis, for patients whose disease progressed while receiving daratumumab and who received:

a. For integrated analysis (for MMY2002 and GEN501) and the MAIC (versus pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone):

i. bortezomib as a subsequent treatment

ii. carfilzomib as a subsequent treatment

iii. lenalidomide as a subsequent treatment

iv. pomalidomide as a subsequent treatment.

b. For individual trials of MMY2002 and GEN501:

i. no subsequent treatment

ii. any subsequent treatment.

NB: Total of 16 estimates.

A7. **Priority question**: Please provide details on the methodology used to generate clinical efficacy results in the “integrated analysis” of data from MMY2002 and GEN501. In addition, please specify how the integrated analysis differs from the “crude pooling” referred to in the footnote of Table 46 of the company submission.

A8. **Priority question**: Please provide the MAIC analysis for TTD, similar to the MAIC analysis undertaken for OS and PFS and detailed in Section 4.10.3 of the company submission. Additionally, please provide the patient characteristics used to conduct the MAIC for TTD, along with the results of the analysis, including the adjusted Kaplan-Meier data and curves derived from the MAIC for TTD.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

A9. **Priority question**: Please provide details on treatment duration for each of the treatments received in a sequential order for MMY2002, GEN502 separately and in the integrated dataset. More specifically, please provide mean treatment duration per treatment with respective minimum and maximum treatment period.

A10. Please provide separate diagrams illustrating patient flow for MMY2002 and GEN501.

A11. Please clarify whether the duration of response reported in Table 15 (page 79 of the company submission) is for patients whose disease responded (as opposed to the entire trial population as stated in the text).

A11. Please provide the rationale for using different cut-off dates for MMY2002 (9th Jan 2015) and GEN501 (31st Dec 2015) for ORR and PFS as presented in the company submission. Additionally, please provide:

a. summary data for ORR in patients receiving daratumumab 16 mg/kg in MMY2002 at a cut-off date of 31 December 2015, and in GEN501 at a cut-off date of 9 January 2015 (in the format presented in Table 13 of the company submission)

b. summary data for PFS in patients receiving daratumumab 16 mg/kg in MMY2002 at a cut-off date of 31 December 2015, and in GEN501 at a cut-off date of 9 January 2015 (in the format presented in Table 17 of the company submission).

A12. The titles of Tables 13-15 and Tables 23-29 of the company submission indicate that the data have been assessed by an independent review committee (IRC). However, earlier in the company submission (page 76), it is stated that, for GEN501, “disease evaluations were conducted through a computerised algorithm, and an IDMC (independent data monitoring committee) reviewed unblinded data on a routine basis and provided recommendations on the continuation, modification, or termination of the study.”

a. Did the IDMC reviewing unblinded data from GEN501 also review the categorisations of clinical outcomes as reported in Tables 13-15, and in the integrated analyses presented in Tables 23-29?

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

b. If not, please discuss whether the reliability of the treatment algorithm in the categorisation of response was evaluated. For example, were any comparisons made between categorisations of response determined by the treatment algorithm and those made by the IRC? If so, what was the level of agreement?

A13. Please populate the table below to provide number of patients (and percentage) at baseline in MMY2002 and GEN501 by number of previous lines of therapy.

Number of lines of prior therapy	**MMY2002**		**GEN501 Part 2**	
	Dara 8mg/kg (n=18)	**Dara 16mg/kg (n=106)**	**Dara 8mg/kg (n=18)**	**Dara 16mg/kg (n=42)**
2				
3				
…				
14				

A14. Please provide data on treatment-related adverse events for:

a. integrated analysis of MMY2002 and GEN501

b. MMY2002

c. GEN501.

A15. For Table 16 (Summary of OS, page 81 of the company submission), please:

a. Clarify whether the number of events is the number of deaths or the number of people alive at the time reported.

b. Provide absolute event rates for the percentages reported at the various time points.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** Please provide the Kaplan–Meir data (in Excel format) for:

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

a. daratumumab from MMY2002 and GEN501 separately, for OS, PFS and TTD (where possible) adjusted with the MAIC to pomalidomide plus dexamethasone (MM-003) and also adjusted to panobinostat plus bortezomib plus dexamethasone (PANORAMA 2)
b. daratumumab unadjusted Kaplan–Meir data from GEN501 for OS, PFS and TTD
c. daratumumab adjusted and unadjusted integrated Kaplan–Meir data excluding pomalidomide pre-treated patients for OS, PFS and TTD (corresponding to the scenario analysis reported in the company submission)
d. the data requested in B1 c) from MMY2002 and GEN501 separately
e. daratumumab integrated adjusted and unadjusted OS Kaplan–Meir data based on subsequent post-daratumumab treatment received, more specifically for:
    i. patients receiving daratumumab with no subsequent treatment received
    ii. patients receiving bortezomib as a subsequent treatment after daratumumab
    iii. patients receiving carfilzomib as a subsequent treatment after daratumumab
    iv. patients receiving lenalidomide as a subsequent treatment after daratumumab
    v. patients receiving pomalidomide as a subsequent treatment after daratumumab
f. the data requested in B1 e) i) for MMY2002 data and GEN501 data, reported separately, for daratumumab alone with no subsequent treatments included
g. daratumumab adjusted and unadjusted OS Kaplan–Meir from MMY2002 and GEN501 separately for all the subsequent therapies received after daratumumab (i.e. excluding the initial treatment with daratumumab).

B2. **Priority question:** Please include an option in the model to allow the user to run the scenario analysis reported in the company submission excluding patients that were pre-treated with pomalidomide (resulting in an ICER of £59,097 per QALY gained).

B3. **Priority question:** Please provide the adjusted and unadjusted integrated OS, PFS and TTD curves for daratumumab that were used to run the scenario analysis reported in the company submission excluding patients that were pre-treated with pomalidomide.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

B4. **Priority question**: Please provide separate base-case analyses for MMY2002 and GEN501 compared with all relevant comparators using appropriate model inputs based on the data requested in B1 e) and f) in terms of OS, as per the analyses below. Please also either adapt the model or provide a new model to allow for each of the analyses:

a) integrated daratumumab patients who received daratumumab and no subsequent treatments against pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone
b) daratumumab patients from MMY2002 and from GEN501, separately, who received no subsequent treatments against pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone
c) integrated patients from MMY2002 and GEN501 receiving bortezomib as a subsequent treatment post-daratumumab against pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone
d) integrated patients from MMY2002 and GEN501 receiving carfilzomib as a subsequent treatment post-daratumumab against pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone
e) integrated patients from MMY2002 and GEN501 receiving lenalidomide as a subsequent treatment post-daratumumab against pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone
f) integrated patients from MMY2002 and GEN501 receiving pomalidomide as a subsequent treatment post-daratumumab against pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone.

B5. **Priority question:** Can you please confirm:

a) Column J on tab “KM Data” in the Excel model is the daratumumab integrated adjusted OS Kaplan–Meir data from the MAIC with respect to pomalidomide plus dexamethasone (MM-003) shown in Figure 11 of appendix 11? If not, please provide these Kaplan–Meir data (the excel tab “OS Curves_PostMAIC_DARAadjPOM” seems to be using the unadjusted Kaplan–Meir data for OS for comparison with the independently fitted curves).
b) Column M on tab “KM Data” in the Excel model is the daratumumab integrated adjusted OS Kaplan–Meir data from the MAIC with respect to panobinostat

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

plus bortezomib plus dexamethasone (PANORAMA 2) as shown in Figure 16 of appendix 11? If not, please provide these Kaplan–Meir data (the excel tab "OS Curves_PostMAIC_DARAadjPANO" seems to be using the unadjusted Kaplan–Meir data for OS for comparison with the independently fitted curves).

c) Column AN on tab "KM Data" in the Excel model is the daratumumab integrated adjusted PFS Kaplan–Meir data from the MAIC with respect to pomalidomide plus dexamethasone (MM-003)? If not, please provide these Kaplan–Meir data.

d) Column AQ on tab "KM Data" in the Excel model is the daratumumab integrated adjusted PFS Kaplan–Meir data from the MAIC with respect to panobinostat plus bortezomib plus dexamethasone (PANORAMA 2)? If not, please provide these Kaplan–Meir data.

e) Column Q on tab "KM Data" in the Excel model is the MM-003 digitised Kaplan–Meir data for pomalidomide plus dexamethasone for OS as seen in Figure 10 of appendix 11? If not, please provide these Kaplan–Meir data.

f) Column AD on tab "KM Data" in the Excel model is the PANORAMA digitised Kaplan–Meir data for panobinostat plus bortezomib plus dexamethasone for OS as seen in Figure 15 of appendix 11? If not, please provide these Kaplan–Meir data.

g) Column AU and column BG on tab "KM Data" in the Excel model is the PFS digitised Kaplan–Meir data used to run the MAIC analysis for pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone respectively? If this is not the case, please provide these Kaplan–Meir data.

h) What data is shown in column BR of the "KM Data" tab of the Excel model?

i) The Kaplan–Meir data used to run the analysis reported in Figure 8 and Figure 13 of appendix 11 of the company submission uses the daratumumab curves adjusted to the respective comparator studies.

B6. **Priority question**: Please provide the weighted hazard ratio for TTD derived from the MAIC in relation to daratumumab versus pomalidomide plus dexamethasone.

B7. **Priority question**: On page 170 of the company submission it is stated that the extrapolation of parametric survival curves followed the NICE TSD number 14. However, the Gompertz distribution is not included in the company's analysis

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

(nonetheless it seems to have been partially included in the economic model). Please provide the following data for OS, PFS and TTD:

a) AIC and BIC criteria for the Gompertz distribution
b) parametric curve for the Gompertz distribution superimposed to the Kaplan–Meir data and other parametric curves for each outcome.

B8. **Priority question:** Please include the Gompertz distribution as an alternative distribution to model OS, PFS and TTD in the economic model in the tab "Controls" of the economic model, cells "Controls.OS_select", "Controls.PFS_select" and "Controls.TTD_select" respectively.

B9. **Priority question:** Please include the Gompertz distribution as an alternative distribution to model OS and PFS in the economic model in the tab "Controls" of the economic model when the cells "Controls.Comp_Method_POM" and "Controls.Comp_Method_POM" are set to fit curves independently instead of through the MAIC analysis; that is, please complete the empty "Gompertz" columns in the different tables of tabs "OS Curves_PostMAIC_DARAadjPANO", "PFS Curves_PostMAIC_POM", "PFS Curves_PostMAIC_PANO", "OS Curves_PostMAIC_PANO", "OS Curves_PostMAIC_POM" and "OS Curves_PostMAIC_DARAadjPOM".

B10. **Priority question**: For OS, PFS and TTD (where possible) for the daratumumab adjusted integrated data versus pomalidomide plus dexamethasone; daratumumab adjusted integrated data versus panobinostat plus bortezomib plus dexamethasone data; MMY2002 adjusted data versus pomalidomide plus dexamethasone; MMY2002 adjusted data versus panobinostat plus bortezomib plus dexamethasone; GEN501 adjusted data versus pomalidomide plus dexamethasone; and GEN501 adjusted data versus panobinostat plus bortezomib plus dexamethasone; please provide:

a) cumulative hazard plot (– log (estimated KM survival)) versus time
b) log(survival function / (1-survival function)) plots versus Log(time)
c) log(inverse standard normal distribution function(1-survival function)) plots versus Log(time)
d) log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) for the MMY2002 versus pomalidomide plus dexamethasone; MMY2002 versus

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

panobinostat plus bortezomib plus dexamethasone; GEN501 versus pomalidomide plus dexamethasone and GEN501 versus panobinostat plus bortezomib plus dexamethasone combinations.

B11. **Priority question**: In appendix 11 of the company submission, the company assessed if the proportional hazards (PH) assumption holds for OS data across the daratumumab integrated data compared with pomalidomide plus dexamethasone, and compared with panobinostat plus bortezomib plus dexamethasone. Please:

a) Undertake the same assessment process with regards to a proportional odds and accelerated failure time assumption based on the plots requested in B7b and B7c.
b) Provide the same analysis for PFS and TTD data, including the assessment requested in B11a.
e) Provide the same assessment requested in B11a and B11b for the adjusted MMY2002 versus pomalidomide plus dexamethasone; adjusted MMY2002 versus panobinostat plus bortezomib plus dexamethasone; adjusted GEN501 versus pomalidomide plus dexamethasone; and adjusted GEN501 versus panobinostat plus bortezomib plus dexamethasone combinations.

B12. **Priority question**: To estimate PFS for the comparator curves in the model, HRs from a Cox proportional hazard model were applied to an accelerated failure time model. Furthermore, the proportional hazard assumption has not been assessed with regards to the PFS data. Therefore, please include the option to independently fit PFS curves in the model (similar to the option given for OS in the "Controls.Comp_Method_POM" cell of the model).

B13. **Priority question**: Please provide a list of the parameters/data ranges that changed in the economic model when individual daratumumab trials (MMY2002 and GEN501) are used instead of the integrated data.

B14. **Priority question**: Please explain why the tab "Survival and Progression" of the Excel model had no HRs provided for GEN501 but only for MMY2002 and the integrated analysis. When cell "Controls.Population" in tab "Controls" is changed from MMY2002 to GEN501, the HRs given in the "Survival and Progression" do not change (they still reflect the HRs for MMY2002). Please correct this in the model.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

B15. **Priority question:** A Cox proportional hazard model was used to analyse the reweighted daratumumab individual patient-level data (IPD) data together with the simulated IPD data from pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone. Please explain why this was used since it is theoretically incorrect to apply a HR derived from a different parametric model, or one derived from a Cox proportional hazard model (DSU 14).

B16. **Priority question:** An exponential distribution is used to model OS in the model. This has a strong underlying assumption of not only proportional hazard, but also a constant HR throughout the model time horizon. Please justify this assumption as fully as possible.

B17. **Priority question:** Page 182 of the company submission mentions that, "based on statistical fit and clinical plausibility the log-normal curve was deemed most appropriate for use". Based on the AIC and BIC statistics in Table 52 (page 183), the Generalised Gamma function fits the PFS data better. Please explain why the Generalised Gamma was not used in the base-case analysis.

B18. Please clarify why the same resource use was assumed for administering the first dose of bendamustine and daratumumab (i.e. SB14Z Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance) as specified in Table 65 on page 212.

B19. The dosing schedule for bortezomib (with PANO) in cycles 8 to 16 (i.e. Days 1, 2, 8 and 9) reported in Table 64 (page 211) does not reflect what is reported in the European Public Assessment Report for panobinostat, which is cited as the source of the schedule. Please justify the dosage used.

B20. Please clarify whether the UK EQ-5D-5L value set was used to estimate the utility values reported in Table 55 (page 193) of the company submission.

B21. Please clarify why the systematic literature review of economic evaluations was limited to the intervention (i.e. cost-effectiveness studies of daratumumab in multiple myeloma).

B22. The equation used to estimate the proportion of patients assumed to experience nausea (all grades) in the model ('Adverse events'! E31) is as follows = ((4%*124)+ (12.5%*32))/ (124+32). Please clarify where the 4% for the MMY2002 was obtained from, as according to Table 28 on page 96 of the MMY2002 CSR this value should be 28.2%.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

B23. Please clarify whether a weighted average from the GEN501 and MMY2002 trials was used to estimate the proportions of patients experiencing lymphopenia and leukopenia in the tab 'Adverse events'! E21:E22. If so, please provide the equation used.

B24. Please provide the summary results as reported in Table 76 (page 225), but for mean estimates instead of median.

B25. When cells "Controls.Comp_Method_POM" and "Controls.Comp_Method_PANO" in tab "Controls" are changed to a naïve comparison, the survival curves on tab "Survival and Progression" do not seem to change. Please provide more details on the naïve analysis.

B26. Please clarify why the utility decrements in the model for hypotension, septic shock, syncope, peripheral neuropathy, flatulence, abdominal distention and hypokalaemia are positive while those for the remaining adverse events are negative. This question refers to 'Utility'! G57: G61 and 63:G66.

B27. The OS curve from Gooding *et al.* is missing from Figure 36 (page 182). Please provide Figure 36 including this curve?

B28. The ERG could not replicate the results of the scenario analysis in which utility values from TA380 are used as reported in Row 6 of Table 8 of the Addendum to company evidence submission for any of the comparisons. The resulting ICERs from this scenario in the model are £30,097, £50,470 and £50,048 per QALY gained for daratumumab compared with panobinostat plus bortezomib plus dexamethasone, bendamustine-based therapy, and pomalidomide plus dexamethasone respectively. Please clarify this discrepancy or update the model as appropriate.

B29. Please clarify why treatment-emergent adverse events were used in the model rather than treatment-related adverse events.

B30. Please clarify why the cost-effectiveness model is described as a semi-Markov partitioned survival structure as opposed to a partitioned survival model.

B31. Please provide the p values and respective confidence intervals associated with the scale parameter of the Weibull distribution used to fit the adjusted and unadjusted integrated OS curves for daratumumab and for the MMY2002 and GEN501 OS curves when the trial data for the 2 trials are analysed separately.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Section C: Textual clarifications and additional points

C1. Is the cost per week for bortezomib presented in Table 73 (page 221) correct? The ERG could not replicate this value based on the unit costs and doses assumed per week.

C2. Please clarify this sentence from page 54 of the company submission: “Terms for principal interventions were included in the systematic searches with terms for interventions only used in combination with principal interventions not required.”

The ERG has found an error in the curves included in Figure 37 of the CS (page 183) replicated in Figure 1 below. The PFS data used in the base case analysis is reported to be based on the IRC assessed dataset. However the Gamma curve in Figure 1 (and in tab "PFS Curves_DARA") uses data from the INV assessed PFS dataset. When the ERG replicates Figure 1, using the company's data from tab "PFS Curves_DARA" BD19:BI4039 we get the graph shown in Figure 2. When the ERG uses the company's data from tab "PFS Curves_DARA" BM19:BR4039 to produce the equivalent graph for the INV assessed PFS data we get the graph shown in Figure 3.

Can the company please:

1. Clarify if the data ranges BD19:BI4039 and BM19:BR4039 in tab "PFS Curves_DARA" of the model correctly labelled?
2. Clarify why does Figure 1 (Figure 37 in the CS) include the Gamma distribution taken from the INV dataset?
3. Correct/explain the AIC and BIC statistics for the Gompertz distribution. Figure 2 shows the Gompertz distribution included in the model but excluded from Figure 37. According to visual inspection, the Gompertz distributions seems a good fit (if not the better fit) to the KM curve. Therefore the AIC and BIC statistics shown in "PFS Curves_DARA" tab of the model (cell BH14 and BH15 for IRC and BQ14 and BQ15) do not seem correct.
4. Clarify why the time unit for the Gompertz distribution is months when the time unit for all other distributions is days and adjust the time unit in the Gompertz curve to match the other curves. The same issue is found for OS and TTD data in the "OS Curves_DARA" and TTD Curves_DARA" tabs of the model, respectively. Please correct this in the OS and TTD tabs as well.
5. Provide the KM data in Excel format to derive the curve for the KM INV PFS curve for superimposition with the derived curves in Figure 3. The ERG notes that these data were used to derive the curves, so there is no need for additional analysis but simply providing the KM data.

Figure 1. Replication of Figure 37 in CS

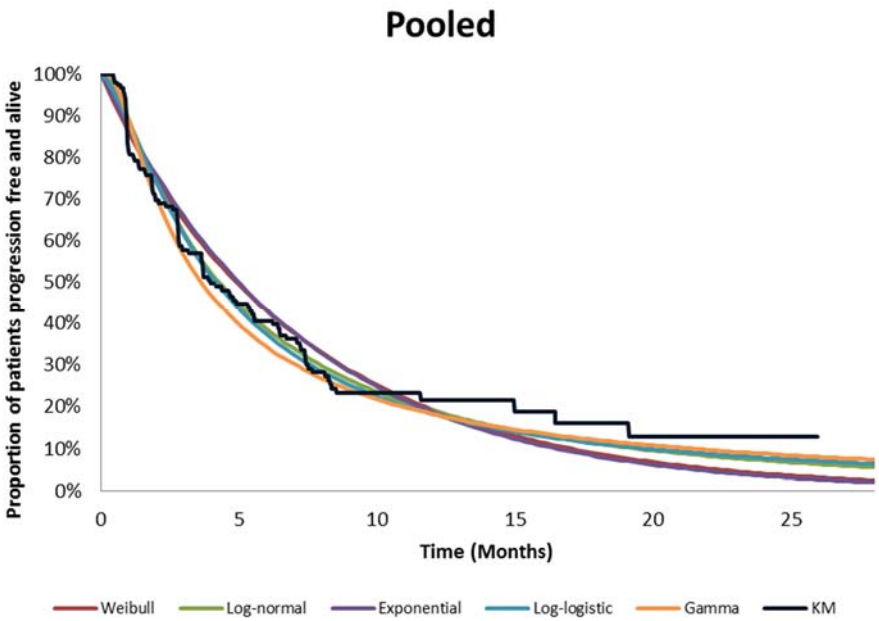


Figure 2. IRC PFS curves

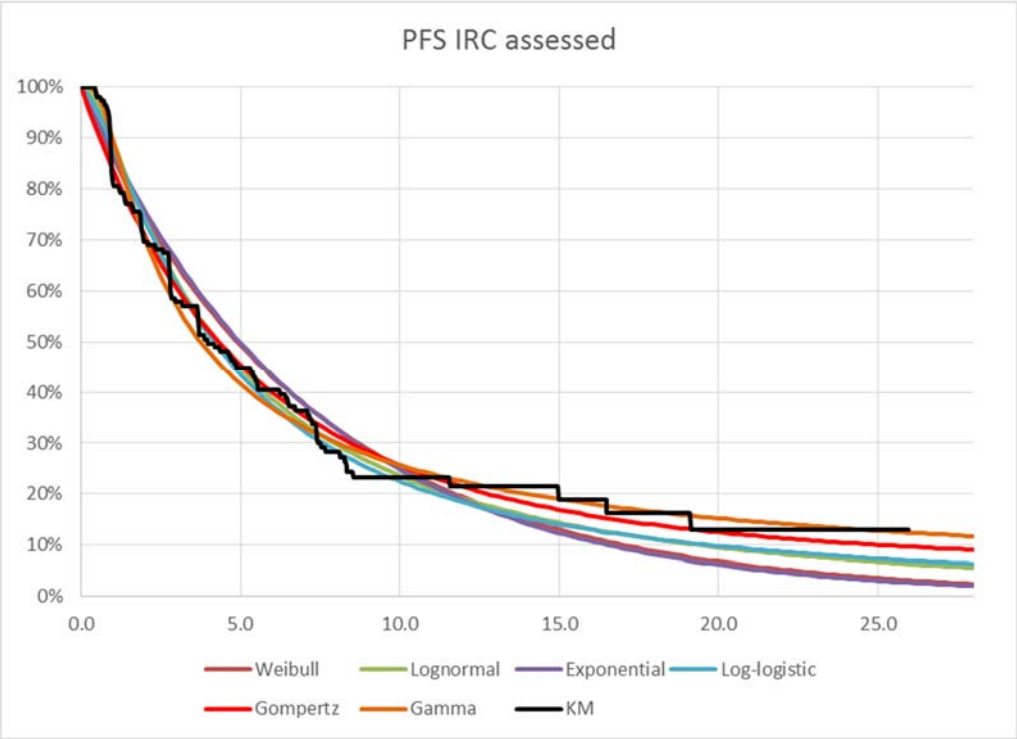
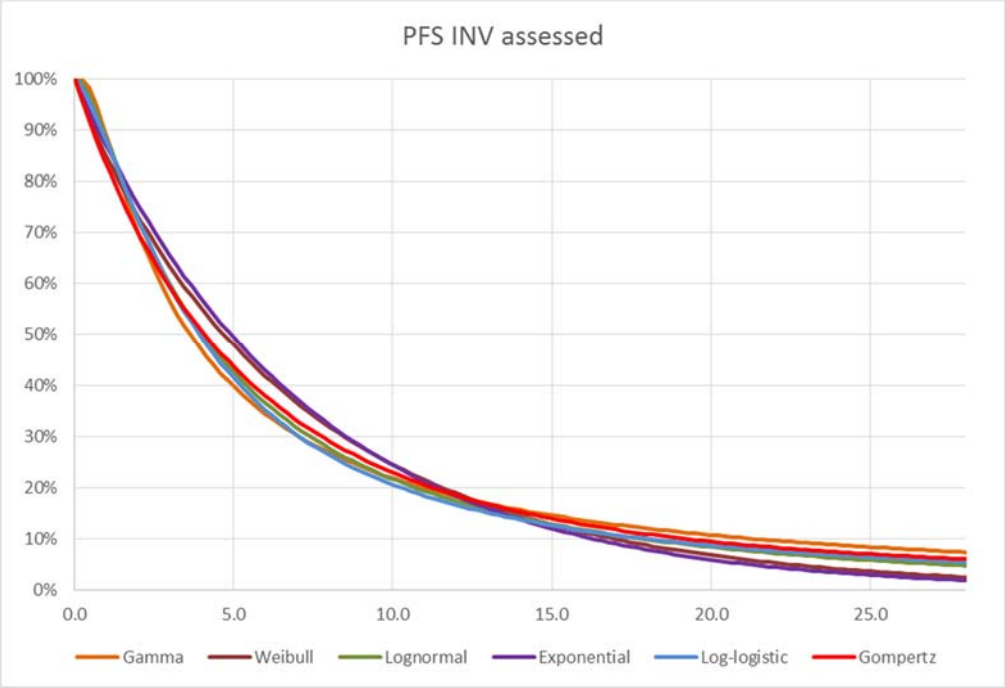


Figure 3. INV PFS curves



Single Technology Appraisal (STA)

Daratumumab for treating relapsed and refractory multiple myeloma [ID933]

Janssen are pleased to have the opportunity to provide clarification on the above submission. Every effort has been made to answer all questions herein and to provide additional requested analyses.

During the clarification stage, Janssen requested further information on the rationale and priority of the additional analyses requested. As this was not forthcoming, Janssen have addressed priority questions in the order presented below. In addition to this, Janssen requested clarification on some questions for which it was unclear what was required. As no clarification was received, Janssen have interpreted these questions as best as we are able and apologise if the data presented is not what was required.

It is important to note that a large amount of additional analysis has been requested and that some of these analyses have not been possible given available data. Many of the analyses requested focus on *post-hoc* subgroups or on the individual, rather than pooled, trial data. Janssen acknowledge that it is important to understand the data as fully as possible; however, Janssen question the relevance and statistical plausibility of some of the analyses requested and advise caution in the interpretation of these data.

The following notation is used: information submitted under 'commercial in confidence (CIC)' is highlighted in turquoise, and all information submitted under 'academic in confidence (AIC)' in yellow.

Encl. checklist for in confidence information
Encl. Excel files of requested data: There are several Excel files accompanying this document that contain requested data. File keys for each Excel file are contained within this document, all these files are CIC.

Section A: Clarification on effectiveness data

A1. **Priority question**: Please clarify which characteristics have been matched/adjusted for each estimate in Tables 40-42 in the company submission and Tables 21-22 in the appendices.

The characteristics matched for each estimate in Table 40 of the submission are detailed in Table 36 of the submission. That is, the 'Number of matched characteristics' column of Table 40 corresponds to the cumulative number of baseline variables 'nrbl' column in Table 36. For example, matching 3 characteristics corresponds to matching the 3 characteristics around refractory status; the details of which are provided in Table 35 of the submission. Whereas, matching 11 characteristics corresponds to matching the 3 characteristics around refractory

status, plus the 2 characteristics relating to prior therapy, plus the 3 characteristics relating to creatinine clearance and plus the 3 characteristics relating to ECOG score.

Similarly, the characteristics matched for each estimate in Table 42 of the submission are detailed in Table 37 of the submission, with further details of characteristics within each cluster provided in Table 35.

As an aid to understanding, these tables have been combined and are summarised in Table 1 and Table 3 below. In addition details of the characteristics matched for each estimate in Table 41 of the submission and Tables 21-22 of the appendices are provided in Table 2, Table 4 and Table 5 below, respectively.

Table 1. MAIC base-case results for OS and PFS before and after matching, daratumumab monotherapy versus POM+DEX, including list of characteristics matched in each analysis

Number of matched characteristics	N	Neff	HR (95% CI)		Characteristics matched
			OS	PFS	
Unadjusted	148		0.61 (0.46, 0.81)	0.88 (0.69, 1.12)	-
26	136	55	0.56 (0.38, 0.83)	0.72 (0.50, 1.05)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgM (%)

Number of matched characteristics	N	Neff	HR (95% CI)		Characteristics matched
			OS	PFS	
					• Myeloma subtype, IgD (%) • Light chain Kappa (%) • Light chain lambda (%) Race: • White (%) • Asian (%) • Black (%) Bone lesions: • Bone lesions (%) ASCT: • Prior ASCT (%) Age: • Mean age (years) • Age >65 years (%) • Age >75 years (%)

23	136	58	0.57 (0.34, 0.84)	0.75 (0.52, 1.08)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgM (%) • Myeloma subtype, IgD (%) • Light chain Kappa (%) • Light chain lambda (%) Race: • White (%) • Asian (%)

					• Black (%) Bone lesions: • Bone lesions (%) ASCT: • Prior ASCT (%)
22	136	62	0.59 (0.41, 0.86)	0.81 (0.58, 1.13)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgM (%) • Myeloma subtype, IgD (%)

					• Light chain Kappa (%) • Light chain lambda (%) Race: • White (%) • Asian (%) • Black (%) Bone lesions: • Bone lesions (%)
21	137	63	0.59 (0.41, 0.86)	0.81 (0.59, 1.13)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%)

					• Myeloma subtype, IgG (%) • Myeloma subtype, IgM (%) • Myeloma subtype, IgD (%) • Light chain Kappa (%) • Light chain lambda (%) Race: • White (%) • Asian (%) • Black (%)
18	148	71	0.55 (0.39, 0.78)	0.78 (0.57, 1.07)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype:

					• Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgM (%) • Myeloma subtype, IgD (%) • Light chain Kappa (%) • Light chain lambda (%)
12	148	82	0.55 (0.39, 0.77)	0.78 (0.58, 1.05)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years)
11	**148**	**84**	**0.57 (0.41, 0.81)**	**0.81 (0.60, 1.09)**	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%)

					Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%)
8	148	106	0.56 (0.41, 0.76)	0.83 (0.63, 1.09)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%)

5	148	108	0.60 (0.45, 0.81)	0.85 (0.64, 1.12)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%)
3	148	110	0.61 (0.45, 0.83)	0.84 (0.64, 1.11)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%)
Key: ASCT, Autologous stem cell transplant; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; Neff, net effective sample size; OS, overall survival; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.					

Table 2. MAIC results for OS and PFS before and after matching, daratumumab monotherapy versus POM+DEX in POM+DEX-naïve patients, including list of characteristics matched in each analysis

Number of matched characteristics	N	Neff	HR (95% CI)		Characteristics matched
			OS	PFS	
Unadjusted	66		0.38 (0.25, 0.60)	0.77 (0.55, 1.09)	-
18	66	19	0.33 (0.17, 0.66)	0.51 (0.24, 1.06)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgM (%)

					• Myeloma subtype, IgD (%) • Light chain Kappa (%) • Light chain lambda (%)

12	66	29	0.40 (0.20, 0.80)	0.57 (0.31, 1.05)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years)
11	**66**	**29**	**0.40 (0.20, 0.80)**	**0.57 (0.31, 1.05)**	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%)

					• Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%)

8	66	44	0.40 (0.24, 0.67)	0.72 (0.47, 1.10)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%)
5	66	46	0.46 (0.29, 0.74)	0.73 (0.49, 1.11)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%)
3	66	51	0.47 (0.30, 0.74)	0.78 (0.53, 1.16)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%)
Key: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; Neff, net effective sample size; OS, overall survival; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.					

Table 3. MAIC base-case results for OS and PFS before and after matching, daratumumab monotherapy versus PANO+BORT+DEX, including list of characteristics matched in each analysis

Number of matched characteristics	N	Neff	HR (95% CI)		Characteristics matched
			OS	PFS	
Non-BORT refractory included Unadjusted	148	-	0.82 (0.53, 1.26)	1.05 (0.75, 1.47)	-
Non-BORT refractory excluded Unadjusted	125	-	0.93 (0.60, 1.44)	1.09 (0.77, 1.56)	-
12	125	46	0.76 (0.44, 1.30)	0.96 (0.60, 1.55)	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgM (%) ASCT: • Prior ASCT (%) Age: • Median age (years) • Age ≥65 years (%)
10	125	52	0.81 (0.48, 1.37)	0.98 (0.63, 1.53)	Number of prior therapies:

Number of matched characteristics	N	Neff	HR (95% CI)		Characteristics matched
			OS	PFS	
					• Median number of prior regimens • >3 prior regimens (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgM (%) ASCT: • Prior ASCT (%)
9	125	67	0.84 (0.51, 1.38)	1.04 (0.69, 1.58)	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype:

Number of matched characteristics	N	Neff	HR (95% CI)		Characteristics matched
			OS	PFS	
					• Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgM (%)
6	125	79	0.83 (0.51, 1.35)	1.08 (0.73, 1.59)	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years)
5	**125**	**80**	**0.84 (0.52, 1.37)**	**1.09 (0.74, 1.61)**	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%)

Number of matched characteristics	N	Neff	HR (95% CI)		Characteristics matched
			OS	PFS	
2	125	91	0.91 (0.57, 1.45)	1.19 (0.83, 1.72)	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%)
Key: ASCT, Autologous stem cell transplant; BORT, bortezomib; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; Neff, net effective sample size; OS, overall survival; PANO+BORT+DEX, Panobinostat plus bortezomib plus dexamethasone; PFS, progression-free survival.					

Table 4. MAIC sensitivity analysis results for OS and PFS before and after matching, daratumumab monotherapy utilising MMY2002 data versus PANO+BORT+DEX, including list of characteristics matched in each analysis

Number of matched characteristics	N	Neff	HR (95% CI)		Characteristics matched
			OS	PFS	
Non-BORT refractory included Unadjusted	106	-	0.96 (0.61, 1.51)	1.22 (0.84, 1.76)	-
Non-BORT refractory excluded Unadjusted	95	-	1.03 (0.65, 1.63)	1.26 (0.87, 1.84)	-
16	84	13	0.61 (0.25, 1.45)	0.85 (0.39, 1.88)	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%) ISS: • ISS 1 (%) • ISS 2 (%) • ISS 3 (%)

					ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Cytogenetics: • (modified) high cytogenetic risk (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) Beta-microglubin: • beta-microglubin<2.5 (%) ASCT: • Prior ASCT (%) Age: • Median age (years) • Age ≥65 years (%)
14	84	14	0.63 (0.28, 1.4%)	0.92 (0.46, 1.86)	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%) ISS: • ISS 1 (%) • ISS 2 (%) • ISS 3 (%) ECOG score: • ECOG 0 (%)

					• ECOG 1 (%) • ECOG 2 (%) Cytogenetics: • (modified) high cytogenetic risk (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) Beta-microglubin: • beta-microglubin<2.5 (%) ASCT: • Prior ASCT (%)
13	84	22	0.86 (0.46, 1.58)	1.05 (0.62, 1.77)	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%) ISS: • ISS 1 (%) • ISS 2 (%) • ISS 3 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Cytogenetics: • (modified) high cytogenetic risk (%) Time since diagnosis:

					• Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) Beta-microglubin: • beta-microglubin<2.5 (%)
12	84	41	0.92 (0.54, 1.59)	1.10 (0.67, 1.79)	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%) ISS: • ISS 1 (%) • ISS 2 (%) • ISS 3 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Cytogenetics: • (modified) high cytogenetic risk (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%)
10	84	45	0.94 (0.55, 1.61)	1.17 (0.73, 1.89)	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%)

					ISS: • ISS 1 (%) • ISS 2 (%) • ISS 3 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Cytogenetics: • (modified) high cytogenetic risk (%) Time since diagnosis: • Median time since diagnosis (years)
9	84	46	0.97 (0.57, 1.64)	1.20 (0.76, 1.92)	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%) ISS: • ISS 1 (%) • ISS 2 (%) • ISS 3 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Cytogenetics: • (modified) high cytogenetic risk (%)
8	**95**	**56**	**0.92 (0.56, 1.52)**	**1.20 (0.77, 1.87)**	Number of prior therapies: • Median number of prior regimens

					• >3 prior regimens (%) ISS: • ISS 1 (%) • ISS 2 (%) • ISS 3 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%)
5	95	64	0.93 (0.56, 1.53)	1.31 (0.87, 1.98)	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%) ISS: • ISS 1 (%) • ISS 2 (%) • ISS 3 (%)
2	95	68	1.03 (0.63, 1.68)	1.40 (0.94, 1.09)	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%)
Key: ASCT, Autologous stem cell transplant; BORT, bortezomib; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ISS, International Staging System; MAIC, matching-adjusted indirect comparison; Neff, net effective sample size; OS, overall survival; PANO+BORT+DEX, Panobinostat plus bortezomib plus dexamethasone; PFS, progression-free survival.					

Table 5. MAIC sensitivity analysis results for OS and PFS before and after matching, daratumumab monotherapy utilising MMY2002 data versus POM+DEX, including list of characteristics matched in each analysis

Number of matched characteristics	N	Neff	HR (95% CI)		Characteristics matched
			OS	PFS	
Unadjusted	106	-	0.72 (0.54, 0.98)	1.03 (0.79, 1.35)	-
28	93	19	0.88 (0.44, 1.77)	1.14 (0.64, 2.03)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) ISS: • ISS 2 (%) • ISS 3 (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Cytogenetics: • (modified) high cytogenetic risk (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%)

					• Myeloma subtype, IgG (%) • Myeloma subtype, IgD (%) • Light chain Kappa (%) • Light chain lambda (%) Beta-microglubin: • beta-microglubin<3.5 (%) • beta-microglubin>=3.5 and beta-microglubin<5.5 (%) • beta-microglubin>=5.5 (%) Race: • White (%) • Asian (%) • Black (%) Bone lesions: • Bone lesions (%) ASCT: • Prior ASCT (%)
27	93	20	0.88 (0.46, 1.68)	1.18 (0.68, 2.03)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) ISS: • ISS 2 (%) • ISS 3 (%)

					Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Cytogenetics: • (modified) high cytogenetic risk (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgD (%) • Light chain Kappa (%) • Light chain lambda (%) Beta-microglubin: • beta-microglubin<3.5 (%) • beta-microglubin>=3.5 and beta-microglubin<5.5 (%) • beta-microglubin>=5.5 (%) Race: • White (%) • Asian (%) • Black (%) Bone lesions:

					• Bone lesions (%)
26	94	22	0.88 (0.47, 1.66)	1.18 (0.68, 2.03)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) ISS: • ISS 2 (%) • ISS 3 (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Cytogenetics: • (modified) high cytogenetic risk (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgD (%)

					• Light chain Kappa (%) • Light chain lambda (%) Beta-microglubin: • beta-microglubin<3.5 (%) • beta-microglubin>=3.5 and beta-microglubin<5.5 (%) • beta-microglubin>=5.5 (%) Race: • White (%) • Asian (%) • Black (%)
23	95	27	0.92 (0.54, 1.59)	1.27 (0.79, 2.04)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) ISS: • ISS 2 (%) • ISS 3 (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%)

					• ECOG 1 (%) • ECOG 2 (%) Cytogenetics: • (modified) high cytogenetic risk (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgD (%) • Light chain Kappa (%) • Light chain lambda (%) Beta-microglubin: • beta-microglubin<3.5 (%) • beta-microglubin>=3.5 and beta-microglubin<5.5 (%) • beta-microglubin>=5.5 (%)
20	95	36	0.69 (0.39, 1.21)	0.87 (0.54, 1.40)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) ISS: • ISS 2 (%) • ISS 3 (%)

					Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Cytogenetics: • (modified) high cytogenetic risk (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgD (%) • Light chain Kappa (%) • Light chain lambda (%)
15	95	44	0.68 (0.40, 1.14)	0.94 (0.60, 1.46)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) ISS: • ISS 2 (%)

					• ISS 3 (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Cytogenetics: • (modified) high cytogenetic risk (%) Time since diagnosis: • Median time since diagnosis (years)
14	95	47	0.75 (0.46, 1.22)	1.03 (0.68, 1.56)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) ISS: • ISS 2 (%) • ISS 3 (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%)

					ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Cytogenetics: • (modified) high cytogenetic risk (%)
13	**106**	**55**	**0.65, (0.41, 1.04)**	**0.95 (0.64, 1.40)**	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) ISS: • ISS 2 (%) • ISS 3 (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%)
10	106	69	0.62 (0.42, 0.93)	0.99 (0.70, 1.39)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%)

					• Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) ISS: • ISS 2 (%) • ISS 3 (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%)
7	106	72	0.67 (0.45, 0.98)	0.99 (0.71, 1.39)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) ISS: • ISS 2 (%) • ISS 3 (%)
5	106	73	0.70 (0.48, 1.02)	1.01 (0.73, 1.42)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens

					• >2 prior regimens (%)
3	106	75	0.69 (0.48, 0.99)	0.97 (0.69, 1.37)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%)
Key: ASCT, Autologous stem cell transplant; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ISS, International Staging System; MAIC, matching-adjusted indirect comparison; Neff, net effective sample size; OS, overall survival; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.					

A2. **Priority question**: Please provide results for all outcomes reported in the matching-adjusted indirect comparison (MAIC) sensitivity analyses using data only from the GEN501 trial (as presented for MMY2002 in Tables 21 and 22 in the appendices). Also, please provide for each outcome details of any patient characteristics that were matched/adjusted to estimate relative effects.

These are provided in Table 6 and Table 7 below.

Table 6. MAIC sensitivity analysis results for OS and PFS before and after matching, daratumumab monotherapy utilising GEN501 data versus POM+DEX, including list of characteristics matched in each analysis

Number of matched characteristics	N	Neff	HR (95% CI)		Characteristics matched
			OS	PFS	
Unadjusted	42	-	0.39 (0.23, 0.65)	0.60 (0.39, 0.93)	-
18	42	15	0.53 (0.33, 0.83)	0.62 (0.35, 1.12)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens

					• >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgM (%) • Myeloma subtype, IgD (%) • Light chain Kappa (%) • Light chain lambda (%)
12	42	21	0.39 (0.23, 0.67)	0.55 (0.31, 0.98)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%)

					• Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years)
11	42	22	0.40 (0.23, 0.69)	0.56 (0.32, 1.0)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%)
8	42	28	0.52 (0.32, 0.85)	0.67 (0.41, 1.09)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%)

					Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%)
5	42	28	0.53 (0.33, 0.87)	0.67 (0.41, 1.09)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%)
3	42	32	0.46 (0.29; 0.76)	0.57 (0.35; 0.91)	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%)
Key: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; Neff, net effective sample size; OS, overall survival; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.					

Table 7. MAIC sensitivity analysis results for OS and PFS before and after matching, daratumumab monotherapy utilising GEN501 data versus PANO+BORT+DEX, including list of characteristics matched in each analysis

Number of matched characteristics	N	Neff	HR (95% CI)		Characteristics matched
			OS	PFS	
Non-BORT	42	-	0.51 (0.27, 0.95)	0.74 (0.44, 1.23)	-

refractory included Unadjusted					
Non-BORT refractory excluded Unadjusted	30	-	0.65 (0.33, 1.25)	0.70 (0.39, 1.27)	-
12	30	8	0.70 (0.36, 1.39)	0.88 (0.45, 1.73)	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgM (%) ASCT: • Prior ASCT (%) Age: • Median age (years) • Age ≥65 years (%)
10	30	9	0.75 (0.39; 1.45)	0.92 (0.49, 1.74)	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%) ECOG score:

					• ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgM (%) ASCT: • Prior ASCT (%)
9	30	9	0.74 (0.39, 1.42)	0.90 (0.48, 1.70)	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgM (%)
6	30	18	0.54 (0.23, 1.25)	0.84 (0.44, 1.62)	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%)

					ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years)
5	30	18	0.55 (0.24; 1.27)	0.86 (0.45; 1.67)	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%)
2	30	21	0.67 (0.32; 1.41)	0.87 (0.46; 1.66)	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%)
Key: BORT, bortezomib; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; Neff, net effective sample size; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PFS, progression-free survival.					

A3. **Priority question**: Please provide a more detailed rationale for the selection and the ranking of the risk factors adjusted for in the MAIC. In particular, please explain the rationale around the order of variables in Tables 36 and 37 of the company submission (pages 123 and 124 respectively). Additionally, please outline the company's view on the impact of not incorporating important clinically relevant risk factors (e.g. cytogenetics and ISS staging) on the MAIC.

As stated on page 121 of the company submission: "Ideally, matching should be based on clinically relevant risk factors that impact the relative treatment effects. Characteristics upon which to match were identified through literature review and consultation with clinical experts in haematology."

Parameters that were considered to be potentially relevant to treatment response were identified based on published literature (Rajkumar and Buadi 2007) and through consultation with clinicians who were experienced in the treatment of MM. Identified parameters were categorised in to those of high relevance, i.e. having an expected measureable consistent effect on survival, and those of less or inconsistent relevance. These included (in order of relevance to the outcome): refractory status to lenalidomide and/or bortezomib; number of prior therapies; creatinine clearance; performance status (ECOG score); time since diagnosis; myeloma subtype; race; presence of bone lesions; autologous stem cell transplant; age, cytogenetics and International Staging System (ISS) staging. Hence, the ordering of available variables in Tables 36 and 37 of the company submission.

Of the variables identified as potentially relevant to the outcome and as a consequence the relative treatment effect, cytogenetics and ISS staging were ranked lowest. Therefore, the impact of omitting these variables from the MAIC is expected to be minimal. Furthermore, as cytogenetics and ISS staging data are available for MMY2002, a sensitivity analysis was provided using data from MMY2002 to inform MAIC and cost-effectiveness analyses; resulting in reduced ICERs of £54,851 versus POM+DEX (base case: £56,361) and dominance of daratumumab monotherapy versus PANO+BORT+DEX (base case: £33,260). However, it is important to note the lower statistical power of the MAIC based solely on MMY2002 as a result of the smaller sample size and decreased effective sample size of the MAIC.

A4. **Priority Question:** Please provide the weights attributed to the different patient characteristics adjusted for in the pomalidomide plus dexamethasone, and in the panobinostat plus bortezomib plus dexamethasone MAIC analyses for the:

a) integrated daratumumab data

b) MMY2002

c) GEN501.

As stated on page 121 of the company submission:

"IPD from the remaining patients in the daratumumab cohort were then weighted such that the mean values for relevant baseline parameters reflected the means reported in the comparator studies. This was achieved through a propensity score model, in which patients from the daratumumab cohort were weighted by the inverse odds of being in the daratumumab trials, rather than MM-003 or PANORAMA 2, respectively. The weighting used the generalised method of moments to estimate propensity scores and has previously been described in detail by Signorovitch et al. It should be noted that the algorithm does not directly match median values; rather, it calculates the weights such that the proportion of patients with a value below the median is matched to the proportion with a value above the median."

Therefore, please note that this question is unclear; MAIC does not apply weights to patient characteristics but rather to the individual patient level data. Janssen requested clarification around which weights the ERG required; however, this was not forthcoming and so Janssen have provided Excel files of the individual patient level weighting for each MAIC undertaken. A key to these files is provided in Table 8.

Table 8. Key to Excel files of MAIC weights

MAIC analysis	Excel file
Integrated data versus POM+DEX, 26 characteristics matched	[redacted]
Integrated data versus POM+DEX, 23 characteristics matched	[redacted]
Integrated data versus POM+DEX, 22 characteristics matched	[redacted]
Integrated data versus POM+DEX, 21	[redacted]

characteristics matched	[redacted]
Integrated data versus POM+DEX, 18 characteristics matched	[redacted]
Integrated data versus POM+DEX, 12 characteristics matched	[redacted]
Integrated data versus POM+DEX, 11 characteristics matched	[redacted]
Integrated data versus POM+DEX, 8 characteristics matched	[redacted]
Integrated data versus POM+DEX, 5 characteristics matched	[redacted]
Integrated data versus POM+DEX, 3 characteristics matched	[redacted]
Integrated data versus PANO+BORT+DEX, 12 characteristics matched	[redacted]
Integrated data versus PANO+BORT+DEX, 10 characteristics matched	[redacted]
Integrated data versus PANO+BORT+DEX, 9 characteristics matched	[redacted]
Integrated data versus PANO+BORT+DEX, 6 characteristics matched	[redacted]
Integrated data versus PANO+BORT+DEX, 5 characteristics matched	[redacted]
Integrated data versus PANO+BORT+DEX, 2 characteristics matched	[redacted]
MMY2002 data versus POM+DEX, 28 characteristics matched	[redacted]
MMY2002 data versus POM+DEX, 27 characteristics matched	[redacted]
MMY2002 data versus POM+DEX, 26 characteristics matched	[redacted]
MMY2002 data versus POM+DEX, 23 characteristics matched	[redacted]
MMY2002 data versus POM+DEX, 20 characteristics matched	[redacted]
MMY2002 data versus POM+DEX, 15 characteristics matched	[redacted]
MMY2002 data versus POM+DEX, 14 characteristics matched	[redacted]
MMY2002 data versus POM+DEX, 13 characteristics matched	[redacted]
MMY2002 data versus POM+DEX, 10 characteristics matched	[redacted]

MMY2002 data versus POM+DEX, 7 characteristics matched	[redacted]
MMY2002 data versus POM+DEX, 5 characteristics matched	[redacted]
MMY2002 data versus POM+DEX, 3 characteristics matched	[redacted]
MMY2002 data versus PANO+BORT+DEX, 16 characteristics matched	[redacted]
MMY2002 data versus PANO+BORT+DEX, 14 characteristics matched	[redacted]
MMY2002 data versus PANO+BORT+DEX, 13 characteristics matched	[redacted]
MMY2002 data versus PANO+BORT+DEX, 12 characteristics matched	[redacted]
MMY2002 data versus PANO+BORT+DEX, 10 characteristics matched	[redacted]
MMY2002 data versus PANO+BORT+DEX, 9 characteristics matched	[redacted]
MMY2002 data versus PANO+BORT+DEX, 8 characteristics matched	[redacted]
MMY2002 data versus PANO+BORT+DEX, 5 characteristics matched	[redacted]
MMY2002 data versus PANO+BORT+DEX, 2 characteristics matched	[redacted]
GEN501 data versus POM+DEX, 18 characteristics matched	[redacted]
GEN501 data versus POM+DEX, 12 characteristics matched	[redacted]
GEN501 data versus POM+DEX, 11 characteristics matched	[redacted]
GEN501 data versus POM+DEX, 8 characteristics matched	[redacted]
GEN501 data versus POM+DEX, 5 characteristics matched	[redacted]
GEN501 data versus POM+DEX, 3 characteristics matched	[redacted]
GEN501 data versus PANO+BORT+DEX, 12 characteristics matched	[redacted]
GEN501 data versus PANO+BORT+DEX, 10 characteristics matched	[redacted]
GEN501 data versus PANO+BORT+DEX, 9 characteristics matched	[redacted]
GEN501 data versus PANO+BORT+DEX, 6	[redacted]

characteristics matched	
GEN501 data versus PANO+BORT+DEX, 5 characteristics matched	[redacted]
GEN501 data versus PANO+BORT+DEX, 2 characteristics matched	[redacted]
Key: MAIC, matched adjusted indirect comparison; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; POM+DEX, pomalidomide plus dexamethasone.	

A5. **Priority question**: Please provide the effect estimates for the outcomes listed below in patients from MMY2002 who did not receive pomalidomide as a previous therapy:

a. overall response rate (ORR)

b. best ORR (with accompanying breakdown of number of events in each categorisation of response)

c. overall survival (OS)

d. progression-free survival (PFS)

e. time to response (TTR)

f. duration of response

g. time to discontinuation (TTD).

These are summarised in Table 9.

Table 9. Effect estimates for POM+DEX naïve patients, MMY2002

Effect	n	Median (95%CI)	%
ORR	31	-	29
Best ORR		-	
sCR	3		3
CR	0		0
VGPR	10		9
PR	18		17
MR	5		5
SD	46		43
PD	18		17
NE	6		6
OS	39	NE (95% CI: 15.08,NE)	-
PFS	39	3.98 (95% CI: 2.60, 7.39)	-

TTR	39	NE (95% CI: 2.73, NE)	-
DoR	11	15.90 (95%CI: 3.71, NE)	-
TTD	39	3.25 (95% CI: 2.33, 5.09)	-
Key: CI, confidence interval; CR, complete response; DoR, duration of response; MR, minimal response; NE, not evaluable; OS, overall survival; ORR, overall response rate; PD, progressive disease; PFS, progression free survival; POM+DEX, pomalidomide plus dexamethasone; PR, partial response; sCR, stringent complete response; SD, stable disease; TTD, time to treatment discontinuation; TTR, time to response; VGPR, very good partial response.			

A6. **Priority question**: For the analyses and populations listed below, please provide estimates of OS, and number of patients included in the analysis, for patients whose disease progressed while receiving daratumumab and who received:

a. For integrated analysis (for MMY2002 and GEN501) and the MAIC (versus pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone):

i. bortezomib as a subsequent treatment

ii. carfilzomib as a subsequent treatment

iii. lenalidomide as a subsequent treatment

iv. pomalidomide as a subsequent treatment.

b. For individual trials of MMY2002 and GEN501:

i. no subsequent treatment

ii. any subsequent treatment.

NB: Total of 16 estimates.

Janssen understand the ERG's concern around potential bias in MAIC caused by differences in subsequent treatment. As stated on page 138 of the company submission:

"Of the 148 patients treated with daratumumab 16mg/kg monotherapy in the MMY2002/GEN501 cohort, 72% went on to receive subsequent therapy compared with 39% of the 302 patients randomised to POM+DEX in MM-003. This is thought to be a result of the novel and unique MoA associated with daratumumab, alongside the favourable safety profile, that culminate in an improved health status of patients."

However, it is not possible to adjust the MAIC for the impact of subsequent treatment. Moreover, should such an adjustment be possible, it may not necessarily be appropriate. This is because the increase in subsequent treatment is a key benefit resulting from therapy with daratumumab. That is, the favourable safety profile of daratumumab provides patients with time to recover from the cumulative toxicity of previous treatments allowing a greater proportion of patients to receive subsequent therapy. In addition to this, it is thought that the novel MoA of daratumumab, which includes immune-mediated mechanisms, increases the likelihood of benefitting from subsequent therapy.

As such, adjusting for the impact of subsequent therapy would fail to capture a key benefit of daratumumab therapy and also not be reflective of anticipated clinical practice.

With regards to the additional *post-hoc* analyses requested above, Janssen are able to provide OS estimates for the requested subgroups (Table 10).

It is important to note that the *post-hoc* analyses presented in Table 10 are subject to a high level of selection bias as a result of indirectly selecting patients based on their outcome. That is, patients need to survive longer in order to receive subsequent treatment and as such these subgroups are selecting patients based on overall survival outcomes. In addition to this, patients are being indirectly selected based on fitness, as fitter patients will receive the more effective and more toxic treatments resulting in better outcomes. Furthermore, there is much heterogeneity between the patients within each subgroup; For example, in the subgroup of patients receiving bortezomib as a subsequent treatment, some patients will have received bortezomib directly after daratumumab, whereas others will have received bortezomib at a later stage. In addition, bortezomib may have been received as a monotherapy or as a combination therapy, as a fourth line treatment or as a seventh line treatment. As such, it is not possible to draw any conclusions as to the meaning of these data and great caution is advised in interpreting these analyses.

Table 10. Estimates of OS from *post-hoc* subgroup analyses

Dataset	Subgroup	Median OS (95% CI)	Sample size
Integrated	Bortezomib as a subsequent treatment	[redacted]	[redacted]
	Carfilzomib as a subsequent treatment	[redacted]	[redacted]

	Lenalidomide as a subsequent treatment	[redacted]	[redacted]
	Pomalidomide as a subsequent treatment.	[redacted]	[redacted]
MMY2002	No subsequent treatment	[redacted]	[redacted]
	Any subsequent treatment.	[redacted]	[redacted]
GEN501	No subsequent treatment	[redacted]	[redacted]
	Any subsequent treatment.	[redacted]	[redacted]
Key: CI, confidence interval; NE, not evaluable; OS, overall survival.			

MAIC of the integrated data versus POM+DEX and versus PANO+BORT+DEX was technically possible and the results with respect to OS are presented in Table 11 to Table 18, including lists of characteristics matched in each analysis. However, these analyses are statistically inappropriate as a result of:

- Small sample sizes, resulting in low effective sample sizes
- Selection bias, patients are being indirectly selected based on their fitness and outcome (i.e., being fit enough and surviving long enough to receive subsequent treatment). Matching to baseline characteristics is unlikely to overcome this bias as time dependent covariates are likely to be influential
- Insufficient overlap, daratumumab patients are being selected based on fitness and outcome, whereas patients from the comparator trials are not, this reduces the level of overlap between the datasets. The consequence of this is a reduction in the number of characteristics that can be matched thereby reducing the reliability of the MAIC.

Table 11. MAIC results for OS before and after matching, daratumumab monotherapy utilising post-hoc subgroup of patients receiving subsequent treatment with bortezomib versus POM+DEX, including list of characteristics matched in each analysis

Number of matched characteristics	N	Neff	OS HR (95% CI)	Characteristics matched
Unadjusted	[redacted]	[redacted]	[redacted]	-
8	[redacted]	[redacted]	[redacted]	Refractory status: Refractory to lenalidomide (%) Refractory to bortezomib (%) Refractory to both (%) Number of prior therapies: Mean number of prior regimens >2 prior regimens (%) Creatinine clearance: Creatinine clearance <30 (%) Creatinine clearance 30-60 (%) Creatinine clearance ≥60 (%)
5	[redacted]	[redacted]	[redacted]	Refractory status: Refractory to lenalidomide (%) Refractory to bortezomib (%) Refractory to both (%) Number of prior therapies: Mean number of prior regimens >2 prior regimens (%)
3	[redacted]	[redacted]	[redacted]	Refractory status: Refractory to lenalidomide (%) Refractory to bortezomib (%)

				Refractory to both (%)
Key: CI, confidence interval; HR, hazard ratio; MAIC, matched adjusted indirect comparison; Neff, net effective sample size; OS, overall survival; POM+DEX, pomalidomide plus dexamethasone.				

Table 12. MAIC results for OS before and after matching, daratumumab monotherapy utilising post-hoc subgroup of patients receiving subsequent treatment with carfilzomib versus POM+DEX, including list of characteristics matched in each analysis

Number of matched characteristics	N	Neff	OS HR (95% CI)	Characteristics matched
Unadjusted	[redacted]	[redacted]	[redacted]	-
22	[redacted]	[redacted]	[redacted]	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis:

				• Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgM (%) • Myeloma subtype, IgD (%) • Light chain Kappa (%) • Light chain lambda (%) Race: • White (%) • Asian (%) • Black (%) Bone lesions: • Bone lesions (%)
21	[redacted]	[redacted]	[redacted]	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%)

				• ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgM (%) • Myeloma subtype, IgD (%) • Light chain Kappa (%) • Light chain lambda (%) Race: • White (%) • Asian (%) • Black (%)
18	[redacted]	[redacted]	[redacted]	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%)

				• ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years) Myeloma subtype: • Myeloma subtype, IgA (%) • Myeloma subtype, IgG (%) • Myeloma subtype, IgM (%) • Myeloma subtype, IgD (%) • Light chain Kappa (%) • Light chain lambda (%)
12	[redacted]	[redacted]	[redacted]	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%) Time since diagnosis: • Median time since diagnosis (years)
11	[redacted]	[redacted]	[redacted]	Refractory status:

				• Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%)
8	[redacted]	[redacted]	[redacted]	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%)
5	[redacted]	[redacted]	[redacted]	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%)

				• Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%)
3	[redacted]	[redacted]	[redacted]	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%)
Key: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MAIC, matched adjusted indirect comparison; Neff, net effective sample size; OS, overall survival; POM+DEX, pomalidomide plus dexamethasone.				

Table 13. MAIC results for OS before and after matching, daratumumab monotherapy utilising post-hoc subgroup of patients receiving subsequent treatment with lenalidomide versus POM+DEX, including list of characteristics matched in each analysis

Number of matched characteristics	N	Neff	OS HR (95% CI)	Characteristics matched
Unadjusted	[redacted]	[redacted]	[redacted]	-
5	[redacted]	[redacted]	[redacted]	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%)
3	[redacted]	[redacted]	[redacted]	Refractory status: • Refractory to lenalidomide (%)

				• Refractory to bortezomib (%) • Refractory to both (%)
Key: CI, confidence interval; HR, hazard ratio; MAIC, matched adjusted indirect comparison; Neff, net effective sample size; OS, overall survival; POM+DEX, pomalidomide plus dexamethasone.				

Table 14. MAIC results for OS before and after matching, daratumumab monotherapy utilising post-hoc subgroup of patients receiving subsequent treatment with pomalidomide versus POM+DEX, including list of characteristics matched in each analysis

Number of matched characteristics	N	Neff	OS HR (95% CI)	Characteristics matched
Unadjusted	[redacted]	[redacted]	[redacted]	-
8	[redacted]	[redacted]	[redacted]	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) Creatinine clearance: • Creatinine clearance <30 (%) • Creatinine clearance 30-60 (%) • Creatinine clearance ≥60 (%)
5	[redacted]	[redacted]	[redacted]	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%) Number of prior therapies:

				• Mean number of prior regimens • >2 prior regimens (%)
3	[redacted]	[redacted]	[redacted]	Refractory status: • Refractory to lenalidomide (%) • Refractory to bortezomib (%) • Refractory to both (%)
Key: CI, confidence interval; HR, hazard ratio; MAIC, matched adjusted indirect comparison; Neff, net effective sample size; OS, overall survival; POM+DEX, pomalidomide plus dexamethasone.				

Table 15. MAIC results for OS before and after matching, daratumumab monotherapy utilising post-hoc subgroup of patients receiving subsequent treatment with bortezomib versus PANO+BORT+DEX, including list of characteristics matched in each analysis

Number of matched characteristics	N	Neff	OS HR (95% CI)	Characteristics matched
Non-BORT refractory included Unadjusted	[redacted]	[redacted]	[redacted]	-
Non-BORT refractory excluded Unadjusted	[redacted]	[redacted]	[redacted]	-
2	[redacted]	[redacted]	[redacted]	Number of prior therapies: • Median number of prior regimens • >3 prior regimens (%)

Table 16. MAIC results for OS before and after matching, daratumumab monotherapy utilising post-hoc subgroup of patients receiving subsequent treatment with carfilzomib versus PANO+BORT+DEX, including list of characteristics matched in each analysis

Number of matched characteristics	N	Neff	OS HR (95% CI)	Characteristics matched
Non-BORT refractory included Unadjusted	[redacted]	[redacted]	[redacted]	-
Non-BORT refractory excluded Unadjusted	[redacted]	[redacted]	[redacted]	-
5	[redacted]	[redacted]	[redacted]	Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%)
2	[redacted]	[redacted]	[redacted]	Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%)

Key: BORT, bortezomib; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MAIC, matched adjusted indirect comparison; Neff, net effective sample size; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone.

Table 17. MAIC results for OS before and after matching, daratumumab monotherapy utilising post-hoc subgroup of patients receiving subsequent treatment with lenalidomide versus PANO+BORT+DEX, including list of characteristics matched in each analysis

Number of matched characteristics	N	Neff	OS HR (95% CI)	Characteristics matched
Non-BORT refractory included Unadjusted	[redacted]	[redacted]	[redacted]	-
Non-BORT refractory excluded Unadjusted	[redacted]	[redacted]	[redacted]	-
5	[redacted]	[redacted]	[redacted]	Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%) ECOG score: • ECOG 0 (%) • ECOG 1 (%) • ECOG 2 (%)
2	[redacted]	[redacted]	[redacted]	Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%)

Key: BORT, bortezomib; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MAIC, matched adjusted indirect comparison; Neff, net effective sample size; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone.

Table 18. MAIC results for OS before and after matching, daratumumab monotherapy utilising post-hoc subgroup of patients receiving subsequent treatment with pomalidomide versus PANO+BORT+DEX, including list of characteristics matched in each analysis

Number of matched characteristics	N	Neff	OS HR (95% CI)	Characteristics matched
Non-BORT refractory included Unadjusted	[redacted]	[redacted]	[redacted]	-
Non-BORT refractory excluded Unadjusted	[redacted]	[redacted]	[redacted]	-
2	[redacted]	[redacted]	[redacted]	Number of prior therapies: • Mean number of prior regimens • >2 prior regimens (%)

Key: BORT, bortezomib; CI, confidence interval; HR, hazard ratio; MAIC, matched adjusted indirect comparison; Neff, net effective sample size; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone.

A7. **Priority question**: Please provide details on the methodology used to generate clinical efficacy results in the "integrated analysis" of data from MMY2002 and GEN501. In addition, please specify how the integrated analysis differs from the "crude pooling" referred to in the footnote of Table 46 of the company submission.

In addition to independent study data, an integrated analysis of patients treated with daratumumab 16mg/kg across the MMY2002 and GEN501 is presented in the company submission. For all outcomes except safety, which is reassessed in all patients from the integrated analysis set, the integrated analysis pools the latest data available from individual trials; across datasets, the median follow-up for the 31 December 2015 data cut-off was 20.7 months (range: 0.5, 27. 1).

Table 19: Overview of outcomes assessed at different trial datacuts

Trial ID	Datacut	Median (range) duration of follow-up	Outcomes assessed
MMY2002	Primary analysis: January 9, 2015	9.3 months (0.5-14.4)	ORR, DoR, PFS, OS, clinical benefit rate (MR plus ORR), TTR and safety.
	6-month interim analysis: June 30, 2015	14.7 months (0.5-20.0)	OS
	18-month analysis: December 31, 2015	20.7 months (0.5-26.3)	DoR, OS
GEN501	Primary analysis: January 9, 2015	10.2 months (1.2-16.0)	Safety.
	6-month interim analysis: June 30, 2015	15.2 months (1.2-21.4)	OS
	18-month analysis: December 31, 2015	20.5 (1.2-27.1)	ORR, DoR, PFS, OS
Integrated analysis	December 31, 2015	20.7 (0.5-27.1)	Safety

Key: DoR, duration of response; MR, minimal response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTR, time to response

A8. **Priority question**: Please provide the MAIC analysis for TTD, similar to the MAIC analysis undertaken for OS and PFS and detailed in Section 4.10.3 of the company submission. Additionally, please provide the patient characteristics used to conduct the MAIC for TTD, along with the results of the analysis, including the adjusted Kaplan-Meier data and curves derived from the MAIC for TTD.

As stated on page 188 and page 191 of the company submission:
"For the POM+DEX arm of MM-003, only mean and median TTD could be obtained from the literature (mean TTD: 4.656; median TTD: 2.854), therefore, the TTD curves for daratumumab were calibrated to match the observed mean and median from MM-003" (pg 188, company submission).

"There are no TTD data available for patients in the PANORAMA 2 clinical trial. Therefore, in the model, patients receive PANO+BORT+DEX for the maximum number of treatment cycles allowed in the dosing regimen or until progression" (pg 191, company submission)

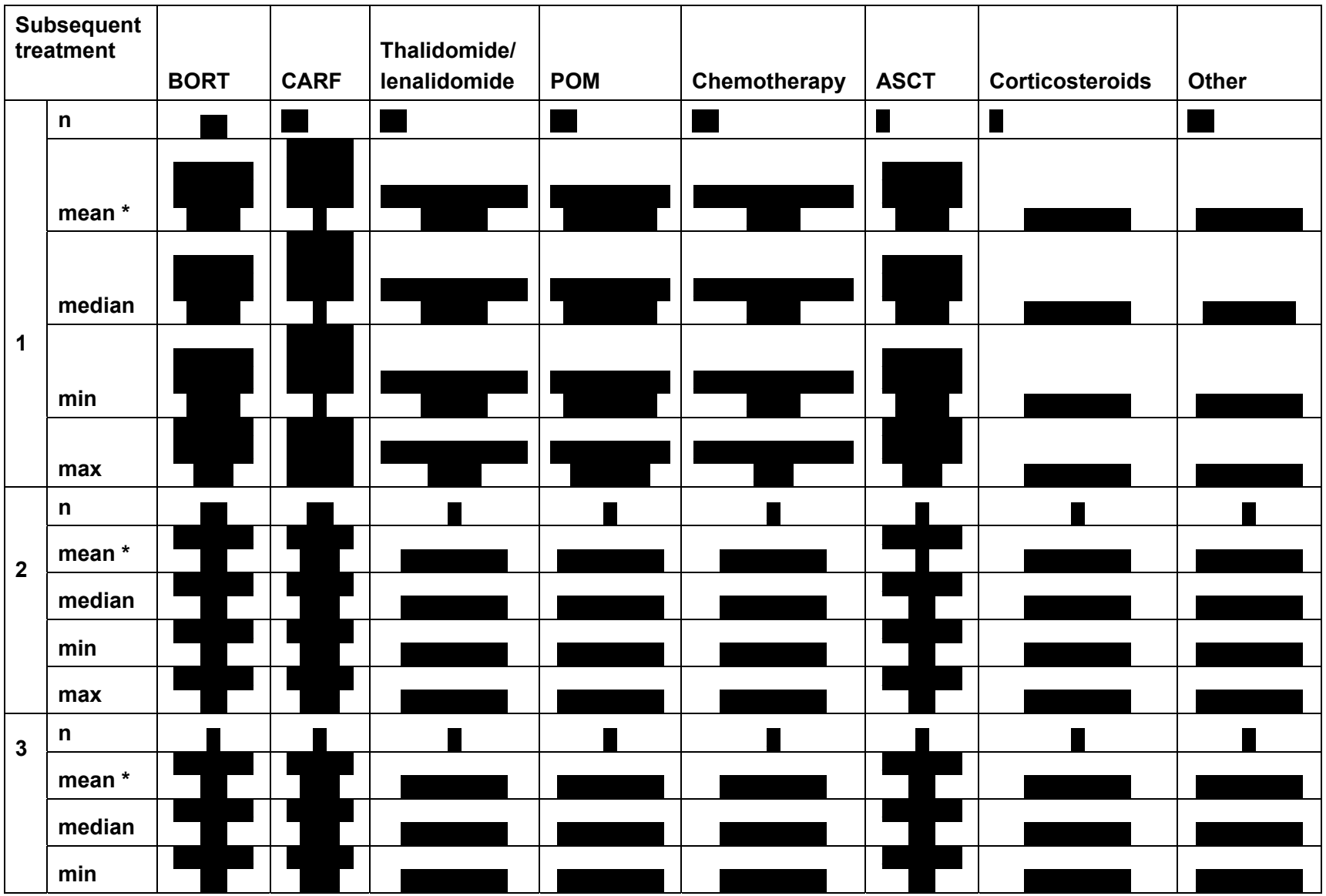
In the absence of sufficient TTD data from the comparator trials a MAIC of TTD was not possible.

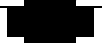
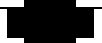
A9. **Priority question**: Please provide details on treatment duration for each of the treatments received in a sequential order for MMY2002, GEN502 separately and in the integrated dataset. More specifically, please provide mean treatment duration per treatment with respective minimum and maximum treatment period.

These data are presented in Table 20, Table 21 and Table 22 for the integrated analysis, GEN501 and MMY2002, respectively.

Table 20. Treatment duration (in months) of subsequent therapy after daratumumab, by order of sequence, integrated data

Subsequent treatment		BORT	CARF	Thalidomide/ lenalidomide	POM	Chemotherapy	ASCT	Corticosteroids	Other
1	n								
	mean *								
	median								
	min								
	max								
2	n								
	mean *								
	median								
	min								
	max								
3	n								
	mean *								
	median								
	min								



	max								
4	**n**								
	mean *								
	median								
	min								
	max								
5	**n**								
	mean *								
	median								
	min								
	max								
6	**n**								
	mean *								
	median								
	min								
	max								
7	**n**								
	mean *								
	median								
	min								

	max								
Key: ASCT, Autologous stem cell transplant; BORT, bortezomib; CARF, carfilzomib; POM, pomalidomide.									

Table 21. Treatment duration (in months) of subsequent therapy after daratumumab, by order of sequence, GEN501

Subsequent treatment		BORT	CARF	Thalidomide/ lenalidomide	POM	Chemotherapy	ASCT	Corticosteroids	Other
1	n								
	mean *								
	median								
	min								
	max								
2	n								
	mean *								
	median								
	min								
	max								
3	n								
	mean *								
	median								
	min								
	max								

4	**n**								
	mean *								
	median								
	min								
	max								
5	**n**								
	mean *								
	median								
	min								
	max								
6	**n**								
	mean *								
	median								
	min								
	max								
7	**n**								
	mean *								
	median								
	min								
	max								

Key: ASCT, Autologous stem cell transplant; BORT, bortezomib; CARF, carfilzomib; POM, pomalidomide.

Table 22. Treatment duration (in months) of subsequent therapy after daratumumab, by order of sequence, MMY2002

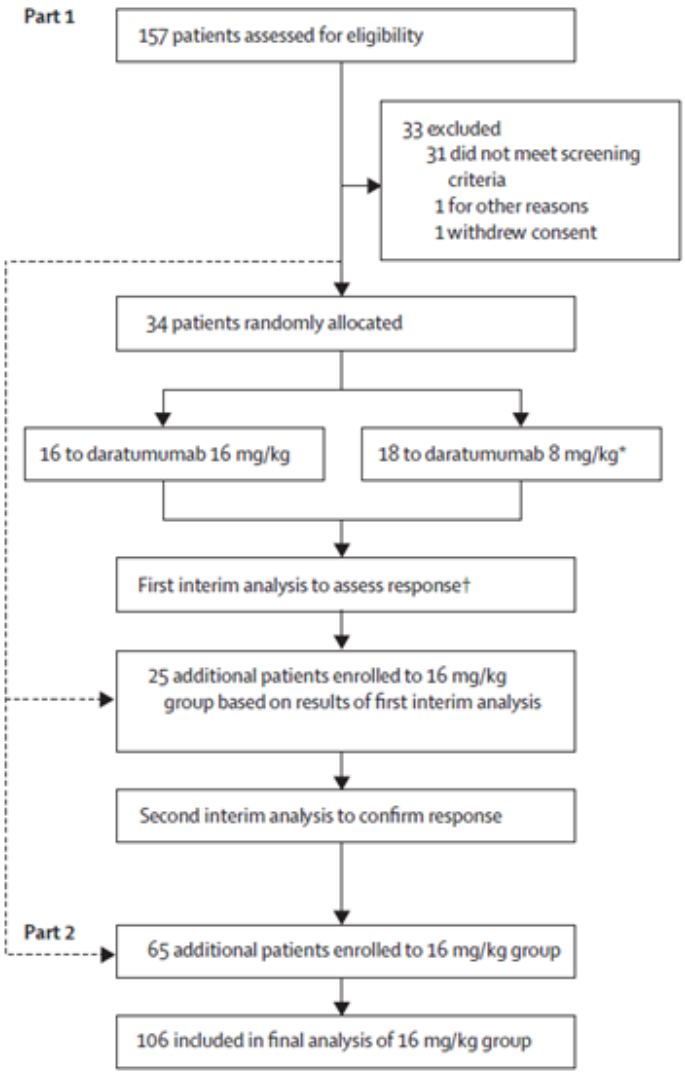
Subsequent treatment		BORT	CARF	Thalidomide/ lenalidomide	POM	Chemotherapy	ASCT	Corticosteroids	Other
1	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	mean *	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	mean *	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	mean *	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	mean *	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	mean *	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	**n**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	mean *	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	**n**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	mean *	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ASCT, Autologous stem cell transplant; BORT, bortezomib; CARF, carfilzomib; POM, pomalidomide.									

A10. Please provide separate diagrams illustrating patient flow for MMY2002 and GEN501.

A separate diagram illustrating patient flow in MMY2002 is presented in Figure 1. Please note that this is a partial CONSORT diagram as only part 1 stage 1 of MMY2002 was randomized. No diagram is available for GEN501. However, Table 10 of the company submission provides patient flow for both trials.

Figure 1. Patient flow of MMY2002, part 1 stage 1



A11. Please clarify whether the duration of response reported in Table 15 (page 79 of the company submission) is for patients whose disease responded (as opposed to the entire trial population as stated in the text).

Duration of response data reported in Table 15 of the submission is for patients who responded to daratumumab 16mg/kg rather than all treated patients.

A11. Please provide the rationale for using different cut-off dates for MMY2002 (9th Jan 2015) and GEN501 (31st Dec 2015) for ORR and PFS as presented in the company submission. Additionally, please provide:

a. summary data for ORR in patients receiving daratumumab 16 mg/kg in MMY2002 at a cut-off date of 31 December 2015, and in GEN501 at a cut-off date of 9 January 2015 (in the format presented in Table 13 of the company submission)

b. summary data for PFS in patients receiving daratumumab 16 mg/kg in MMY2002 at a cut-off date of 31 December 2015, and in GEN501 at a cut-off date of 9 January 2015 (in the format presented in Table 17 of the company submission).

For study MMY2002, the primary efficacy analyses were based on independent review committee (IRC) assessment, where IRC evaluated all efficacy data only up to cutoff of Jan 9, 2015. For study GEN501, IRC assessment of efficacy data was not planned and the primary efficacy analyses were based on computerized algorithm assessment, which was validated by the IRC assessment using MMY2002 data, and carried out throughout the whole study of GEN501 (included all data up to cutoff of Dec 31, 2015). Therefore, two different cutoff dates were presented in the company submission.

As such, ORR and PFS data are not available in patients receiving daratumumab 16 mg/kg in MMY2002 at a cut-off date of 31 December 2015 or in GEN501 at a cut-off date of 9 January 2015.

A12. The titles of Tables 13-15 and Tables 23-29 of the company submission indicate that the data have been assessed by an independent review committee (IRC). However, earlier in the company submission (page 76), it is stated that, for GEN501, “disease evaluations were conducted through a computerised algorithm, and an IDMC (independent data monitoring committee) reviewed unblinded data on a routine basis and provided recommendations on the continuation, modification, or termination of the study.”

a. Did the IDMC reviewing unblinded data from GEN501 also review the categorisations of clinical outcomes as reported in Tables 13-15, and in the integrated analyses presented in Tables 23-29?

IRC assessment of efficacy data, including clinical outcomes, was not planned for study GEN501. The routine IDMC review in this study was more focused on the safety data.

b. If not, please discuss whether the reliability of the treatment algorithm in the categorisation of response was evaluated. For example, were any comparisons made between categorisations of response determined by the treatment algorithm and those made by the IRC? If so, what was the level of agreement?

A computerized algorithm for assessing efficacy data was developed based on MMY2002 data, and the same algorithm was utilized for efficacy assessment in study GEN501. The validity of this algorithm assessment was evaluated against the IRC assessment in study MMY2002. A detailed summary of the reliability of the computerized algorithm is presented in MMY2002 CSR Section 5.2, which concludes that the agreement between the IRC assessment and computerized algorithm assessment was almost perfect.

A13. Please populate the table below to provide number of patients (and percentage) at baseline in MMY2002 and GEN501 by number of previous lines of therapy.

Table 23. Number of patients at baseline by previous number of therapies

Number of lines of prior therapy	**MMY2002, Dara 16mg/kg (n=106)**		**GEN501 Part 2 Dara 16mg/kg (n=42)**	
	n	**%**	**n**	**%**
2	2	1.89%	9	21.43%
3	17	16.04%	7	16.67%
4	23	21.70%	7	16.67%
5	19	17.92%	5	11.90%
6	14	13.21%	3	7.14%
7	11	10.38%	3	7.14%
8	7	6.60%	3	7.14%
9	6	5.66%	3	7.14%
10	3	2.83%	1	2.38%

Number of lines of prior therapy	MMY2002, Dara 16mg/kg (n=106)		GEN501 Part 2 Dara 16mg/kg (n=42)	
	n	%	n	%
11	2	1.89%	0	0.00%
12	0	0.00%	1	2.38%
13	1	0.94%	0	0.00%
14	1	0.94%	0	0.00%

A14. Please provide data on treatment-related adverse events for:

a. integrated analysis of MMY2002 and GEN501

Table 24 Treatment-Related Adverse Events by System Organ Class and Preferred Term; All Treated Analysis Set - 16mg/kg Group (Studies: MMY2002 and GEN501 Part 2)

	Daratumumab 16 mg/kg
Analysis set: all treated	148
Total number of subjects with related TEAE	117 (79.1%)
MedDRA system organ class / Preferred term	
Respiratory, thoracic and mediastinal disorders	61 (41.2%)
Nasal congestion	17 (11.5%)
Cough	16 (10.8%)
Dyspnoea	10 (6.8%)
Rhinitis allergic	10 (6.8%)
Throat irritation	9 (6.1%)
Bronchospasm	4 (2.7%)
Wheezing	4 (2.7%)
Sneezing	3 (2.0%)
Throat tightness	3 (2.0%)
Dyspnoea exertional	2 (1.4%)
Oropharyngeal pain	2 (1.4%)
Productive cough	2 (1.4%)
Allergic cough	1 (0.7%)
Hypoxia	1 (0.7%)
Laryngeal oedema	1 (0.7%)
Laryngitis allergic	1 (0.7%)
Nasal disorder	1 (0.7%)
Rhinorrhoea	1 (0.7%)
Sinus congestion	1 (0.7%)

	Daratumumab 16 mg/kg
General disorders and administration site conditions	54 (36.5%)
Fatigue	32 (21.6%)
Chills	12 (8.1%)
Pyrexia	5 (3.4%)
Asthenia	4 (2.7%)
Influenza like illness	4 (2.7%)
Chest discomfort	3 (2.0%)
Chest pain	2 (1.4%)
Malaise	2 (1.4%)
Axillary pain	1 (0.7%)
Infusion site bruising	1 (0.7%)
Injection site bruising	1 (0.7%)
Injection site reaction	1 (0.7%)
Oedema	1 (0.7%)
Oedema peripheral	1 (0.7%)
Pain	1 (0.7%)
Peripheral swelling	1 (0.7%)
Blood and lymphatic system disorders	39 (26.4%)
Anaemia	21 (14.2%)
Thrombocytopenia	18 (12.2%)
Neutropenia	14 (9.5%)
Leukopenia	8 (5.4%)
Lymphopenia	5 (3.4%)
Red blood cell agglutination	1 (0.7%)
Gastrointestinal disorders	37 (25.0%)
Nausea	24 (16.2%)
Vomiting	11 (7.4%)
Diarrhoea	9 (6.1%)
Constipation	7 (4.7%)
Abdominal discomfort	1 (0.7%)
Abdominal distension	1 (0.7%)
Abdominal pain upper	1 (0.7%)
Flatulence	1 (0.7%)
Gastrooesophageal reflux disease	1 (0.7%)
Hypoaesthesia oral	1 (0.7%)
Paraesthesia oral	1 (0.7%)
Stomatitis	1 (0.7%)
Infections and infestations	25 (16.9%)
Upper respiratory tract infection	8 (5.4%)
Pneumonia	5 (3.4%)
Herpes zoster	4 (2.7%)
Nasopharyngitis	3 (2.0%)
Sinusitis	3 (2.0%)
Candida infection	2 (1.4%)
Lobar pneumonia	2 (1.4%)

	Daratumumab 16 mg/kg
Bacterial sepsis	1 (0.7%)
Oral candidiasis	1 (0.7%)
Parainfluenzae virus infection	1 (0.7%)
Pharyngitis	1 (0.7%)
Rhinovirus infection	1 (0.7%)
Sepsis	1 (0.7%)
Varicella	1 (0.7%)
Musculoskeletal and connective tissue disorders	18 (12.2%)
Back pain	6 (4.1%)
Muscle spasms	5 (3.4%)
Arthralgia	2 (1.4%)
Bone pain	2 (1.4%)
Myalgia	2 (1.4%)
Pain in extremity	2 (1.4%)
Limb discomfort	1 (0.7%)
Muscular weakness	1 (0.7%)
Musculoskeletal chest pain	1 (0.7%)
Metabolism and nutrition disorders	17 (11.5%)
Decreased appetite	9 (6.1%)
Hypokalaemia	4 (2.7%)
Hypomagnesaemia	3 (2.0%)
Hyponatraemia	3 (2.0%)
Hypercalcaemia	1 (0.7%)
Hyperglycaemia	1 (0.7%)
Hypoalbuminaemia	1 (0.7%)
Hypoglycaemia	1 (0.7%)
Nervous system disorders	15 (10.1%)
Headache	5 (3.4%)
Dizziness	3 (2.0%)
Dysgeusia	2 (1.4%)
Peripheral sensory neuropathy	2 (1.4%)
Hyperaesthesia	1 (0.7%)
Hypoaesthesia	1 (0.7%)
Lethargy	1 (0.7%)
Neuropathy peripheral	1 (0.7%)
Restless legs syndrome	1 (0.7%)
Tremor	1 (0.7%)
Investigations	10 (6.8%)
Crossmatch incompatible	3 (2.0%)
Aspartate aminotransferase increased	2 (1.4%)
Alanine aminotransferase increased	1 (0.7%)
Blood alkaline phosphatase increased	1 (0.7%)
Blood creatinine increased	1 (0.7%)
Blood phosphorus increased	1 (0.7%)
Oxygen saturation abnormal	1 (0.7%)

	Daratumumab 16 mg/kg
Weight decreased	1 (0.7%)
Weight increased	1 (0.7%)
Skin and subcutaneous tissue disorders	9 (6.1%)
Alopecia	1 (0.7%)
Blister	1 (0.7%)
Dermatitis acneiform	1 (0.7%)
Dermatitis contact	1 (0.7%)
Eczema	1 (0.7%)
Hyperhidrosis	1 (0.7%)
Palmar-plantar erythrodysaesthesia syndrome	1 (0.7%)
Pruritus	1 (0.7%)
Pruritus generalised	1 (0.7%)
Rash	1 (0.7%)
Rash macular	1 (0.7%)
Rash maculo-papular	1 (0.7%)
Urticaria	1 (0.7%)
Vascular disorders	8 (5.4%)
Hypertension	4 (2.7%)
Flushing	2 (1.4%)
Deep vein thrombosis	1 (0.7%)
Hot flush	1 (0.7%)
Hypotension	1 (0.7%)
Cardiac disorders	4 (2.7%)
Tachycardia	2 (1.4%)
Palpitations	1 (0.7%)
Sinus tachycardia	1 (0.7%)
Eye disorders	4 (2.7%)
Eye pruritus	2 (1.4%)
Vision blurred	2 (1.4%)
Dry eye	1 (0.7%)
Psychiatric disorders	4 (2.7%)
Anxiety	2 (1.4%)
Confusional state	1 (0.7%)
Delirium	1 (0.7%)
Ear and labyrinth disorders	2 (1.4%)
Tinnitus	1 (0.7%)
Vertigo	1 (0.7%)
Hepatobiliary disorders	1 (0.7%)
Hyperbilirubinaemia	1 (0.7%)
Immune system disorders	1 (0.7%)
Seasonal allergy	1 (0.7%)
Renal and urinary disorders	1 (0.7%)
Urinary retention	1 (0.7%)

	Daratumumab 16 mg/kg
Keys: TEAE = treatment-emergent adverse event. Adverse events are reported using MedDRA version 17.0.	

a. MMY2002

Table 25 Treatment-Related Adverse Events by System Organ Class and Preferred Term; All Treated Analysis Set - 16mg/kg Group (Study MMY2002)

	Daratumumab 16 mg/kg
Analysis set: all treated	106
Total number of subjects with related TEAE	84 (79.2%)
MedDRA system organ class / Preferred term	
General disorders and administration site conditions	42 (39.6%)
Fatigue	24 (22.6%)
Chills	8 (7.5%)
Asthenia	4 (3.8%)
Influenza like illness	4 (3.8%)
Pyrexia	4 (3.8%)
Chest discomfort	3 (2.8%)
Malaise	2 (1.9%)
Axillary pain	1 (0.9%)
Chest pain	1 (0.9%)
Infusion site bruising	1 (0.9%)
Injection site bruising	1 (0.9%)
Injection site reaction	1 (0.9%)
Oedema	1 (0.9%)
Oedema peripheral	1 (0.9%)
Pain	1 (0.9%)
Blood and lymphatic system disorders	37 (34.9%)
Anaemia	21 (19.8%)
Thrombocytopenia	18 (17.0%)
Neutropenia	13 (12.3%)
Leukopenia	6 (5.7%)
Lymphopenia	5 (4.7%)
Red blood cell agglutination	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	35 (33.0%)
Nasal congestion	13 (12.3%)
Cough	10 (9.4%)
Dyspnoea	8 (7.5%)
Throat irritation	7 (6.6%)
Bronchospasm	4 (3.8%)

	Daratumumab 16 mg/kg
Wheezing	4 (3.8%)
Dyspnoea exertional	2 (1.9%)
Oropharyngeal pain	2 (1.9%)
Productive cough	2 (1.9%)
Sneezing	2 (1.9%)
Laryngeal oedema	1 (0.9%)
Rhinorrhoea	1 (0.9%)
Gastrointestinal disorders	30 (28.3%)
Nausea	18 (17.0%)
Vomiting	10 (9.4%)
Constipation	7 (6.6%)
Diarrhoea	7 (6.6%)
Abdominal discomfort	1 (0.9%)
Abdominal distension	1 (0.9%)
Flatulence	1 (0.9%)
Gastrooesophageal reflux disease	1 (0.9%)
Hypoaesthesia oral	1 (0.9%)
Paraesthesia oral	1 (0.9%)
Stomatitis	1 (0.9%)
Infections and infestations	19 (17.9%)
Upper respiratory tract infection	6 (5.7%)
Pneumonia	4 (3.8%)
Sinusitis	3 (2.8%)
Lobar pneumonia	2 (1.9%)
Candida infection	1 (0.9%)
Herpes zoster	1 (0.9%)
Nasopharyngitis	1 (0.9%)
Oral candidiasis	1 (0.9%)
Parainfluenzae virus infection	1 (0.9%)
Pharyngitis	1 (0.9%)
Rhinovirus infection	1 (0.9%)
Sepsis	1 (0.9%)
Varicella	1 (0.9%)
Metabolism and nutrition disorders	15 (14.2%)
Decreased appetite	7 (6.6%)
Hypokalaemia	4 (3.8%)
Hypomagnesaemia	3 (2.8%)
Hyponatraemia	3 (2.8%)
Hypercalcaemia	1 (0.9%)
Hyperglycaemia	1 (0.9%)
Hypoalbuminaemia	1 (0.9%)
Hypoglycaemia	1 (0.9%)
Musculoskeletal and connective tissue disorders	14 (13.2%)
Back pain	4 (3.8%)
Muscle spasms	4 (3.8%)

	Daratumumab 16 mg/kg
Arthralgia	2 (1.9%)
Bone pain	2 (1.9%)
Pain in extremity	2 (1.9%)
Limb discomfort	1 (0.9%)
Muscular weakness	1 (0.9%)
Musculoskeletal chest pain	1 (0.9%)
Myalgia	1 (0.9%)
Nervous system disorders	12 (11.3%)
Headache	4 (3.8%)
Dizziness	3 (2.8%)
Dysgeusia	2 (1.9%)
Peripheral sensory neuropathy	2 (1.9%)
Hyperaesthesia	1 (0.9%)
Hypoaesthesia	1 (0.9%)
Lethargy	1 (0.9%)
Tremor	1 (0.9%)
Skin and subcutaneous tissue disorders	7 (6.6%)
Blister	1 (0.9%)
Dermatitis acneiform	1 (0.9%)
Eczema	1 (0.9%)
Palmar-plantar erythrodysaesthesia syndrome	1 (0.9%)
Pruritus	1 (0.9%)
Pruritus generalised	1 (0.9%)
Rash	1 (0.9%)
Rash macular	1 (0.9%)
Rash maculo-papular	1 (0.9%)
Urticaria	1 (0.9%)
Investigations	6 (5.7%)
Alanine aminotransferase increased	1 (0.9%)
Aspartate aminotransferase increased	1 (0.9%)
Blood alkaline phosphatase increased	1 (0.9%)
Blood creatinine increased	1 (0.9%)
Blood phosphorus increased	1 (0.9%)
Oxygen saturation abnormal	1 (0.9%)
Weight decreased	1 (0.9%)
Weight increased	1 (0.9%)
Vascular disorders	5 (4.7%)
Hypertension	2 (1.9%)
Deep vein thrombosis	1 (0.9%)
Flushing	1 (0.9%)
Hot flush	1 (0.9%)
Hypotension	1 (0.9%)
Cardiac disorders	3 (2.8%)
Tachycardia	2 (1.9%)
Palpitations	1 (0.9%)

	Daratumumab 16 mg/kg
Eye disorders	3 (2.8%)
Eye pruritus	2 (1.9%)
Vision blurred	1 (0.9%)
Psychiatric disorders	2 (1.9%)
Anxiety	1 (0.9%)
Confusional state	1 (0.9%)
Ear and labyrinth disorders	1 (0.9%)
Vertigo	1 (0.9%)
Hepatobiliary disorders	1 (0.9%)
Hyperbilirubinaemia	1 (0.9%)
Immune system disorders	1 (0.9%)
Seasonal allergy	1 (0.9%)
Renal and urinary disorders	1 (0.9%)
Urinary retention	1 (0.9%)
Keys: TEAE = treatment-emergent adverse event. Adverse events are reported using MedDRA version 17.0.	

b. GEN501.

Table 26 Treatment-Related Adverse Events by System Organ Class and Preferred Term; All Treated Analysis Set - 16mg/kg Group (Study GEN501 Part 2)

	Daratumumab 16 mg/kg
Analysis set: all treated	42
Total number of subjects with related TEAE	33 (78.6%)
MedDRA system organ class / Preferred term	
Respiratory, thoracic and mediastinal disorders	26 (61.9%)
Rhinitis allergic	10 (23.8%)
Cough	6 (14.3%)
Nasal congestion	4 (9.5%)
Throat tightness	3 (7.1%)
Dyspnoea	2 (4.8%)
Throat irritation	2 (4.8%)
Allergic cough	1 (2.4%)
Hypoxia	1 (2.4%)
Laryngitis allergic	1 (2.4%)
Nasal disorder	1 (2.4%)
Sinus congestion	1 (2.4%)
Sneezing	1 (2.4%)
General disorders and administration site conditions	12 (28.6%)
Fatigue	8 (19.0%)
Chills	4 (9.5%)

	Daratumumab 16 mg/kg
Chest pain	1 (2.4%)
Peripheral swelling	1 (2.4%)
Pyrexia	1 (2.4%)
Gastrointestinal disorders	7 (16.7%)
Nausea	6 (14.3%)
Diarrhoea	2 (4.8%)
Abdominal pain upper	1 (2.4%)
Vomiting	1 (2.4%)
Infections and infestations	6 (14.3%)
Herpes zoster	3 (7.1%)
Nasopharyngitis	2 (4.8%)
Upper respiratory tract infection	2 (4.8%)
Bacterial sepsis	1 (2.4%)
Candida infection	1 (2.4%)
Pneumonia	1 (2.4%)
Investigations	4 (9.5%)
Crossmatch incompatible	3 (7.1%)
Aspartate aminotransferase increased	1 (2.4%)
Musculoskeletal and connective tissue disorders	4 (9.5%)
Back pain	2 (4.8%)
Muscle spasms	1 (2.4%)
Myalgia	1 (2.4%)
Nervous system disorders	3 (7.1%)
Headache	1 (2.4%)
Neuropathy peripheral	1 (2.4%)
Restless legs syndrome	1 (2.4%)
Vascular disorders	3 (7.1%)
Hypertension	2 (4.8%)
Flushing	1 (2.4%)
Blood and lymphatic system disorders	2 (4.8%)
Leukopenia	2 (4.8%)
Neutropenia	1 (2.4%)
Metabolism and nutrition disorders	2 (4.8%)
Decreased appetite	2 (4.8%)
Psychiatric disorders	2 (4.8%)
Anxiety	1 (2.4%)
Delirium	1 (2.4%)
Skin and subcutaneous tissue disorders	2 (4.8%)
Alopecia	1 (2.4%)
Dermatitis contact	1 (2.4%)
Hyperhidrosis	1 (2.4%)
Cardiac disorders	1 (2.4%)
Sinus tachycardia	1 (2.4%)
Ear and labyrinth disorders	1 (2.4%)
Tinnitus	1 (2.4%)

	Daratumumab 16 mg/kg
Eye disorders	1 (2.4%)
Dry eye	1 (2.4%)
Vision blurred	1 (2.4%)
Keys: TEAE = treatment-emergent adverse event. Adverse events are reported using MedDRA version 17.0.	

A15. For Table 16 (Summary of OS, page 81 of the company submission), please:

a. Clarify whether the number of events is the number of deaths or the number of people alive at the time reported.

The number of events in Table 16 of the submission is the number of deaths.

b. Provide absolute event rates for the percentages reported at the various time points.

Table 27. OS events over time, MMY2002 and GEN501

	MMY2002				GEN501 Part 2			
	Dara 8mg/kg (n=18)		Dara 16mg/kg (n=106)		Dara 8mg/kg (n=30)		Dara 16mg/kg (n=42)	
	OS rate, % (95% CI)	No. of events	OS rate, % (95% CI)	No. of events	OS rate, % (95% CI)	No. of events	OS rate, % (95% CI)	No. of events
6 months	87.5 (58.6, 96.7)	2	81.8 (73.0, 88.0)	19	76.7 (57.2, 88.1)	7	88.1 (73.7, 94.9)	5
12 months	62.5 (24.9, 81.1)	6	64.7 (54.5, 73.1)	36	56.3 (36.8, 71.8)	13	78.6 (62.9, 88.2)	9
18 months	-	-	51.3 (41.1, 60.6)	49	-		69.0 (52.7, 80.7)	13
24 months	-	-	41.3 (31.0, 51.2)	57	-		57.4 (38.7, 72.3)	16
Key: CI, confidence interval; Dara, daratumumab; OS, overall survival. **Notes:** Analysis based on 9 January 2015 data cut-off for 8mg/kg arms, 31 December 2015 data cut-off for 16mg/kg arms.								

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** Please provide the Kaplan–Meir data (in Excel format) for:

a. daratumumab from MMY2002 and GEN501 separately, for OS, PFS and TTD (where possible) adjusted with the MAIC to pomalidomide plus dexamethasone (MM-003) and also adjusted to panobinostat plus bortezomib plus dexamethasone (PANORAMA 2)

These data are provided in the respective Excel files (Table 28, Table 29). Of note, conducting an MAIC with TTD data is not possible in the absence of TTD KM data from MM-003 and PANORAMA 2.

Table 28. Key to Excel files of K-M OS data

KM data requested (OS)	File name
MMY2002 OS adjusted with the MAIC to POM+DEX, 28 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to POM+DEX, 27 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to POM+DEX, 26 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to POM+DEX, 23 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to POM+DEX, 20 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to POM+DEX, 15 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to POM+DEX, 14 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to POM+DEX, 13 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to POM+DEX, 10 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to POM+DEX, 7 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to POM+DEX, 5 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to	[redacted]

POM+DEX, 3 characteristics matched	
MMY2002 OS adjusted with the MAIC to PANO+BORT+DEX, 16 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to PANO+BORT+DEX, 14 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to PANO+BORT+DEX, 13 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to PANO+BORT+DEX, 12 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to PANO+BORT+DEX, 10 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to PANO+BORT+DEX, 9 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to PANO+BORT+DEX, 8 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to PANO+BORT+DEX, 5 characteristics matched	[redacted]
MMY2002 OS adjusted with the MAIC to PANO+BORT+DEX, 2 characteristics matched	[redacted]
GEN501 OS adjusted with the MAIC to POM+DEX, 18 characteristics matched	[redacted]
GEN501 OS adjusted with the MAIC to POM+DEX, 12 characteristics matched	[redacted]
GEN501 OS adjusted with the MAIC to POM+DEX, 11 characteristics matched	[redacted]
GEN501 OS adjusted with the MAIC to POM+DEX, 8 characteristics matched	[redacted]
GEN501 OS adjusted with the MAIC to POM+DEX, 5 characteristics matched	[redacted]
GEN501 OS adjusted with the MAIC to POM+DEX, 3 characteristics matched	[redacted]
GEN501 OS adjusted with the MAIC to	[redacted]

PANO+BORT+DEX, 12 characteristics matched	
GEN501 OS adjusted with the MAIC to PANO+BORT+DEX, 10 characteristics matched	[redacted]
GEN501 OS adjusted with the MAIC to PANO+BORT+DEX, 9 characteristics matched	[redacted]
GEN501 OS adjusted with the MAIC to PANO+BORT+DEX, 6 characteristics matched	[redacted]
GEN501 OS adjusted with the MAIC to PANO+BORT+DEX, 5 characteristics matched	[redacted]
GEN501 OS adjusted with the MAIC to PANO+BORT+DEX, 2 characteristics matched	[redacted]
Key: KM, Kaplan-Meier; MAIC, matched adjusted indirect comparison; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; POM+DEX, pomalidomide plus dexamethasone.	

Table 29. Key to Excel files of K-M PFS data

KM data requested (PFS)	File name
MMY2002 PFS adjusted with the MAIC to POM+DEX, 28 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to POM+DEX, 27 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to POM+DEX, 26 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to POM+DEX, 23 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to POM+DEX, 20 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to POM+DEX, 15 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to POM+DEX, 14 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to POM+DEX, 13 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to POM+DEX, 10 characteristics matched	[redacted]

MMY2002 PFS adjusted with the MAIC to POM+DEX, 7 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to POM+DEX, 5 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to POM+DEX, 3 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to PANO+BORT+DEX, 16 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to PANO+BORT+DEX, 14 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to PANO+BORT+DEX, 13 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to PANO+BORT+DEX, 12 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to PANO+BORT+DEX, 10 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to PANO+BORT+DEX, 9 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to PANO+BORT+DEX, 8 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to PANO+BORT+DEX, 5 characteristics matched	[redacted]
MMY2002 PFS adjusted with the MAIC to PANO+BORT+DEX, 2 characteristics matched	[redacted]
GEN501 PFS adjusted with the MAIC to POM+DEX, 18 characteristics matched	[redacted]
GEN501 PFS adjusted with the MAIC to POM+DEX, 12 characteristics matched	[redacted]
GEN501 PFS adjusted with the MAIC to POM+DEX, 11 characteristics matched	[redacted]
GEN501 PFS adjusted with the MAIC to POM+DEX, 8 characteristics matched	[redacted]
GEN501 PFS adjusted with the MAIC to POM+DEX, 5 characteristics matched	[redacted]
GEN501 PFS adjusted with the MAIC to	[redacted]

POM+DEX, 3 characteristics matched	
GEN501 PFS adjusted with the MAIC to PANO+BORT+DEX, 12 characteristics matched	[redacted]
GEN501 PFS adjusted with the MAIC to PANO+BORT+DEX, 10 characteristics matched	[redacted]
GEN501 PFS adjusted with the MAIC to PANO+BORT+DEX, 9 characteristics matched	[redacted]
GEN501 PFS adjusted with the MAIC to PANO+BORT+DEX, 6 characteristics matched	[redacted]
GEN501 PFS adjusted with the MAIC to PANO+BORT+DEX, 5 characteristics matched	[redacted]
GEN501 PFS adjusted with the MAIC to PANO+BORT+DEX, 2 characteristics matched	[redacted]
Key: KM, Kaplan-Meier; MAIC, matched adjusted indirect comparison; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone.	

b. daratumumab unadjusted Kaplan–Meir data from GEN501 for OS, PFS and TTD

These data are provided in the respective Excel files (Table 30).

Table 30. Key to GEN501 K-M files

KM data	File name
GEN501 OS, unadjusted KM data	[redacted]
GEN501 PFS, unadjusted KM data	[redacted]
GEN501 TTD, unadjusted KM data	[redacted]
Key: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.	

c. daratumumab adjusted and unadjusted integrated Kaplan–Meir data excluding pomalidomide pre-treated patients for OS, PFS and TTD (corresponding to the scenario analysis reported in the company submission)

These data are provided in the respective Excel files (Table 31).

Table 31. Key to pomalidomide naïve K-M data, integrated analysis

KM data	File name
Integrated analysis OS of POM-Naïve patients,	INT OS - POMNAIVE - KM data unadjusted

unadjusted KM data	
Integrated analysis PFS of POM-Naïve patients, unadjusted KM data	INT PFS - POMNAIVE - KM data unadjusted
Integrated analysis TTD of POM-Naïve patients, unadjusted KM data	INT TTD - POMNAIVE - KM data unadjusted
Integrated analysis OS of POM-Naïve patients, adjusted (vs POM+DEX) KM data, 11 characteristics matched	INT OS - POMNAIVE - adjusted MAIC to POM+DEX - 11 characteristics matched
Integrated analysis PFS of POM-Naïve patients, adjusted (vs POM+DEX) KM data, 11 characteristics matched	INT PFS - POMNAIVE - adjusted MAIC to POM+DEX - 11 characteristics matched
Key: KM, Kaplan-Meier; MAIC, matched adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone; TTD, time to treatment discontinuation.	

d. the data requested in B1 c) from MMY2002 and GEN501 separately

These data are provided in the respective Excel files (Table 32).

Table 32. Key to pomalidomide naïve K-M data, MMY2002 and GEN501

KM data	File name
MMY2002 OS of POM-naïve patients, unadjusted KM data	[redacted]
MMY2002 PFS of POM-naïve patients, unadjusted KM data	[redacted]
MMY2002 TTD of POM-naïve patients, unadjusted KM data	[redacted]
MMY2002 OS of POM-Naïve patients, adjusted with the MAIC to POM+DEX, 13 characteristics matched	[redacted]
MMY2002 PFS of POM-Naïve patients, adjusted with the MAIC to POM+DEX, 13 characteristics matched	[redacted]
GEN501 OS of POM-Naïve patients, unadjusted KM data	[redacted]
GEN501 PFS of POM-Naïve patients, unadjusted KM data	[redacted]
GEN501 TTD of POM-Naïve patients, unadjusted KM data	[redacted]
GEN501 OS of POM-Naïve patients, adjusted with the MAIC to POM+DEX, 11 characteristics matched	[redacted]

GEN501 PFS of POM-Naïve patients, adjusted with the MAIC, 11 characteristics matched	[redacted]
Key: KM, Kaplan-Meier; MAIC, matched adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone; TTD, time to treatment discontinuation.	

e. daratumumab integrated adjusted and unadjusted OS Kaplan–Meir data based on subsequent post-daratumumab treatment received, more specifically for:
    i. patients receiving daratumumab with no subsequent treatment received
    ii. patients receiving bortezomib as a subsequent treatment after daratumumab
    iii. patients receiving carfilzomib as a subsequent treatment after daratumumab
    iv. patients receiving lenalidomide as a subsequent treatment after daratumumab
    v. patients receiving pomalidomide as a subsequent treatment after daratumumab

The unadjusted OS K-M data are provided in the respective Excel files (Table 33). However, whilst it was possible to derive weighted HRS from a Cox proportional hazards model (using PHREG in SAS) as a consequence of the extreme weights required to perform MAIC on these post-hoc subgroups it was not possible to generate adjusted K-M data files (using LIFEREG in SAS). The extreme weights required to conduct MAIC on these post-hoc subgroups, further emphasises the inappropriateness of these analyses.

Table 33. Key to post-hoc subgroup K-M data, integrated analysis

KM data	File name
Integrated analysis OS, unadjusted KM data for patients receiving no subsequent treatment	[redacted]
Integrated analysis OS, unadjusted KM data for patients receiving bortezomib subsequent treatment	[redacted]
Integrated analysis OS, unadjusted KM data for patients receiving carflizomib subsequent treatment	[redacted]
Integrated analysis OS, unadjusted KM data for patients receiving lenalidomide subsequent	[redacted]

treatment	
Integrated analysis OS, unadjusted KM data for patients receiving pomalidomide subsequent treatment	[redacted]
Key: KM, Kaplan-Meier; OS, overall survival.	

f. the data requested in B1 e) i) for MMY2002 data and GEN501 data, reported separately, for daratumumab alone with no subsequent treatments included

As for B1 e) i) the unadjusted OS K-M data are provided in the respective Excel files (Table 34). However, as a consequence of the extreme weights required to perform MAIC on these post-hoc subgroups it was not possible to generate adjusted K-M data.

HR is generated using a cox PH model PHREG

KM lifetest

Table 34. Key to post-hoc no subsequent treatment subgroup K-M data, MMY2002 and GEN501

KM data	File name
MMY2002 OS, unadjusted KM data for patients receiving no subsequent treatment	[redacted]
GEN501 OS, unadjusted KM data for patients receiving no subsequent treatment	[redacted]
Key: KM, Kaplan-Meier; OS, overall survival.	

g. daratumumab adjusted and unadjusted OS Kaplan–Meir from MMY2002 and GEN501 separately for all the subsequent therapies received after daratumumab (i.e. excluding the initial treatment with daratumumab).

As for B1 e) i) the unadjusted OS K-M data are provided in the respective Excel files (Table 35). However, as a consequence of the extreme weights required to perform MAIC on these post-hoc subgroups it was not possible to generate adjusted K-M data

Table 35. Key to post-hoc any subsequent treatment subgroup K-M data, MMY2002 and GEN501

KM data	File name
MMY2002 OS, unadjusted KM data for patients receiving any subsequent treatment	[redacted]
GEN501 OS, unadjusted KM data for patients receiving any subsequent treatment	[redacted]
Key: KM, Kaplan-Meier; OS, overall survival.	

B2. **Priority question:** Please include an option in the model to allow the user to run the scenario analysis reported in the company submission excluding patients that were pre-treated with pomalidomide (resulting in an ICER of £59,097 per QALY gained).

The scenario analysis where patients in the integrated MMY2002/GEN501 trial data who have been pre-treated with pomalidomide are excluded is included in the automated scenario analysis. The results are presented in Row 26 of Table 83 on page 244 of the submission. The VBA code used for this analysis can be found in Macro "Scenarios". This scenario applied the HR from the MAIC where patients who have been pre-treated with POM+DEX have been excluded to the full daratumumab dataset.

A further scenario is now available in the model where this HR is applied to a subset of the daratumumab data, where patients pre-treated with POM+DEX have been excluded. This can be selected by changing "Controls.Population" to "Pooled Population – POM Naïve Only". This results in an ICER of £31,877 vs POM+DEX.

B3. **Priority question:** Please provide the adjusted and unadjusted integrated OS, PFS and TTD curves for daratumumab that were used to run the scenario analysis reported in the company submission excluding patients that were pre-treated with pomalidomide.

As noted in B2, the scenario presented in the company submission applied the OS and PFS HRs obtained from MAIC in POM+DEX naïve patients (11 characteristics matched) to the extrapolated integrated daratumumab data. An additional scenario has been run that applies the same HRs to the extrapolated POM+DEX naïve data. The results of this analysis are presented in Table 36.

Table 36. Results of additional POM+DEX naïve sensitivity analysis

	Total			Incremental			ICER
	Costs	**QALYs**	**LYs**	**Costs**	**QALYs**	**LYs**	
Daratumumab	£86,248	1.99	3.98				
POM+DEX	£49,879	0.85	1.64	£36,369	1.14	2.34	£31,877

The unadjusted OS, PFS and TTD curves are contained within the updated model, Columns S:X on tab "OS Curves_DARA_POMNAIVE", Columns S:X on tab "PFS Curves_DARA_POMNAIVE" and Columns S:X on tab "TTD Curves_DARA_POMNAIVE", respectively. Curves based on MAIC adjusted data have not been provided for this scenario analysis.

B4. **Priority question**: Please provide separate base-case analyses for MMY2002 and GEN501 compared with all relevant comparators using appropriate model inputs based on the data requested in B1 e) and f) in terms of OS, as per the analyses below. Please also either adapt the model or provide a new model to allow for each of the analyses:

a) integrated daratumumab patients who received daratumumab and no subsequent treatments against pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone
b) daratumumab patients from MMY2002 and from GEN501, separately, who received no subsequent treatments against pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone
c) integrated patients from MMY2002 and GEN501 receiving bortezomib as a subsequent treatment post-daratumumab against pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone
d) integrated patients from MMY2002 and GEN501 receiving carfilzomib as a subsequent treatment post-daratumumab against pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone
e) integrated patients from MMY2002 and GEN501 receiving lenalidomide as a subsequent treatment post-daratumumab against pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone

f) integrated patients from MMY2002 and GEN501 receiving pomalidomide as a subsequent treatment post-daratumumab against pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone.

Sensitivity analyses using data from MMY2002 are available for all comparators in the original model. In addition to this, a sensitivity analysis using GEN501 has been provided in the updated model. Table 37 displays the model results using GEN501.

Table 37. Model results based on GEN501

	Total			Incremental			ICER (Dara vs comparator) at list prices
	Costs	**QALYs**	**LYs**	**Costs**	**QALYs**	**LYs**	
Daratumumab	£113,605	1.94	3.83	-	-	-	-
POM+DEX	£49,865	0.83	1.57	£63,741	1.11	2.26	£57,467
PANO+BORT+DEX	£90,084	1.13	2.15	£23,522	0.81	1.67	£29,183
Bendamustine-based therapy	£57,181	0.86	1.69	£56,424	1.07	2.14	£52,586

Key: ICER, incremental cost-effectiveness ratio; LY, life year; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; POM+DEX, pomalidomide plus dexamethasone; QALY, quality adjusted life-year.

The integrated dataset facilitates more reliable MAIC as a result of increased overlap (with the comparator trials) and sample size, as such additional base case models focussing on the constituent trials would be superfluous (and not possible within the time constraints of the clarification process).

Furthermore, for reasons detailed in A6, analyses of the post-hoc subgroups around subsequent treatment are statistically inappropriate. As such, inclusion of these data into the economic model has not been carried out.

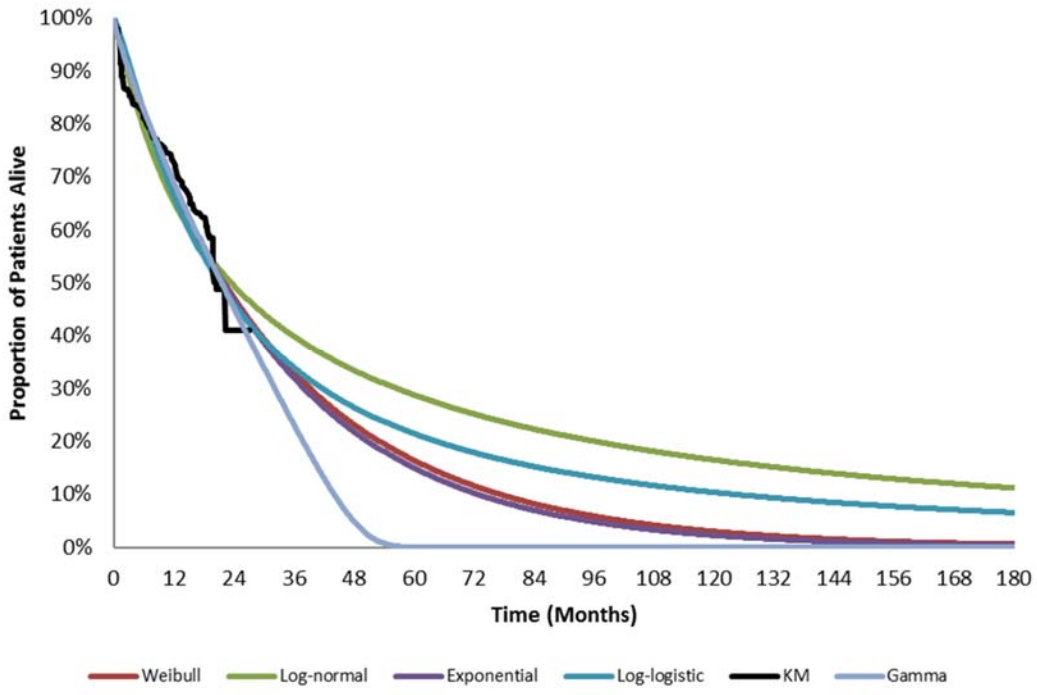
B5. **Priority question:** Can you please confirm:

a) Column J on tab “KM Data” in the Excel model is the daratumumab integrated adjusted OS Kaplan–Meir data from the MAIC with respect to pomalidomide plus

dexamethasone (MM-003) shown in Figure 11 of appendix 11? If not, please provide these Kaplan–Meir data (the excel tab “OS Curves_PostMAIC_DARAadjPOM” seems to be using the unadjusted Kaplan–Meir data for OS for comparison with the independently fitted curves).

Yes, Column J on tab “KM Data” in the Excel model is the daratumumab integrated adjusted OS Kaplan–Meir data from the MAIC with respect to pomalidomide plus dexamethasone (MM-003). The Figure on the tab “OS Curves_PostMAIC_DARAadjPOM” has been corrected to lookup this column and the corrected figure is presented in Figure 2.

Figure 2: Daratumumab OS, post MAIC vs POM+DEX

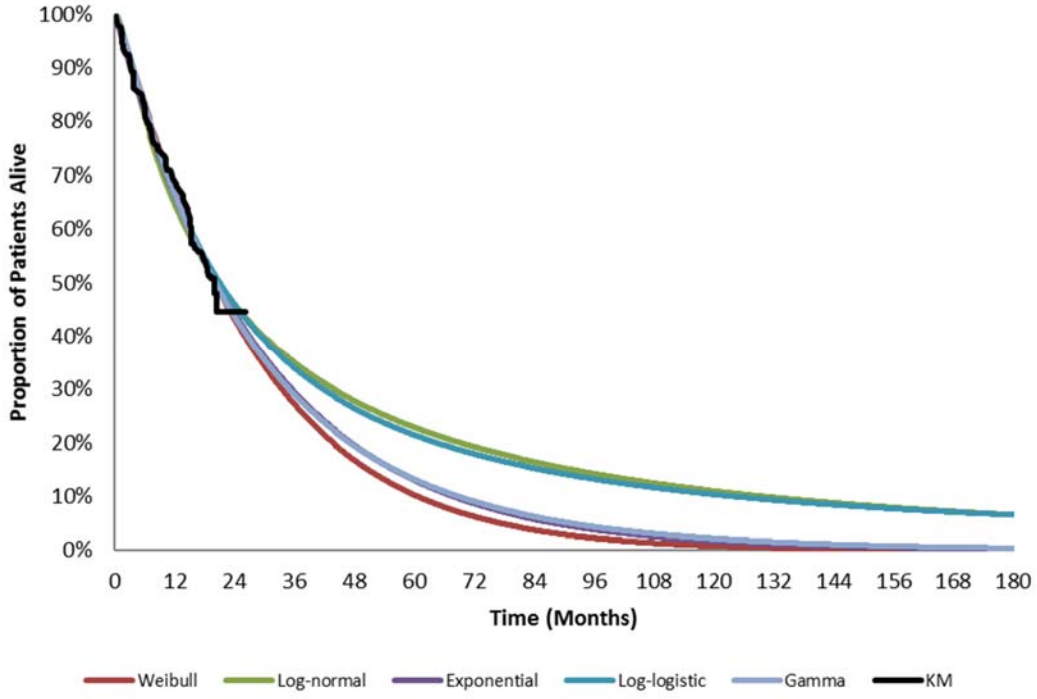


b) Column M on tab “KM Data” in the Excel model is the daratumumab integrated adjusted OS Kaplan–Meir data from the MAIC with respect to panobinostat plus bortezomib plus dexamethasone (PANORAMA 2) as shown in Figure 16 of appendix 11? If not, please provide these Kaplan–Meir data (the excel tab “OS Curves_PostMAIC_DARAadjPANO” seems to be using the unadjusted Kaplan–Meir data for OS for comparison with the independently fitted curves).

Yes, Column M on tab “KM Data” in the Excel model is the daratumumab integrated adjusted OS Kaplan–Meir data from the MAIC with respect to panobinostat plus bortezomib plus dexamethasone (PANORAMA 2). The figure on the excel tab “OS

Curves_PostMAIC_DARAadjPANO" has been corrected to look up this column and the updated figure is presented in Figure 3.

Figure 3: Daratumumab OS, post MAIC vs PANO+BORT+DEX



c) Column AN on tab "KM Data" in the Excel model is the daratumumab integrated adjusted PFS Kaplan–Meir data from the MAIC with respect to pomalidomide plus dexamethasone (MM-003)? If not, please provide these Kaplan–Meir data.

Yes, that is correct.

d) Column AQ on tab "KM Data" in the Excel model is the daratumumab integrated adjusted PFS Kaplan–Meir data from the MAIC with respect to panobinostat plus bortezomib plus dexamethasone (PANORAMA 2)? If not, please provide these Kaplan–Meir data.

Yes, that is correct.

e) Column Q on tab "KM Data" in the Excel model is the MM-003 digitised Kaplan–Meir data for pomalidomide plus dexamethasone for OS as seen in Figure 10 of appendix 11? If not, please provide these Kaplan–Meir data.

Yes, that is correct.

f) Column AD on tab “KM Data” in the Excel model is the PANORAMA digitised Kaplan–Meir data for panobinostat plus bortezomib plus dexamethasone for OS as seen in Figure 15 of appendix 11? If not, please provide these Kaplan–Meir data.

Yes, that is correct. This is from the PANORAMA2 trial.

g) Column AU and column BG on tab “KM Data” in the Excel model is the PFS digitised Kaplan–Meir data used to run the MAIC analysis for pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone respectively? If this is not the case, please provide these Kaplan–Meir data.

Yes, this is correct.

h) What data is shown in column BR of the “KM Data” tab of the Excel model?

Apologies, this is unused, irrelevant data (an erroneous analysis from HMRN data) which was not removed during the model building process. It has now been removed from the model.

i) The Kaplan–Meir data used to run the analysis reported in Figure 8 and Figure 13 of appendix 11 of the company submission uses the daratumumab curves adjusted to the respective comparator studies.

Yes, this is correct

B6. **Priority question**: Please provide the weighted hazard ratio for TTD derived from the MAIC in relation to daratumumab versus pomalidomide plus dexamethasone.

As noted in A8, in the absence of sufficient TTD data from the comparator trials a MAIC of TTD was not possible

B7. **Priority question**: On page 170 of the company submission it is stated that the extrapolation of parametric survival curves followed the NICE TSD number 14. However, the Gompertz distribution is not included in the company’s analysis (nonetheless it seems to have been partially included in the economic model). Please provide the following data for OS, PFS and TTD:

a) AIC and BIC criteria for the Gompertz distribution

b) parametric curve for the Gompertz distribution superimposed to the Kaplan–Meir data and other parametric curves for each outcome.

Table 38 summarises the AIC and BIC for the Gompertz distribution to integrated PFS, OS and TTD dataratumumab data. The parametric curve for the Gompertz distribution superimposed onto the Kaplan–Meir data and other parametric curves for each outcome are presented in Figure 4, Figure 5 and Figure 6, for PFS, OS and TTD, respectively.

Table 38. AIC and BIC statistics for Gompertz distribution

Goodness of fit statistic	PFS	OS	TTD
AIC	602.31	647.68	720.114
BIC	608.30	653.67	726.109
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival; PFS, progression free survival; TTD, time to treatment discontinuation.			

Figure 4: Curve fit to integrated daratumumab PFS data

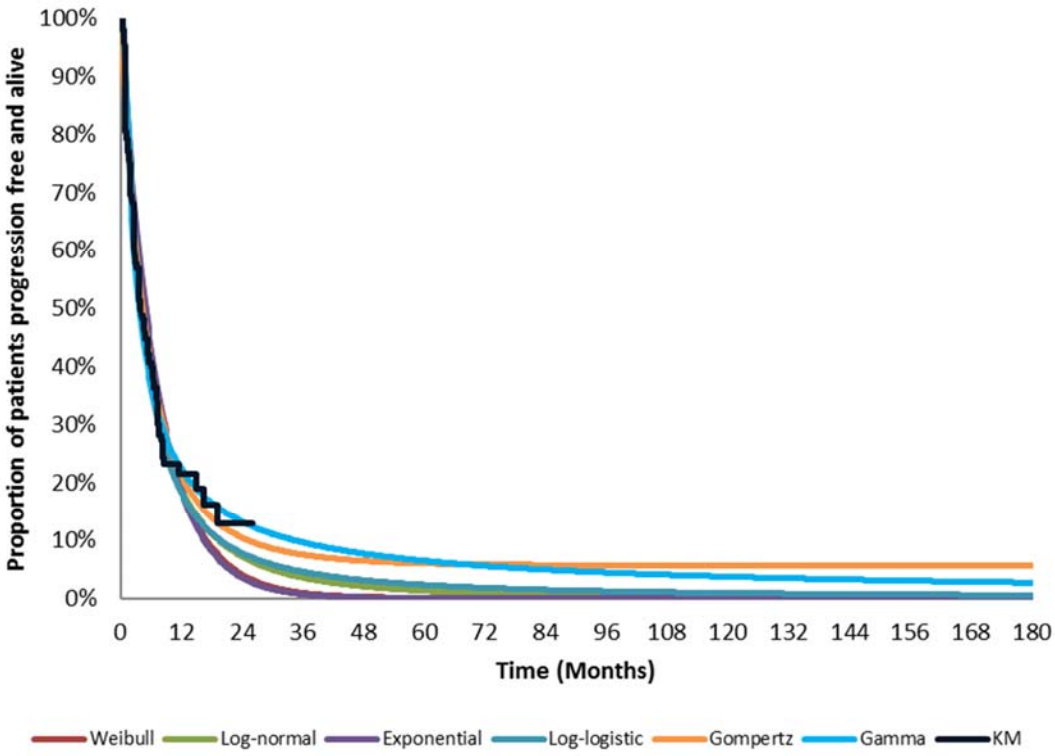


Figure 5: Curve fit to integrated daratumumab OS data

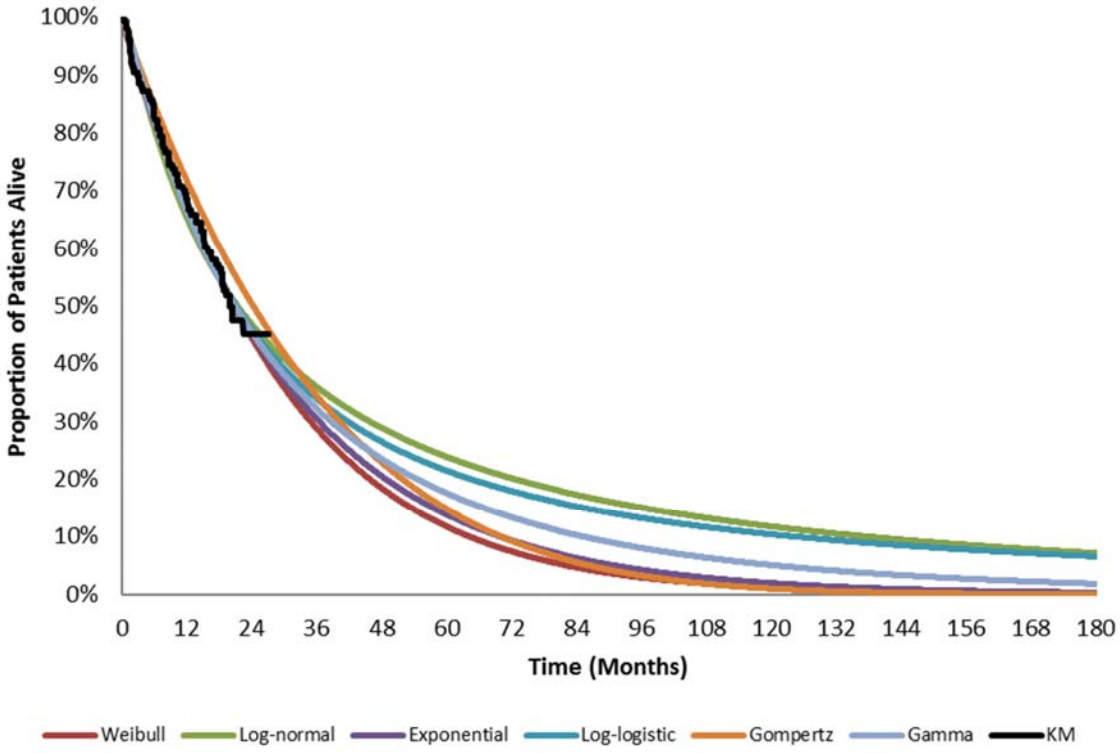
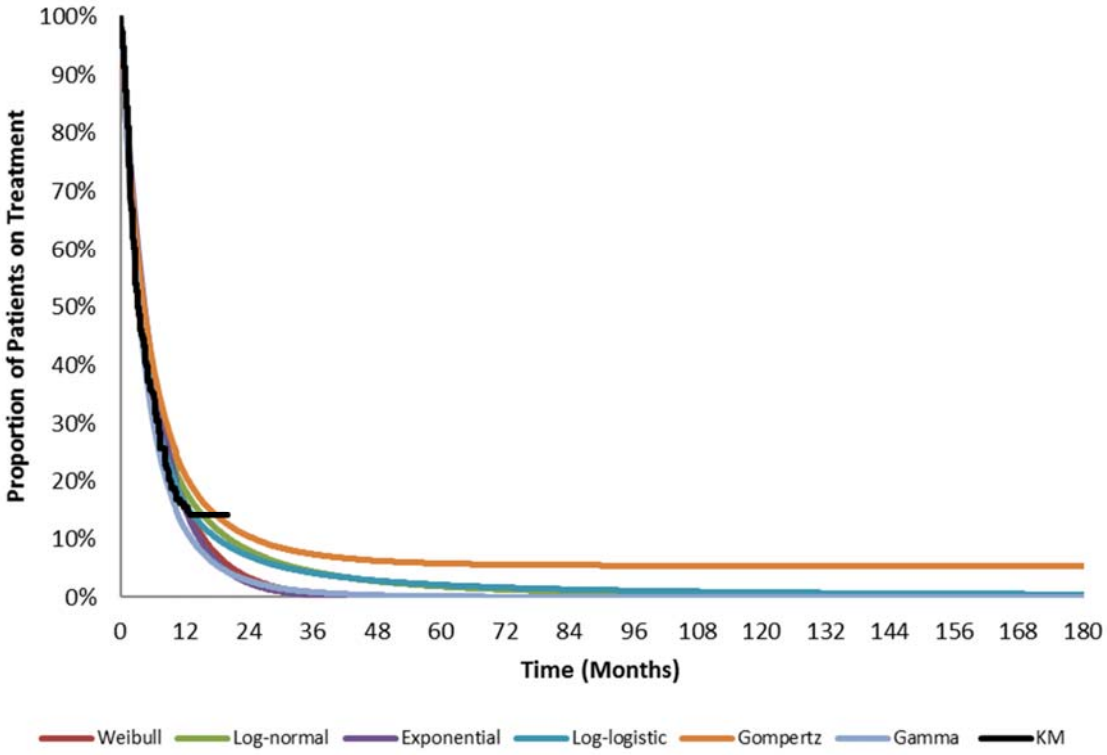


Figure 6: Curve fit to integrated daratumumab TTD data



B8. **Priority question:** Please include the Gompertz distribution as an alternative distribution to model OS, PFS and TTD in the economic model in the tab "Controls" of the economic model, cells "Controls.OS_select", "Controls.PFS_select" and "Controls.TTD_select" respectively.

This is provided in the updated model.

B9. **Priority question:** Please include the Gompertz distribution as an alternative distribution to model OS and PFS in the economic model in the tab "Controls" of the economic model when the cells "Controls.Comp_Method_POM" and "Controls.Comp_Method_POM" are set to fit curves independently instead of through the MAIC analysis; that is, please complete the empty "Gompertz" columns in the different tables of tabs "OS Curves_PostMAIC_DARAadjPANO", "PFS Curves_PostMAIC_POM", "PFS Curves_PostMAIC_PANO", "OS Curves_PostMAIC_PANO", "OS Curves_PostMAIC_POM" and "OS Curves_PostMAIC_DARAadjPOM".

This is provided in the updated model.

B10. **Priority question**: For OS, PFS and TTD (where possible) for the daratumumab adjusted integrated data versus pomalidomide plus dexamethasone; daratumumab adjusted integrated data versus panobinostat plus bortezomib plus dexamethasone data; MMY2002 adjusted data versus pomalidomide plus dexamethasone; MMY2002 adjusted data versus panobinostat plus bortezomib plus dexamethasone; GEN501 adjusted data versus pomalidomide plus dexamethasone; and GEN501 adjusted data versus panobinostat plus bortezomib plus dexamethasone; please provide:

a) cumulative hazard plot (– log (estimated KM survival)) versus time
b) log(survival function / (1-survival function)) plots versus Log(time)
c) log(inverse standard normal distribution function(1-survival function)) plots versus Log(time)
d) log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) for the MMY2002 versus pomalidomide plus dexamethasone; MMY2002 versus panobinostat plus bortezomib plus dexamethasone; GEN501 versus pomalidomide plus dexamethasone and GEN501 versus panobinostat plus bortezomib plus dexamethasone combinations.

These are provided as appropriate for the distributions used in Figure 7 to Figure 78.

Figure 7. Diagnostic plot of adjusted integrated daratumumab OS versus POM+DEX (exponential), 11 characteristics matched

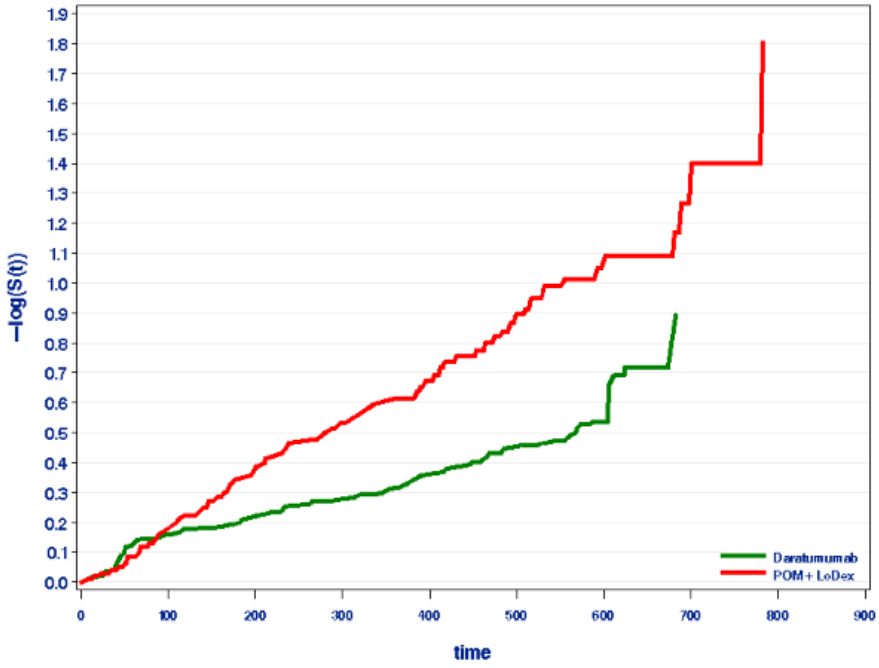


Figure 8. Diagnostic plot of adjusted integrated daratumumab OS versus POM+DEX (Weibull), 11 characteristics matched

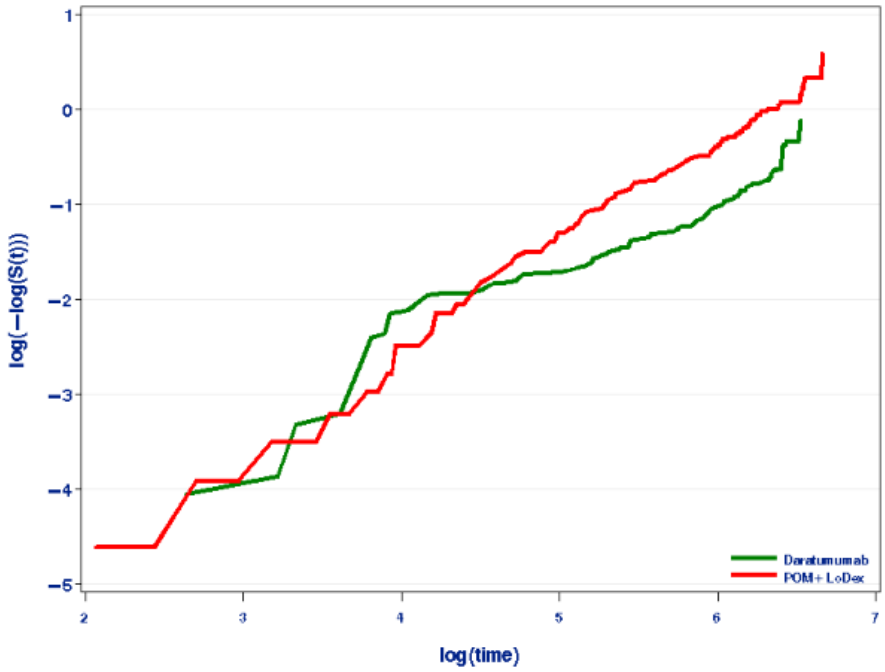


Figure 9. Diagnostic plot of adjusted integrated daratumumab OS versus POM+DEX (loglogistic), 11 characteristics matched

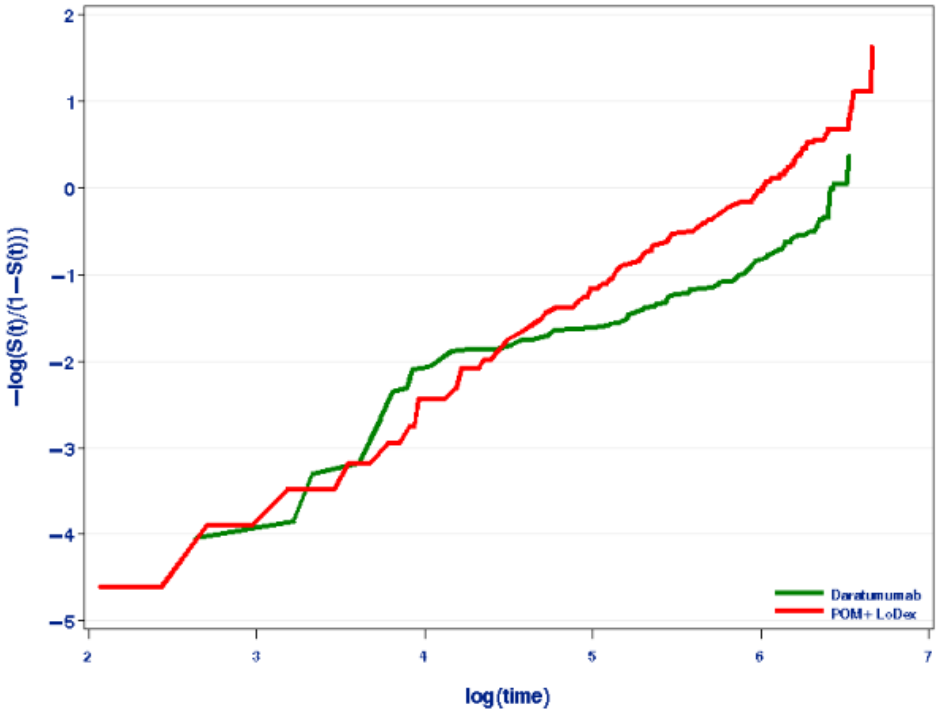


Figure 10. Diagnostic plot of adjusted integrated daratumumab OS versus POM+DEX (lognormal), 11 characteristics matched

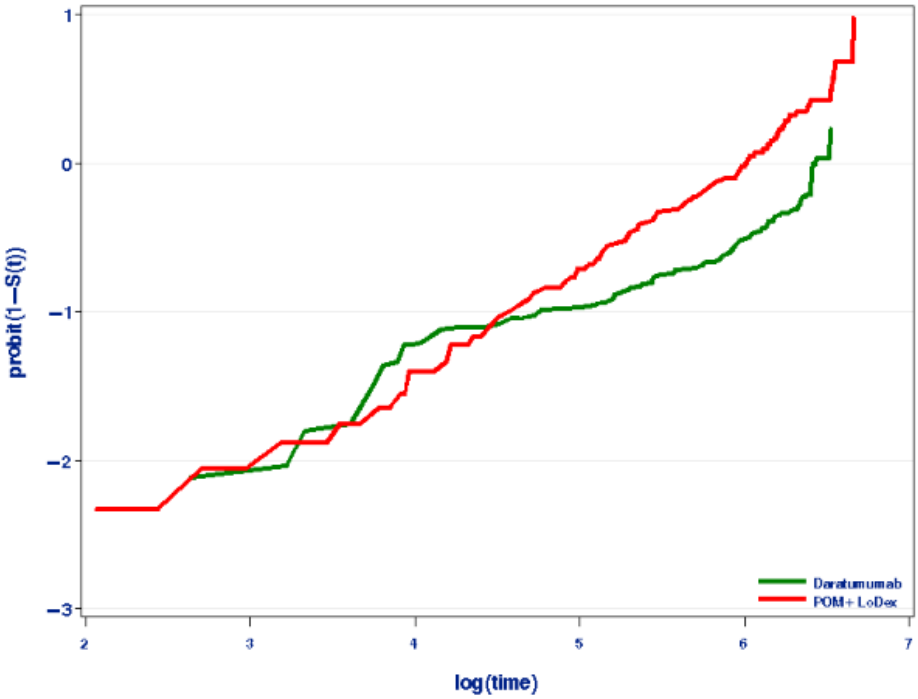


Figure 11. Diagnostic plot of adjusted integrated daratumumab OS versus POM+DEX (Gompertz), 11 characteristics matched

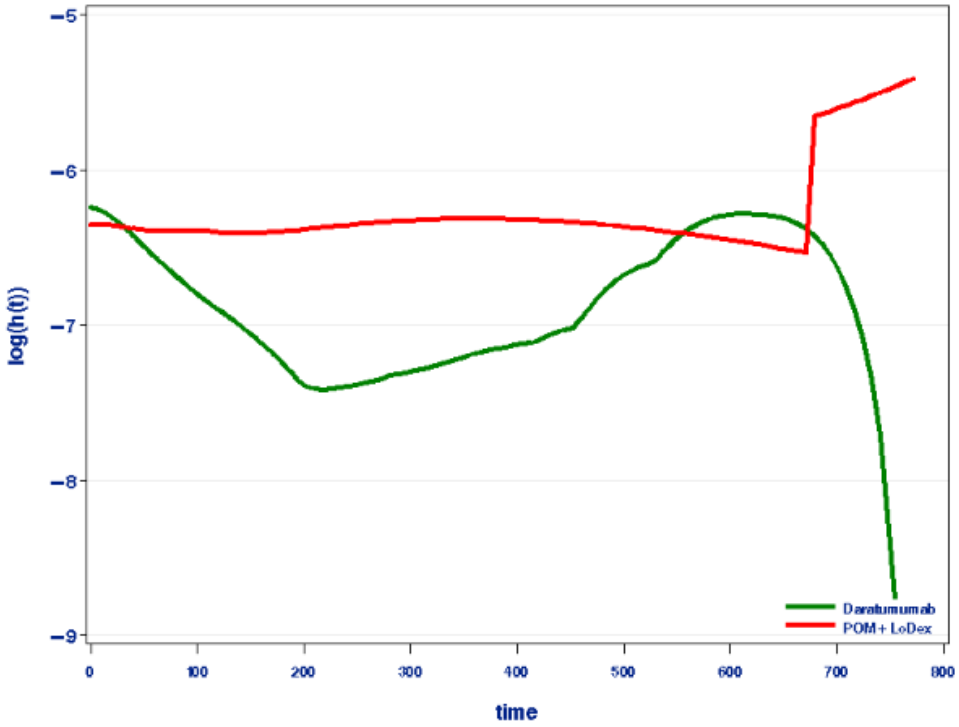


Figure 12. Log-cumulative hazard plots of adjusted integrated daratumumab OS versus POM+DEX, 11 characteristics matched

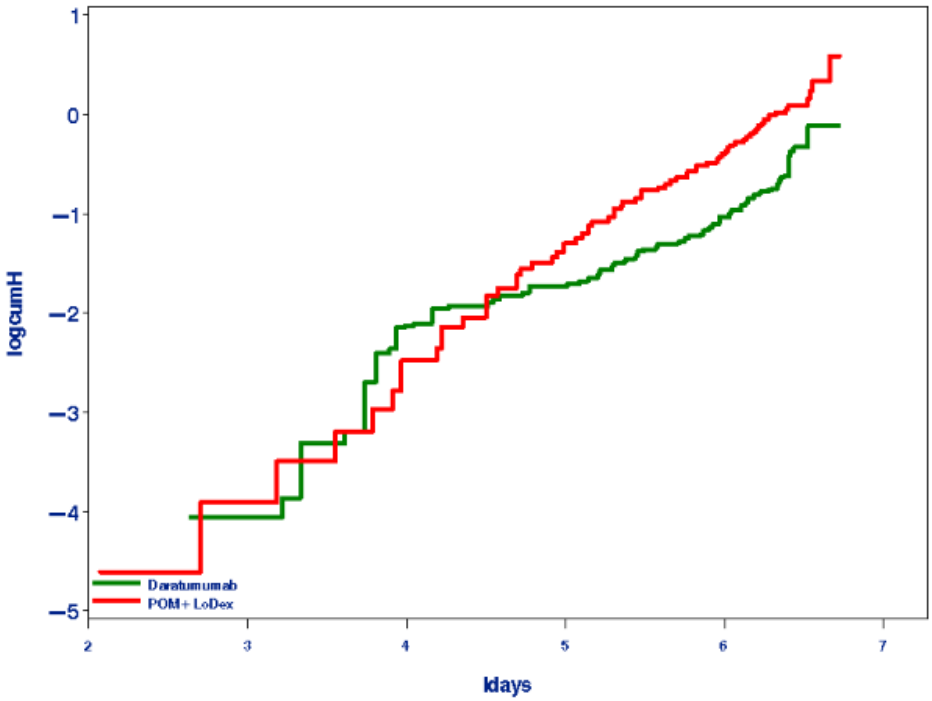


Figure 13. Diagnostic plot of adjusted integrated daratumumab PFS versus POM+DEX (exponential), 11 characteristics matched

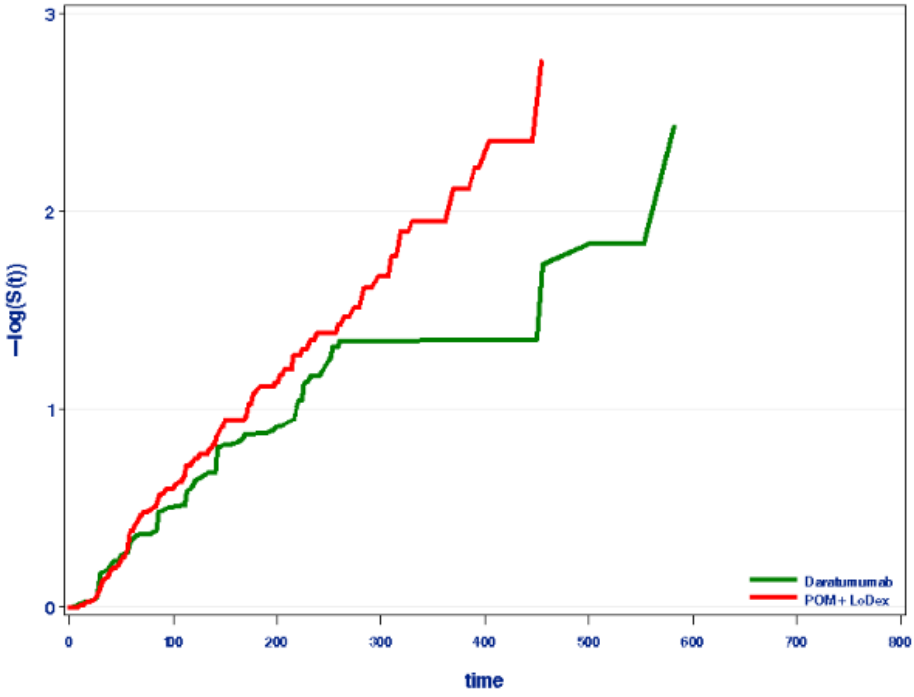


Figure 14. Diagnostic plot of adjusted integrated daratumumab PFS versus POM+DEX (Weibull), 11 characteristics matched

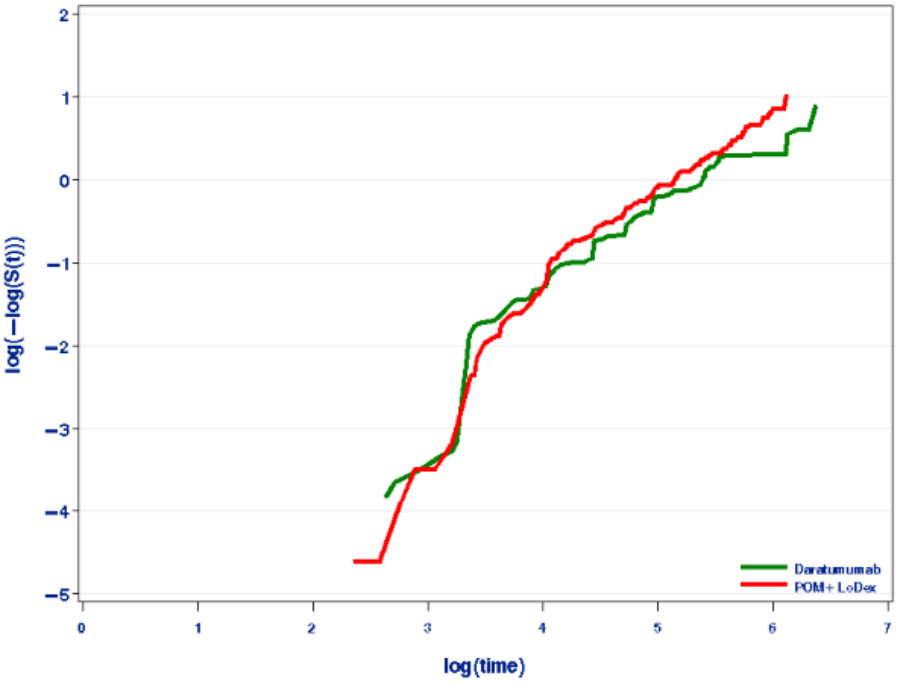


Figure 15. Diagnostic plot of adjusted integrated daratumumab PFS versus POM+DEX (loglogistic), 11 characteristics matched

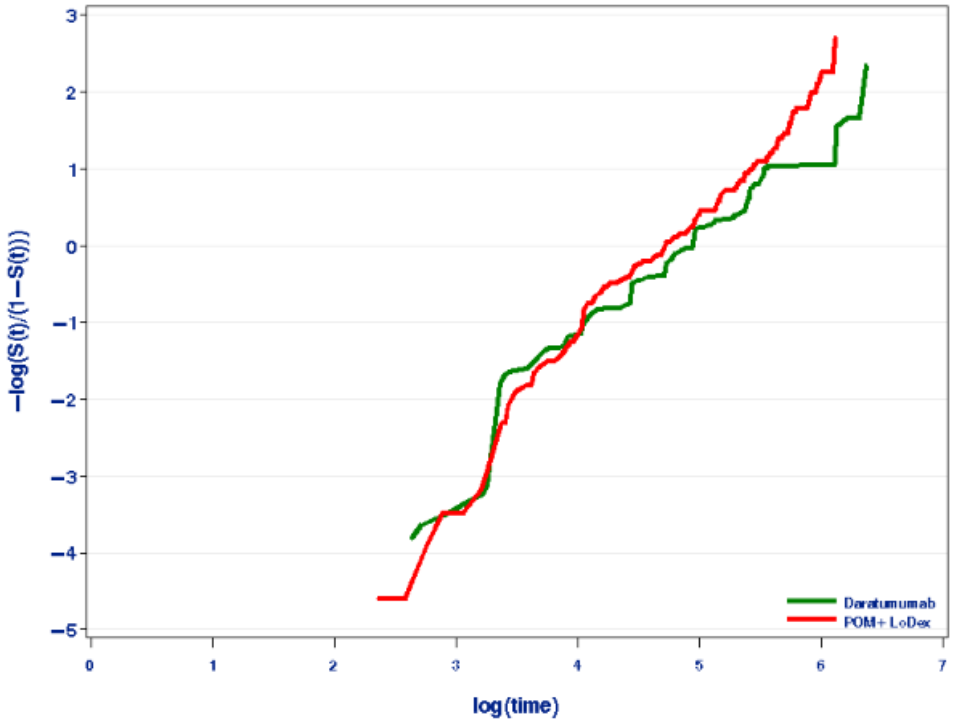


Figure 16. Diagnostic plot of adjusted integrated daratumumab PFS versus POM+DEX (lognormal), 11 characteristics matched

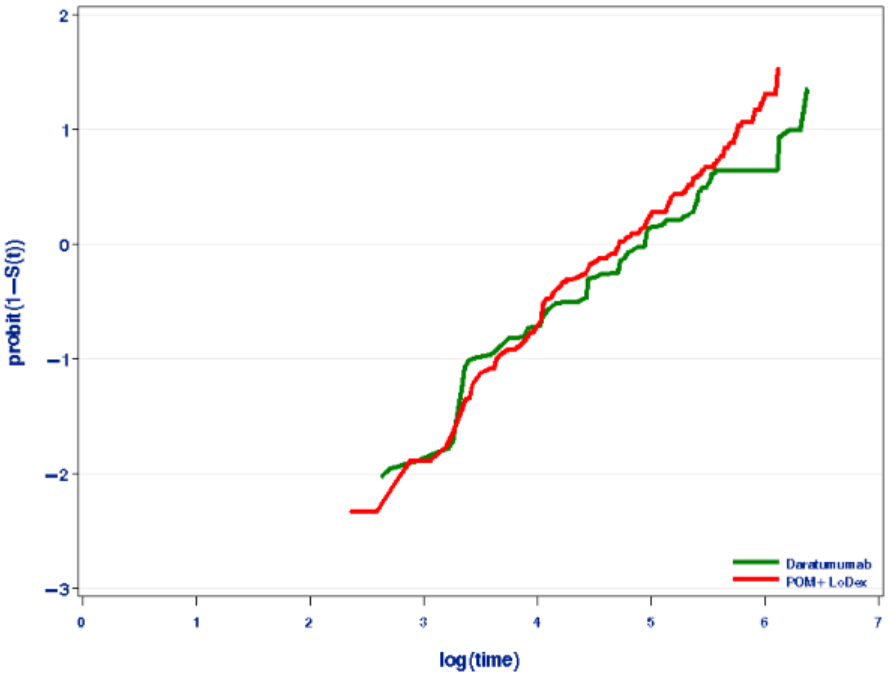


Figure 17. Diagnostic plot of adjusted integrated daratumumab PFS versus POM+DEX (Gompertz), 11 characteristics matched

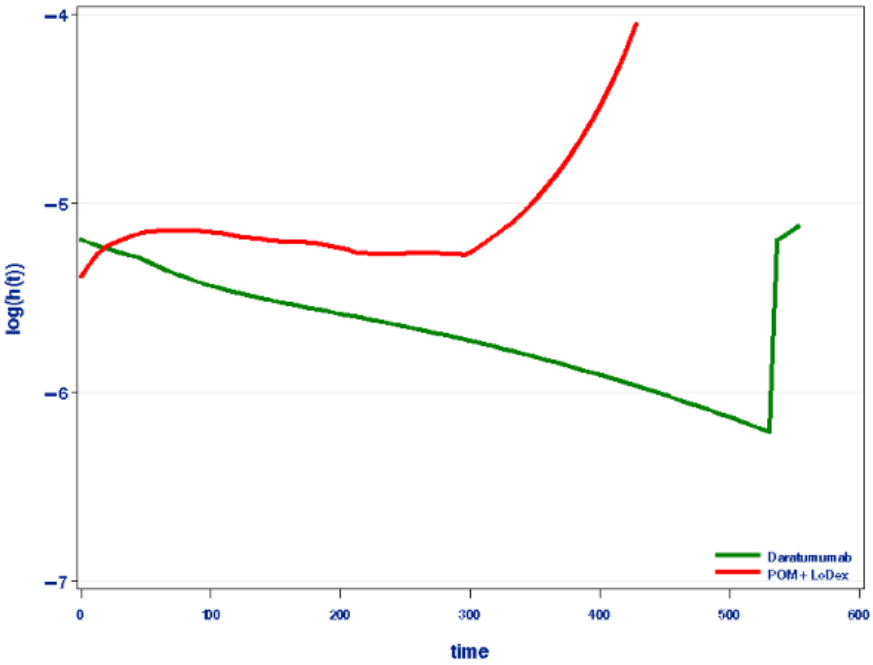


Figure 18. Log-cumulative hazard plots of adjusted integrated daratumumab PFS versus POM+DEX, 11 characteristics matched

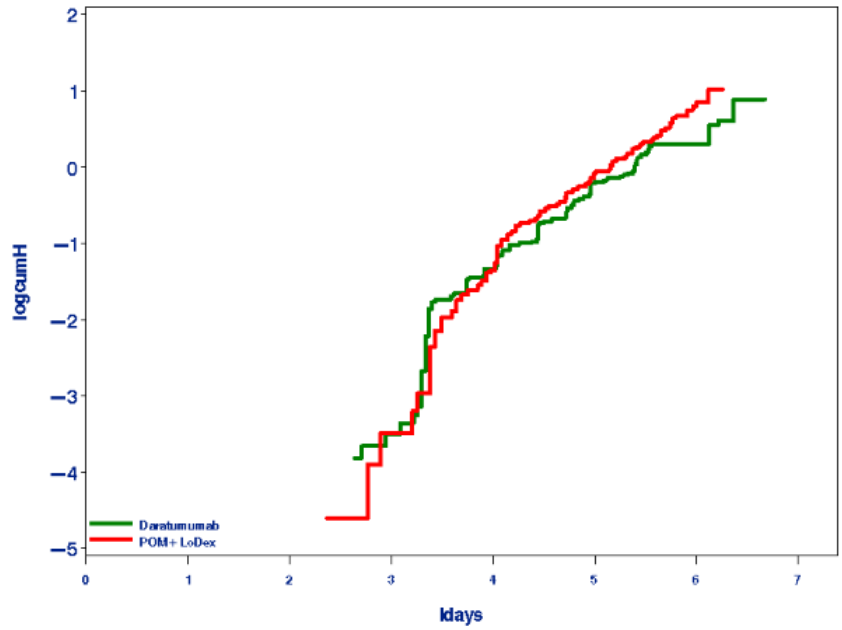


Figure 19. Diagnostic plot of adjusted integrated daratumumab OS versus PANO+BORT+DEX (exponential), 5 characteristics matched

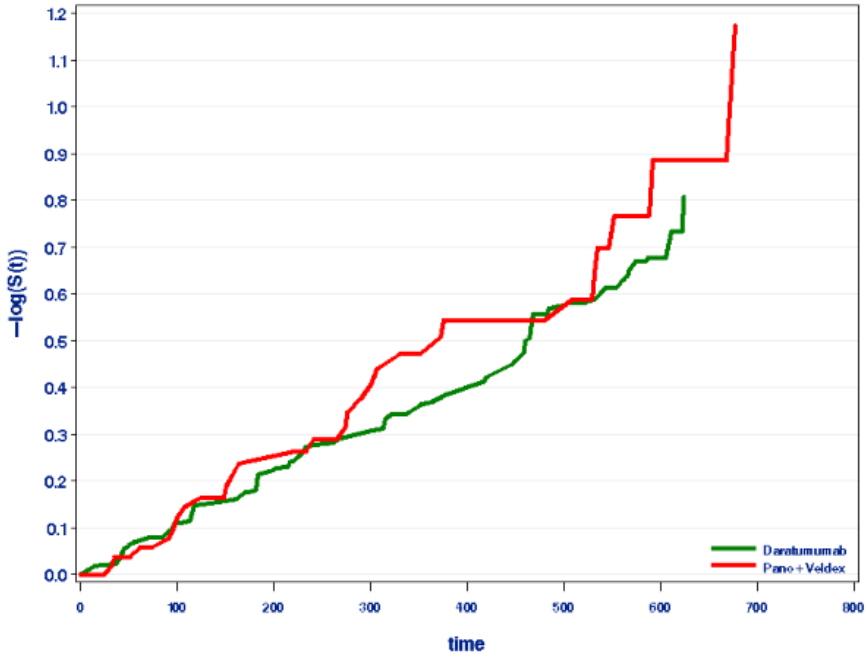


Figure 20. Diagnostic plot of adjusted integrated daratumumab OS versus PANO+BORT+DEX (Weibull), 5 characteristics matched

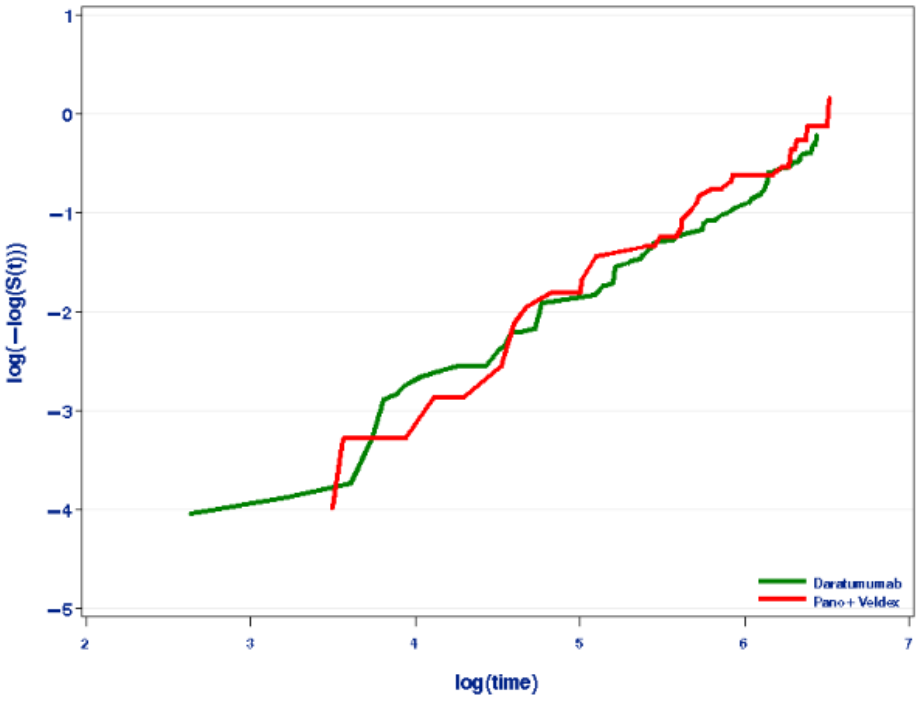


Figure 21. Diagnostic plot of adjusted integrated daratumumab OS versus PANO+BORT+DEX (loglogistic), 5 characteristics matched

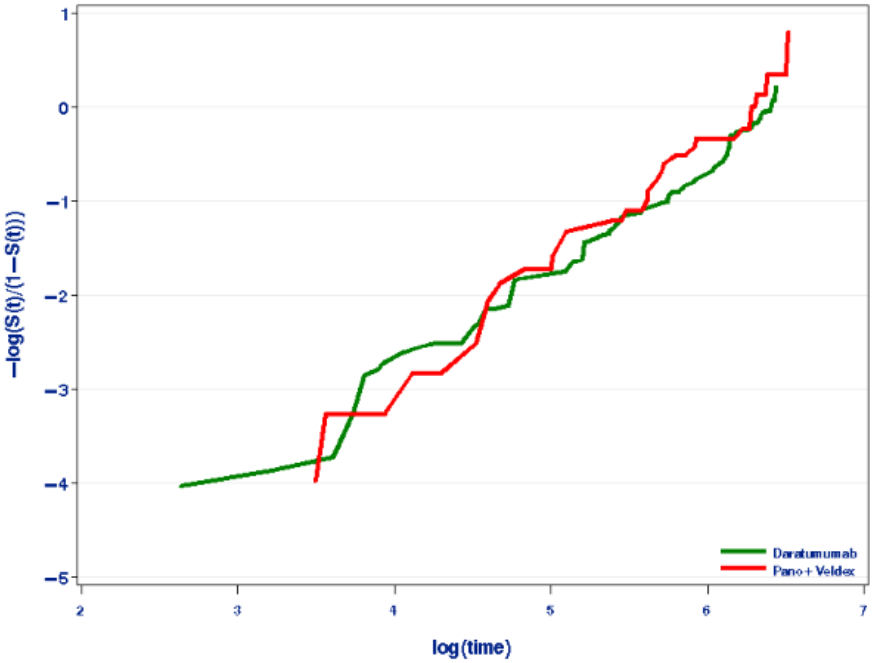


Figure 22. Diagnostic plot of adjusted integrated daratumumab OS versus PANO+BORT+DEX (lognormal), 5 characteristics matched

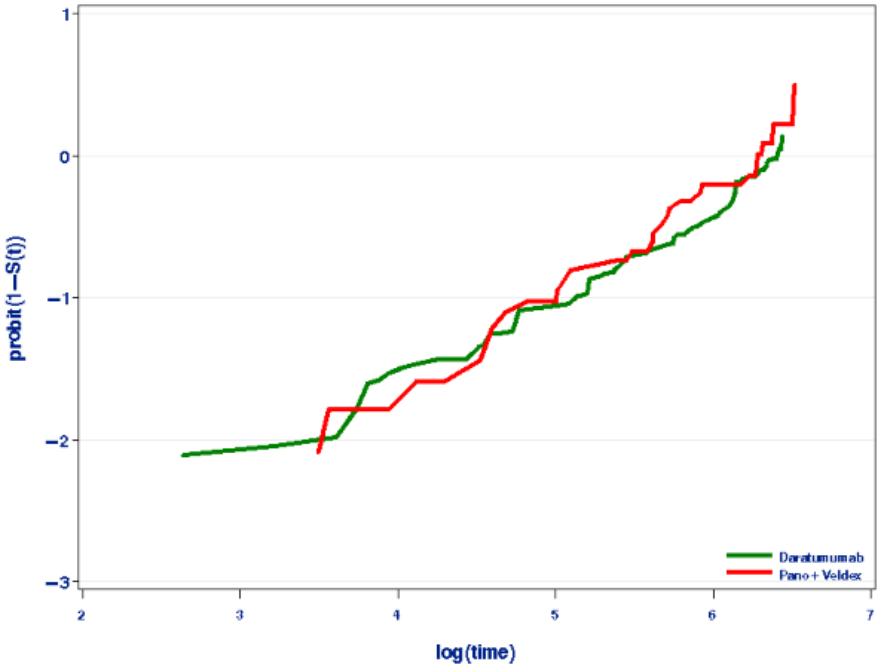


Figure 23. Diagnostic plot of adjusted integrated daratumumab OS versus PANO+BORT+DEX (Gompertz), 5 characteristics matched

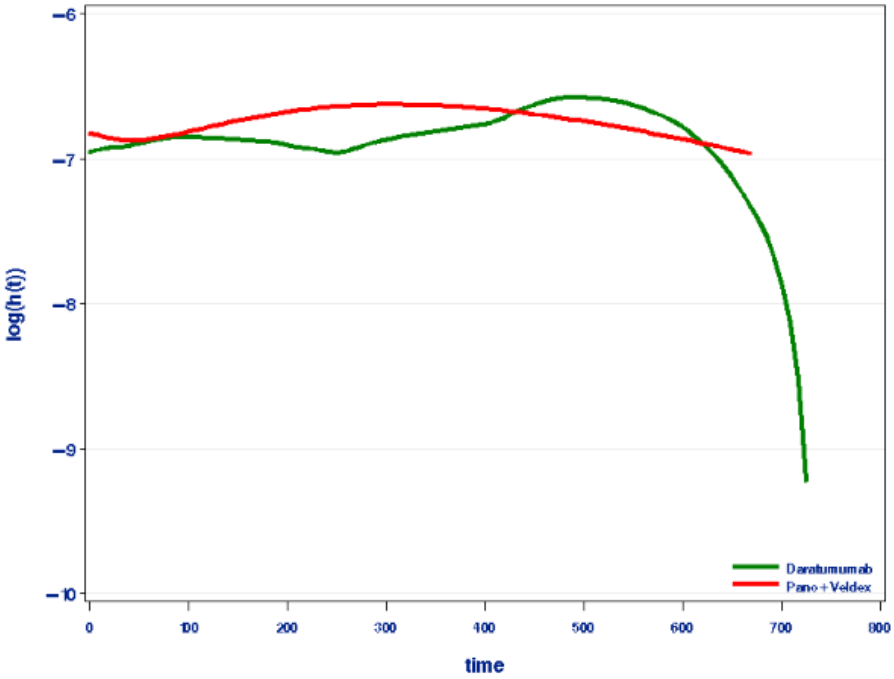


Figure 24. Log-cumulative hazard plots of adjusted integrated daratumumab OS versus PANO+BORT+DEX, 5 characteristics matched

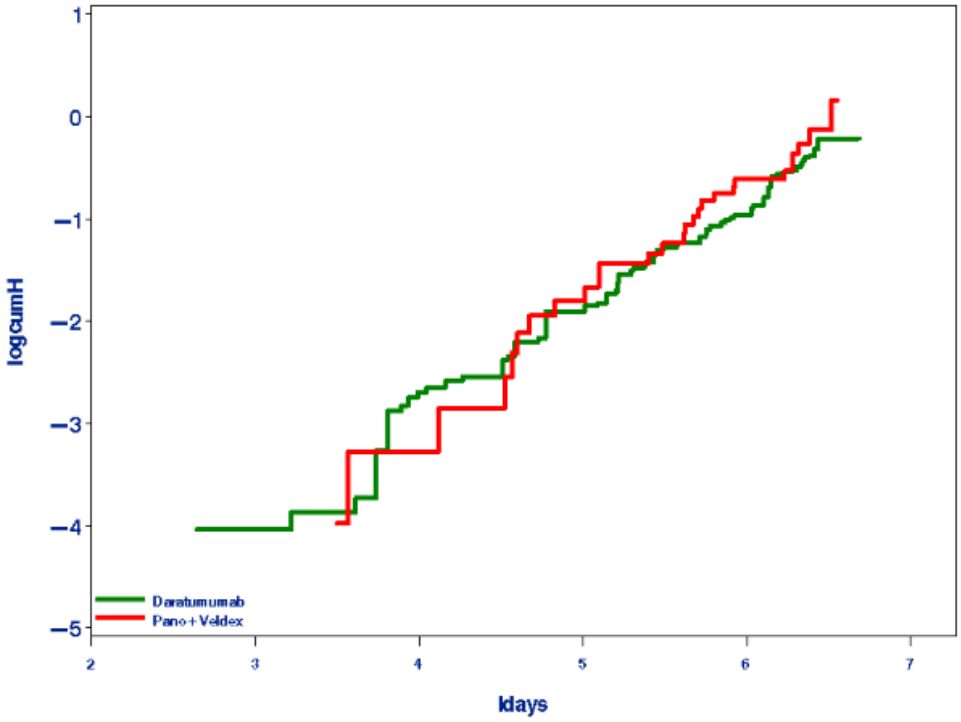


Figure 25. Diagnostic plot of adjusted integrated daratumumab PFS versus PANO+BORT+DEX (exponential), 5 characteristics matched

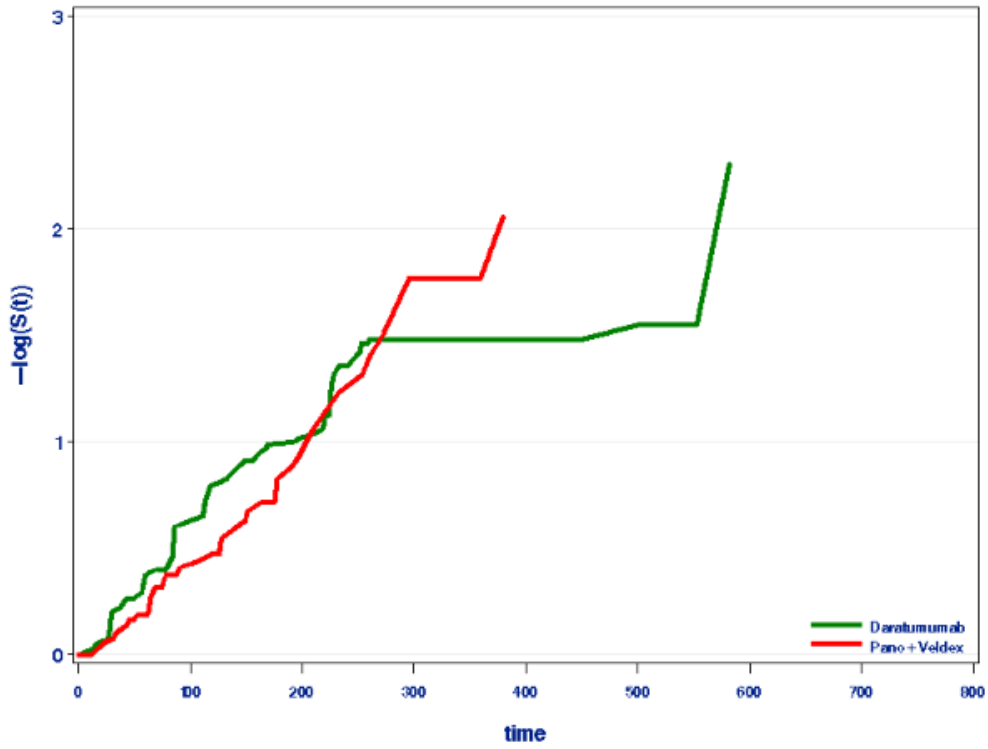


Figure 26. Diagnostic plot of adjusted integrated daratumumab PFS versus PANO+BORT+DEX (Weibull), 5 characteristics matched

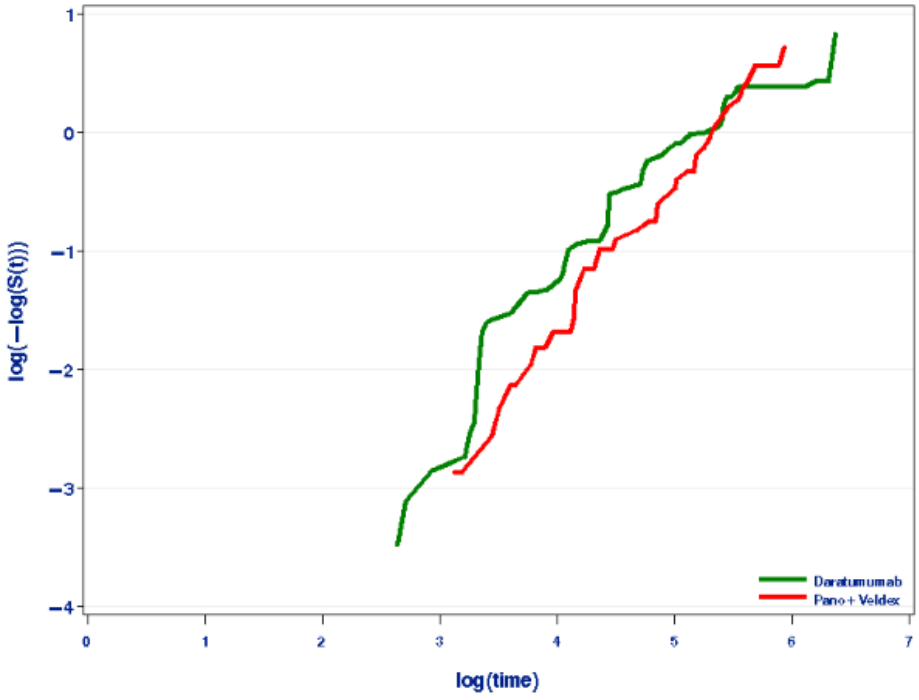


Figure 27. Diagnostic plot of adjusted integrated daratumumab PFS versus PANO+BORT+DEX (loglogistic), 5 characteristics matched

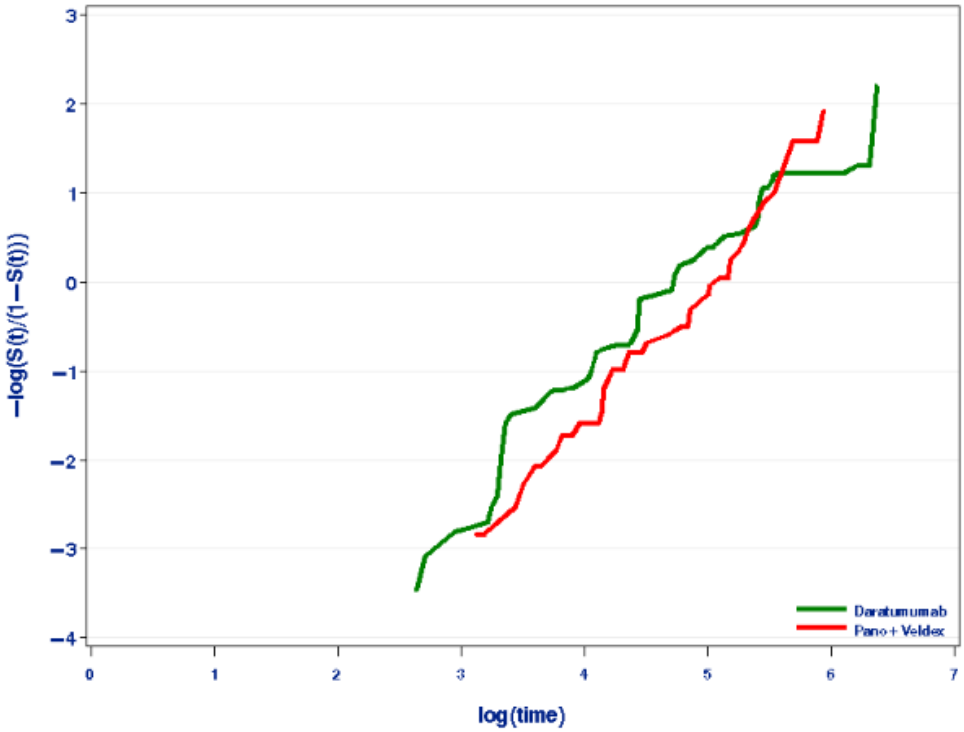


Figure 28. Diagnostic plot of adjusted integrated daratumumab PFS versus PANO+BORT+DEX (lognormal), 5 characteristics matched

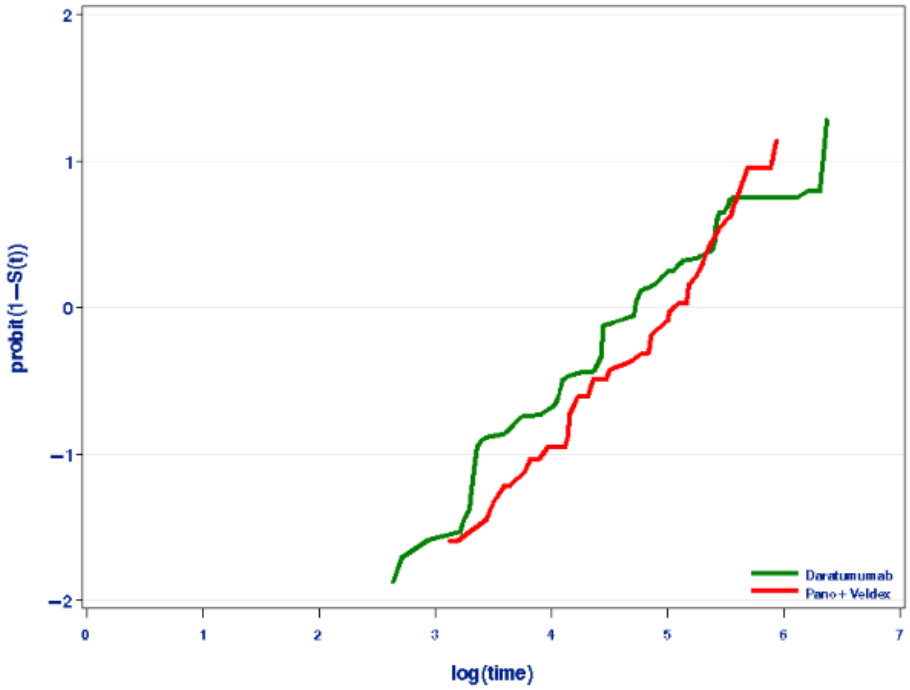


Figure 29. Diagnostic plot of adjusted integrated daratumumab PFS versus PANO+BORT+DEX (Gompertz), 5 characteristics matched

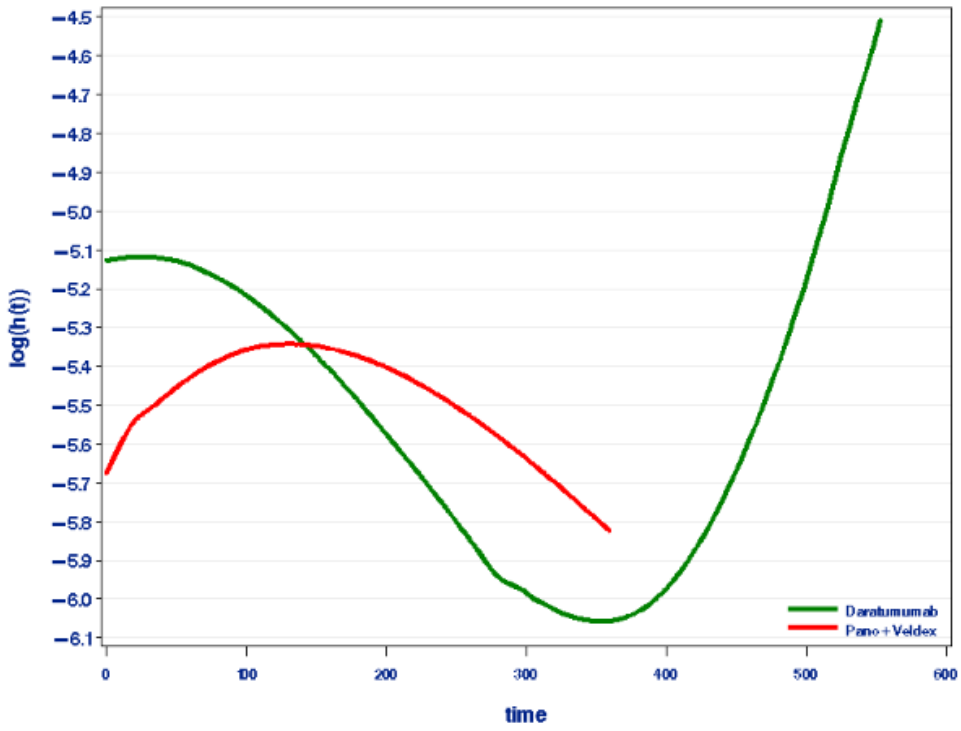


Figure 30. Log-cumulative hazard plots of adjusted integrated daratumumab PFS versus PANO+BORT+DEX, 5 characteristics matched

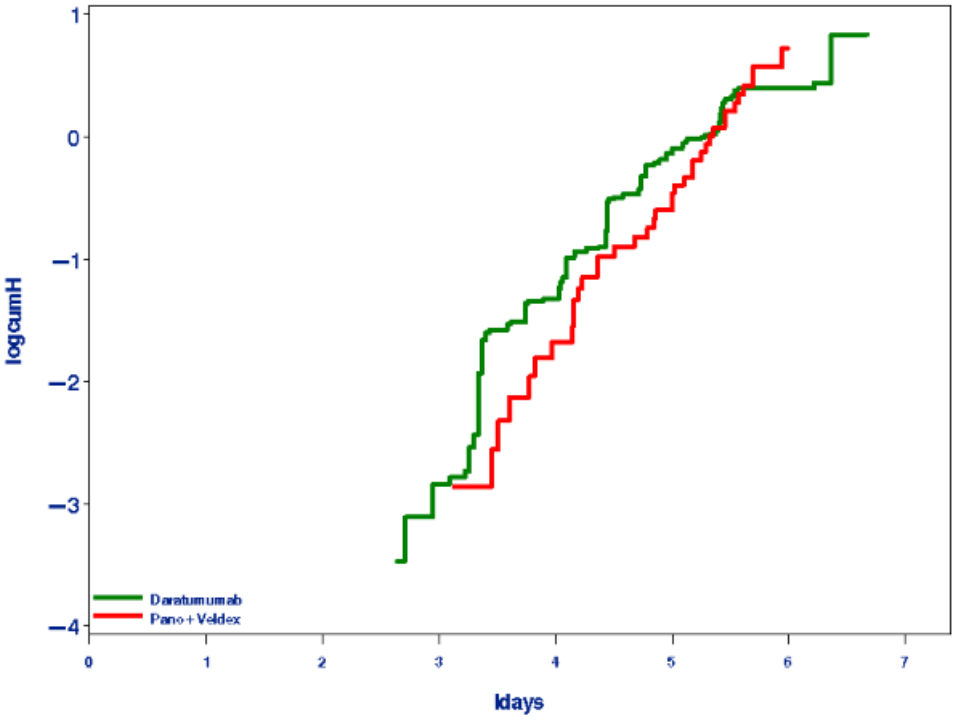


Figure 31. Diagnostic plot of adjusted MMY2002 daratumumab OS versus POM+DEX (exponential), 13 characteristics matched

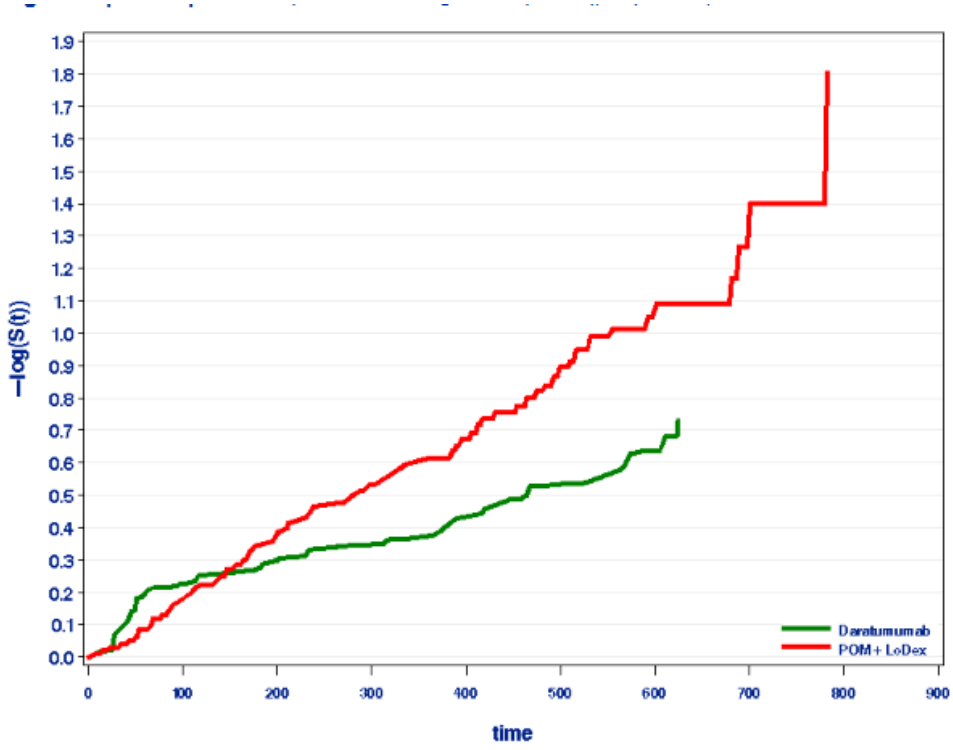


Figure 32. Diagnostic plot of adjusted MMY2002 daratumumab OS versus POM+DEX (Weibull), 13 characteristics matched

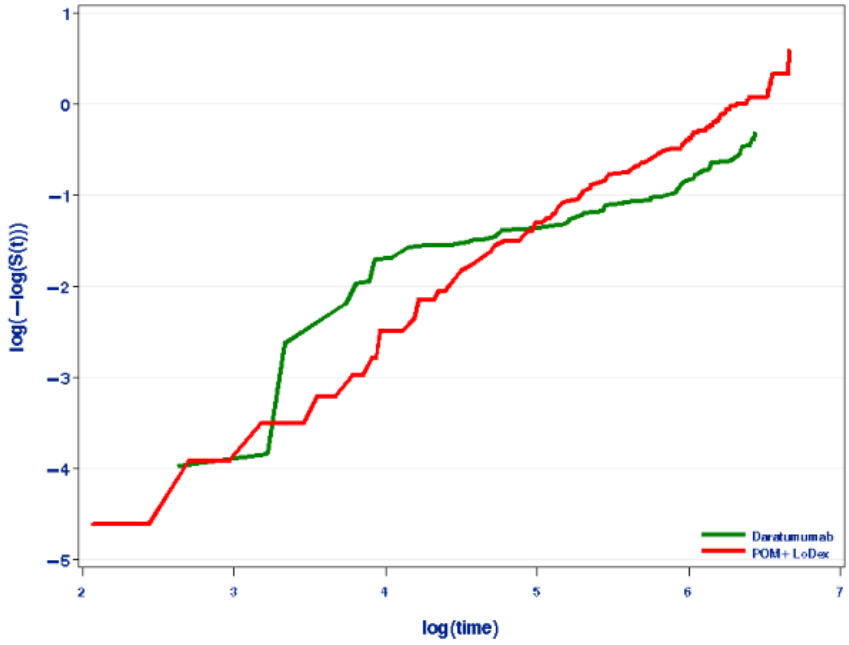


Figure 33. Diagnostic plot of adjusted MMY2002 daratumumab OS versus POM+DEX (loglogistic), 13 characteristics matched

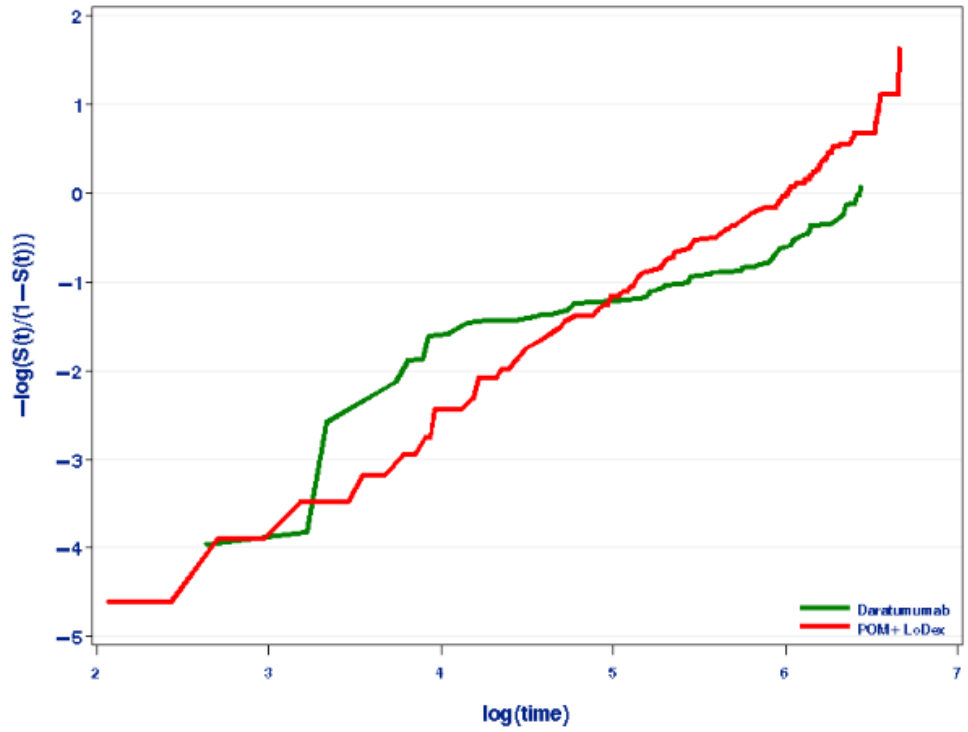


Figure 34. Diagnostic plot of adjusted MMY2002 daratumumab OS versus POM+DEX (lognormal), 13 characteristics matched

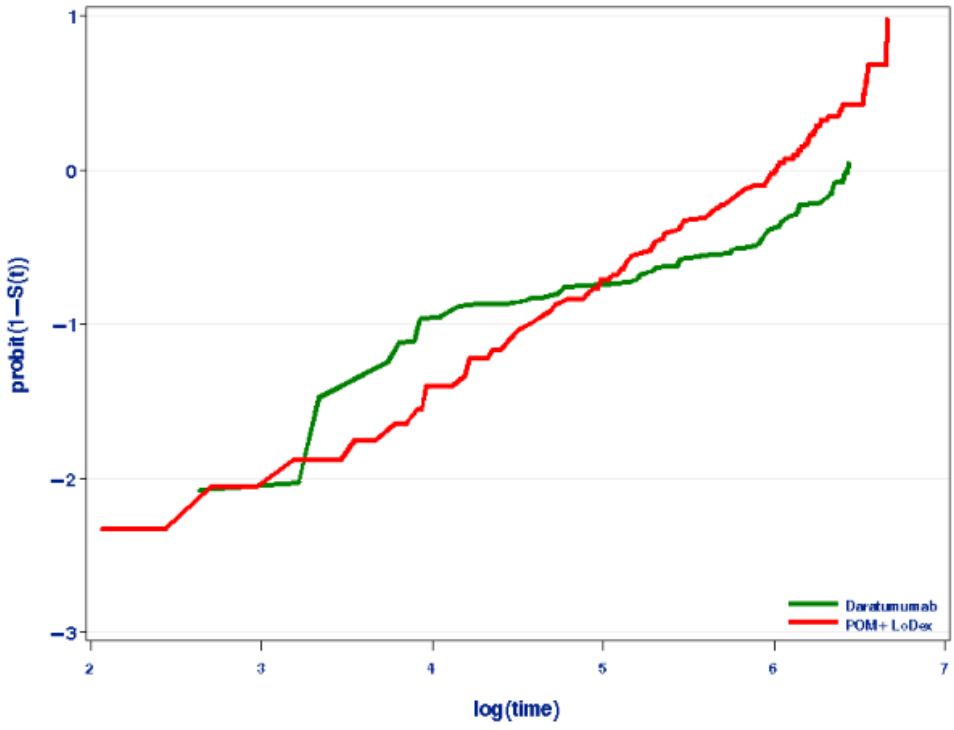


Figure 35. Diagnostic plot of adjusted MMY2002 daratumumab OS versus POM+DEX (Gompertz), 13 characteristics matched

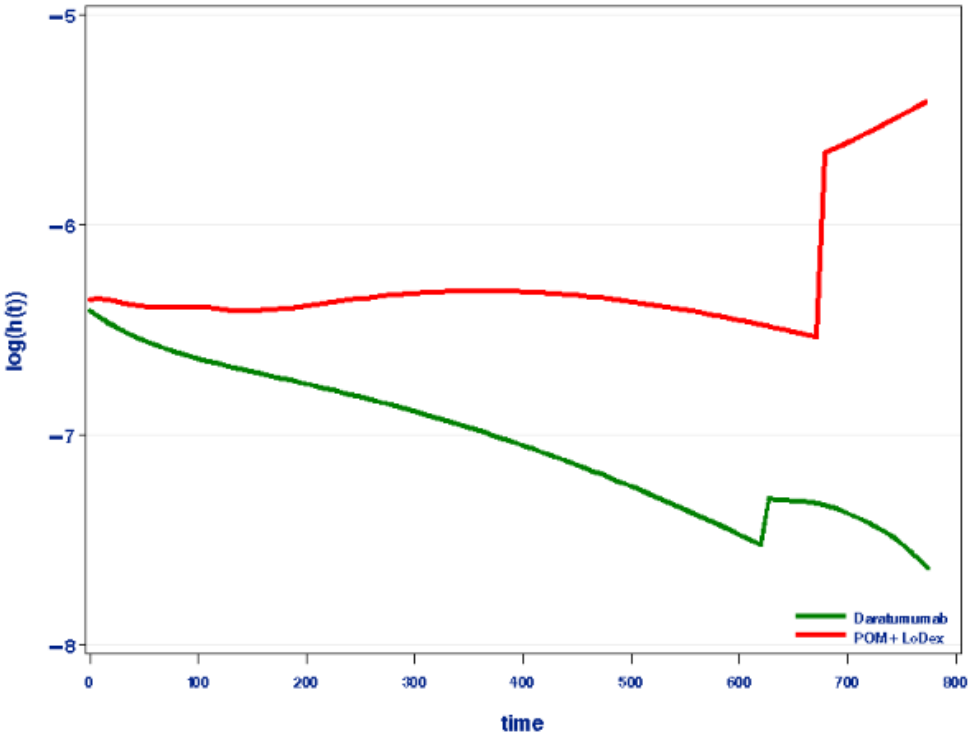


Figure 36. Log-cumulative hazard plots of adjusted MMY2002 daratumumab OS versus POM+DEX, 13 characteristics matched

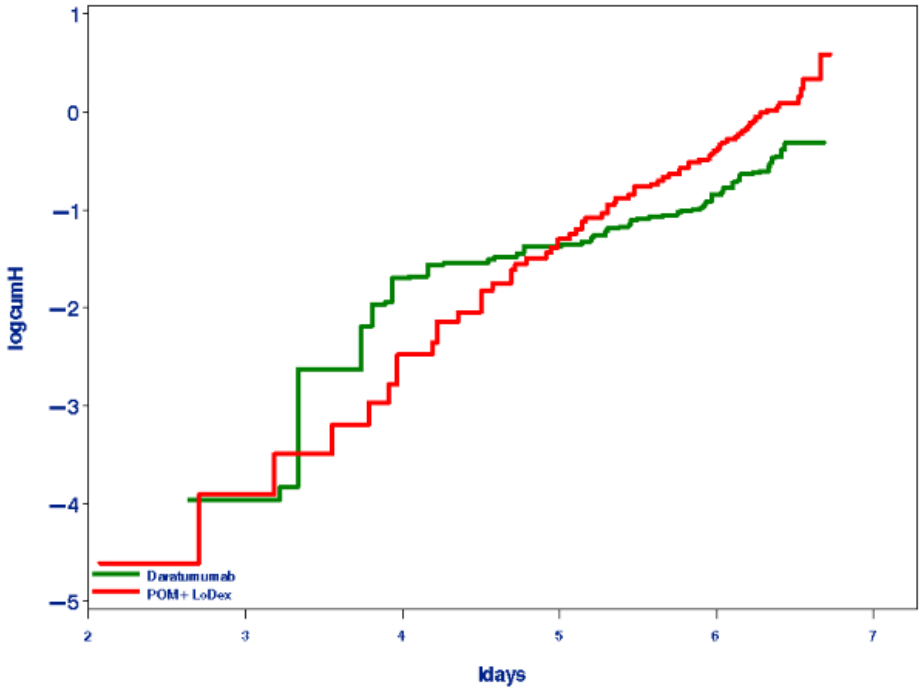


Figure 37. Diagnostic plot of adjusted MMY2002 daratumumab PFS versus POM+DEX (exponential), 13 characteristics matched

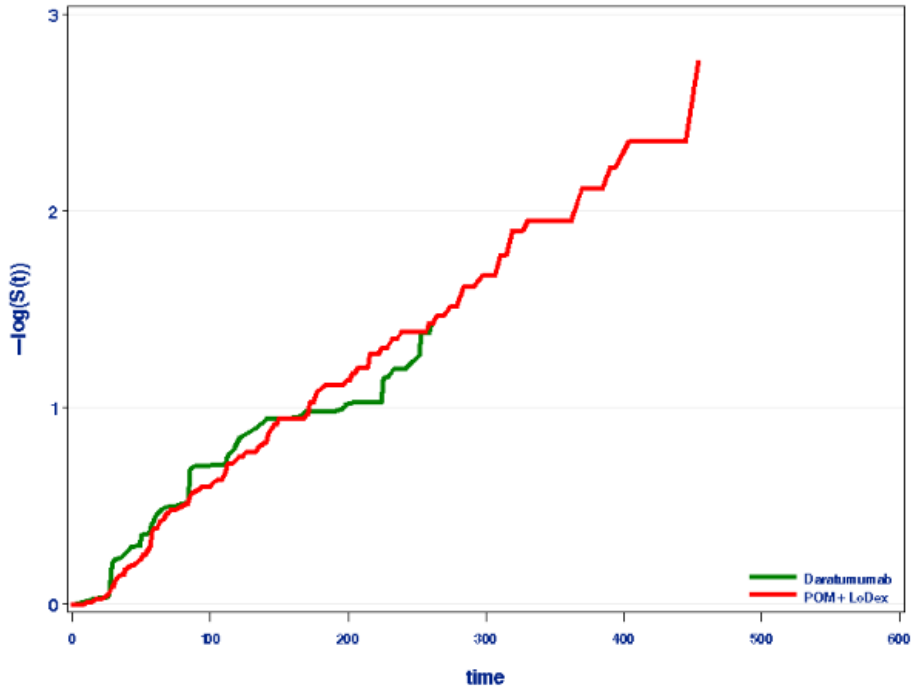


Figure 38. Diagnostic plot of adjusted MMY2002 daratumumab PFS versus POM+DEX (Weibull), 13 characteristics matched

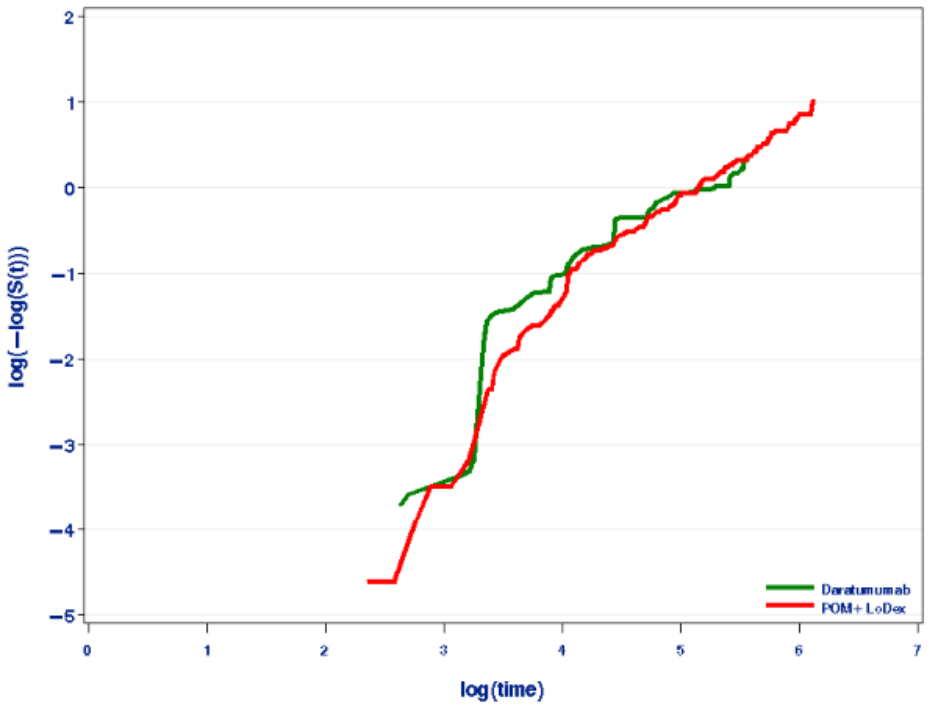


Figure 39. Diagnostic plot of adjusted MMY2002 daratumumab PFS versus POM+DEX (loglogistic), 13 characteristics matched

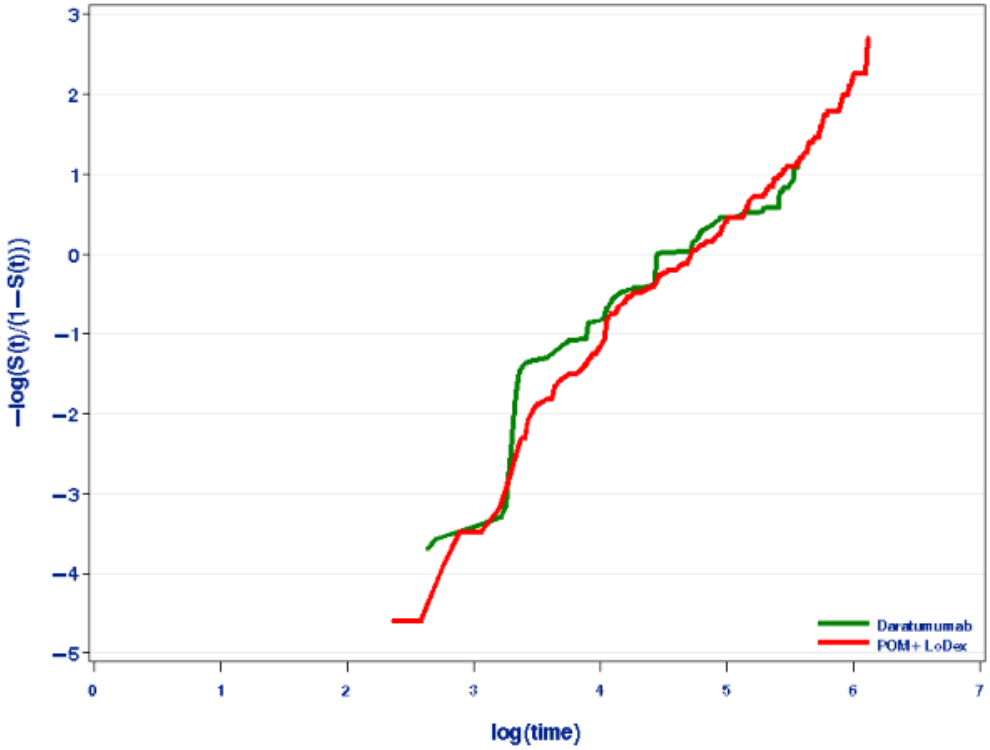


Figure 40. Diagnostic plot of adjusted MMY2002 daratumumab PFS versus POM+DEX (lognormal), 13 characteristics matched

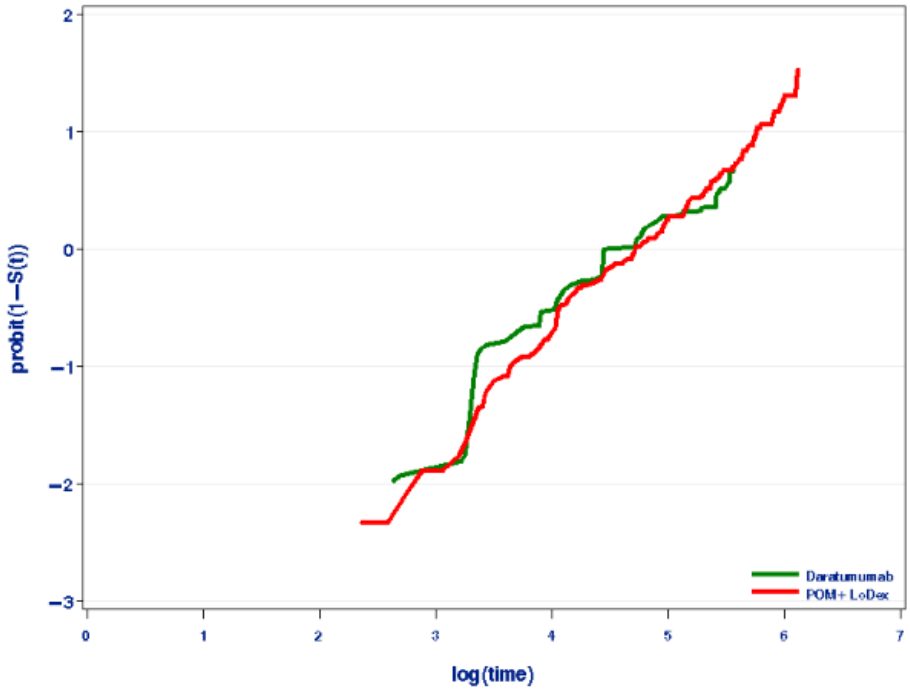


Figure 41. Diagnostic plot of adjusted MMY2002 daratumumab PFS versus POM+DEX (Gompertz), 13 characteristics matched

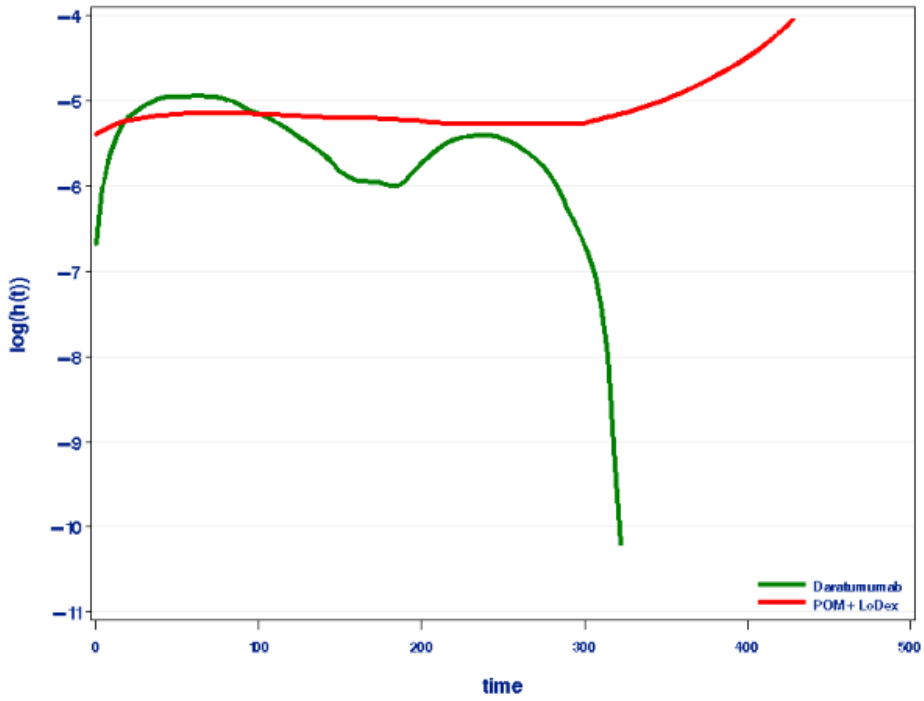


Figure 42. Log-cumulative hazard plots of adjusted MMY2002 daratumumab PFS versus POM+DEX, 13 characteristics matched

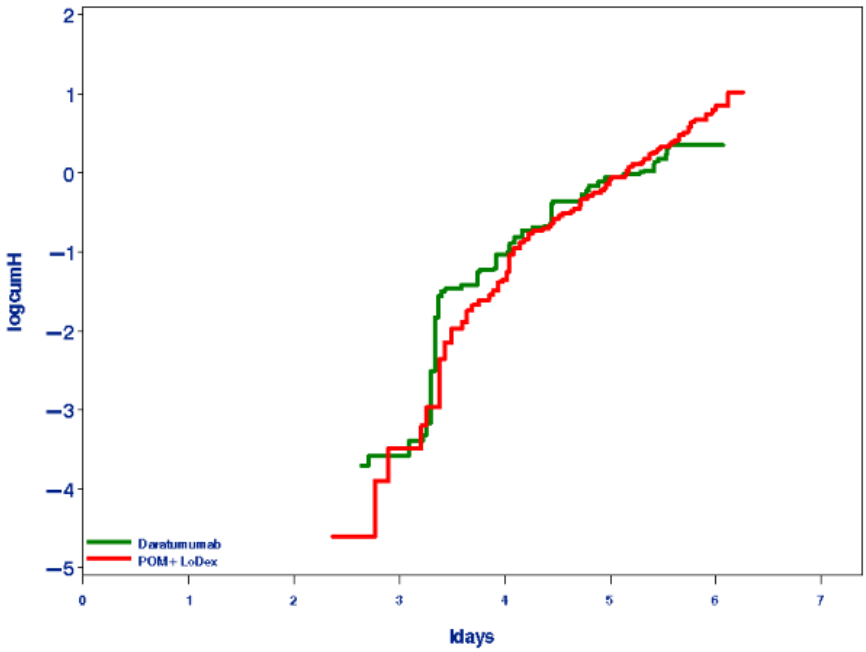


Figure 43. Diagnostic plot of adjusted MMY2002 daratumumab OS versus PANO+BORT+DEX (exponential), 8 characteristics matched

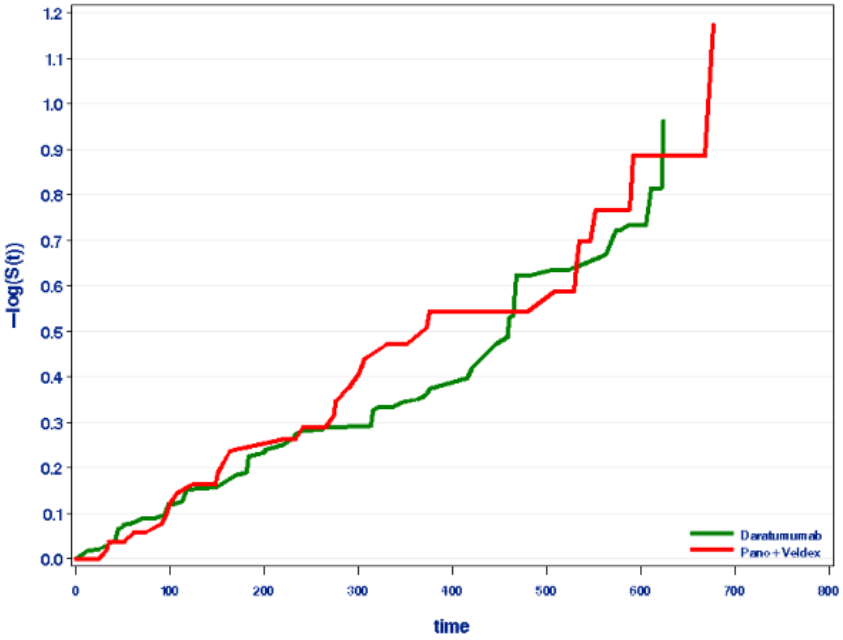


Figure 44. Diagnostic plot of adjusted MMY2002 daratumumab OS versus PANO+BORT+DEX (Weibull), 8 characteristics matched

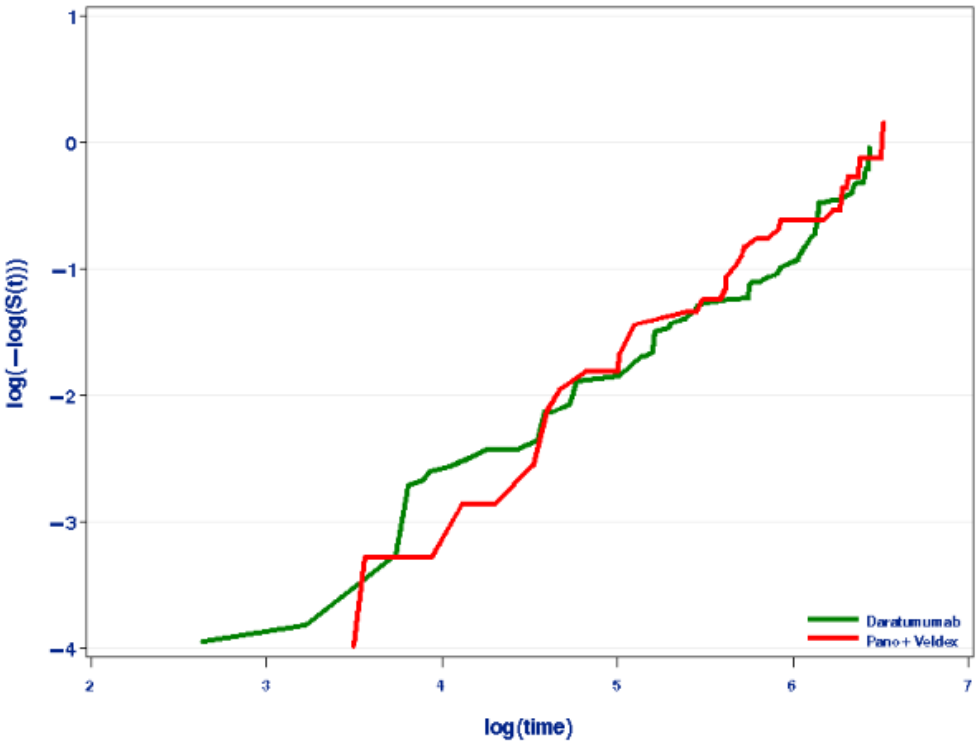


Figure 45. Diagnostic plot of adjusted MMY2002 daratumumab OS versus PANO+BORT+DEX (loglogistic), 8 characteristics matched

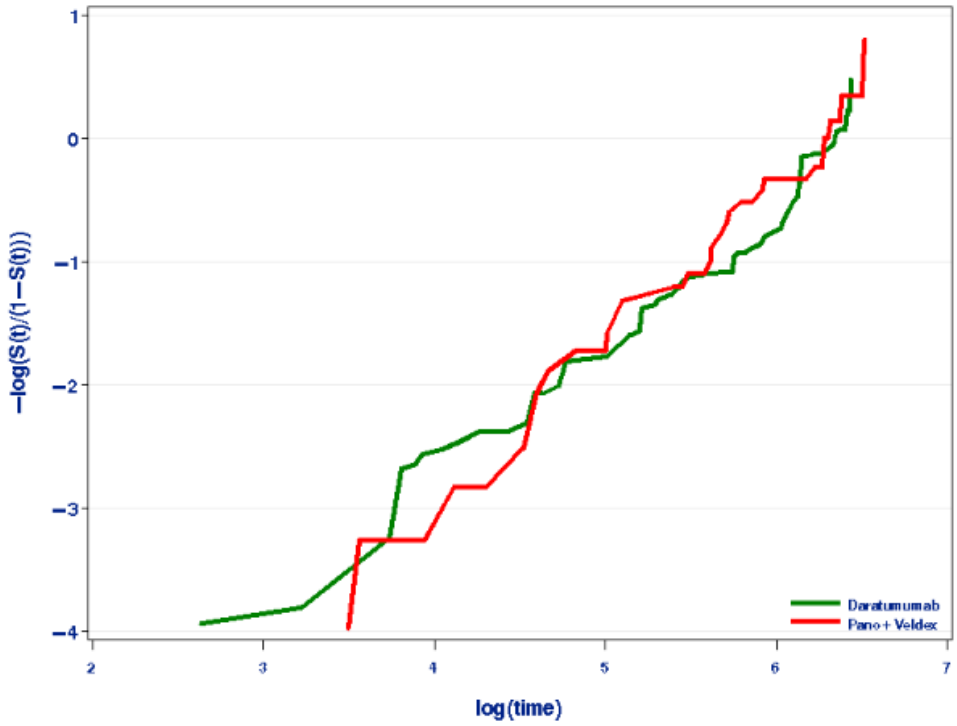


Figure 46. Diagnostic plot of adjusted MMY2002 daratumumab OS versus PANO+BORT+DEX (lognormal), 8 characteristics matched

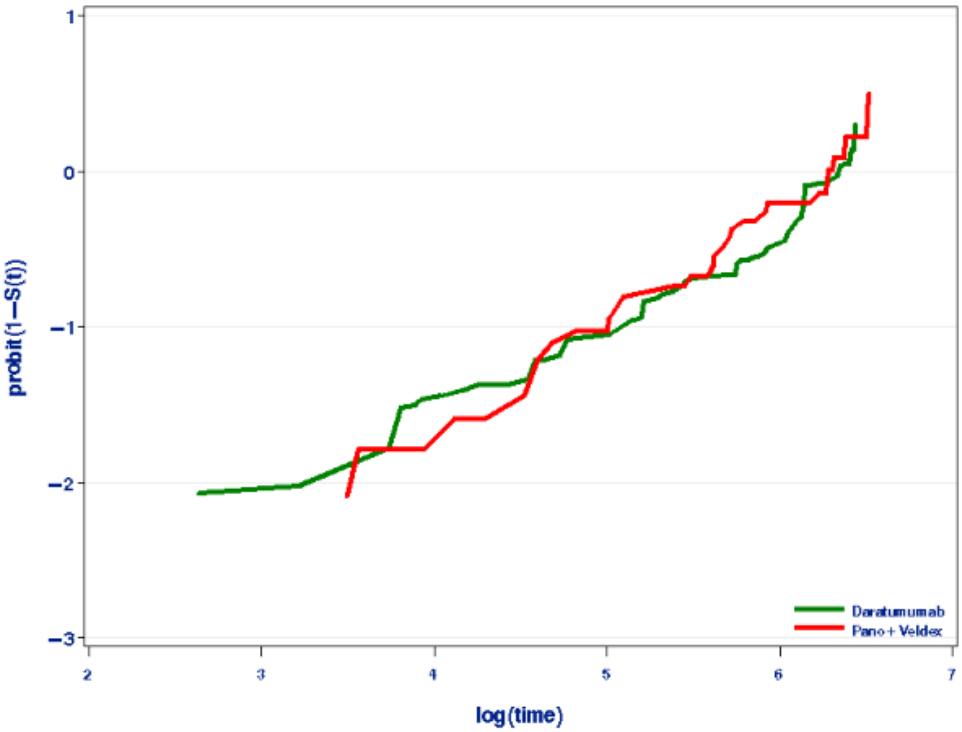


Figure 47. Diagnostic plot of adjusted MMY2002 daratumumab OS versus PANO+BORT+DEX (Gompertz), 8 characteristics matched

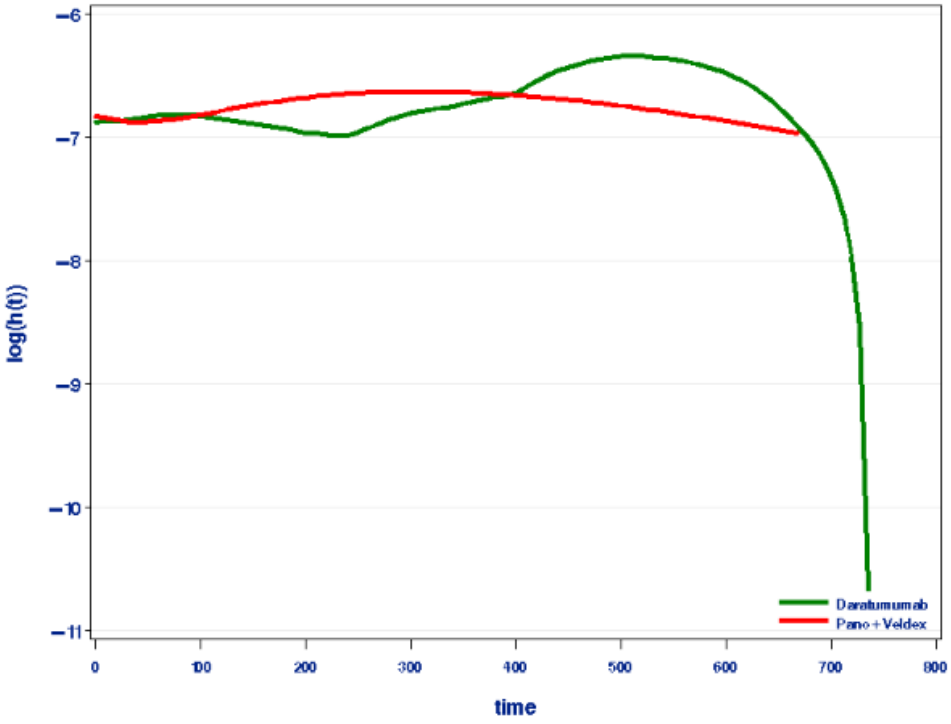


Figure 48. Log-cumulative hazard plots of adjusted MMY2002 daratumumab OS versus PANO+BORT+DEX, 8 characteristics matched

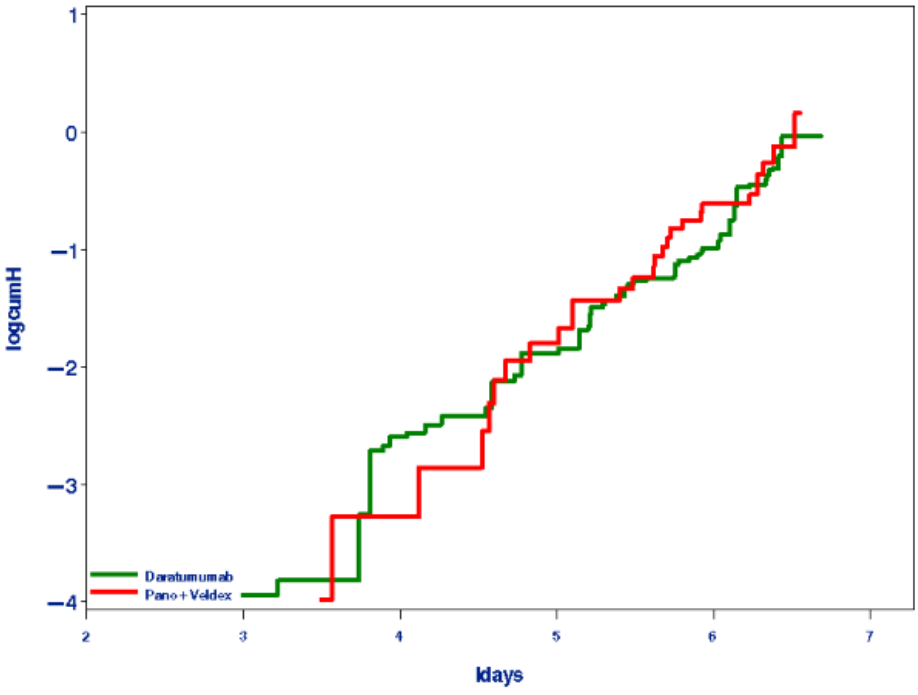


Figure 49. Diagnostic plot of adjusted MMY2002 daratumumab PFS versus PANO+BORT+DEX (exponential), 8 characteristics matched

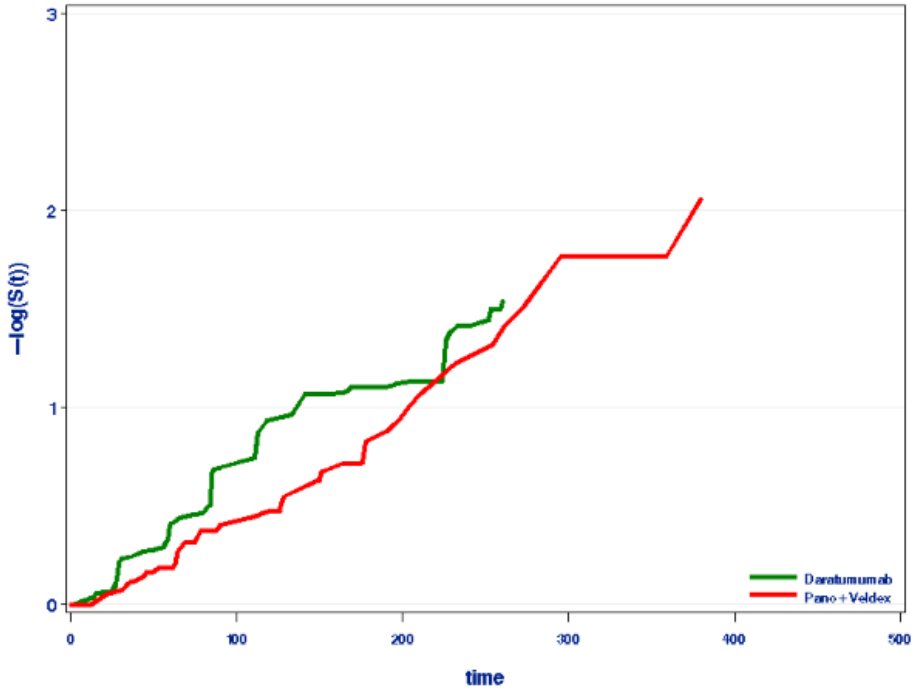


Figure 50. Diagnostic plot of adjusted MMY2002 daratumumab PFS versus PANO+BORT+DEX (Weibull), 8 characteristics matched

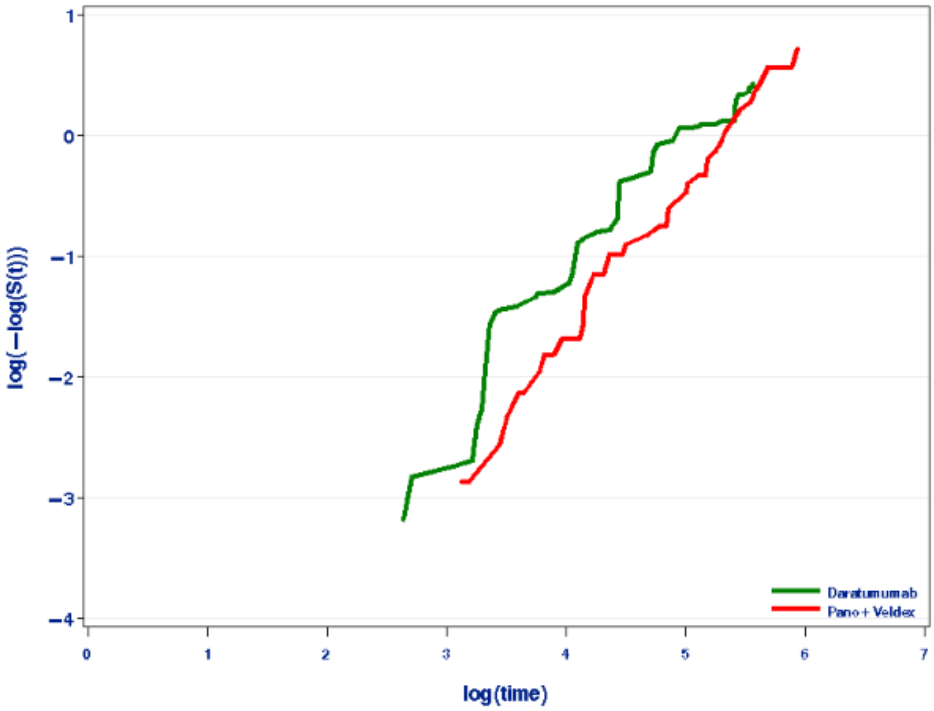


Figure 51. Diagnostic plot of adjusted MMY2002 daratumumab PFS versus PANO+BORT+DEX (loglogistic), 8 characteristics matched

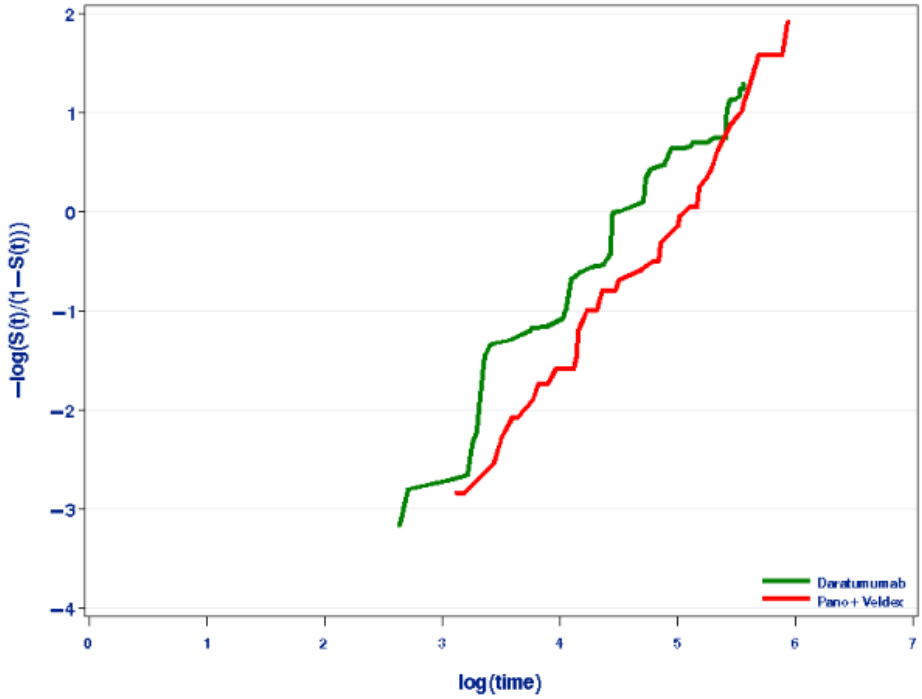


Figure 52. Diagnostic plot of adjusted MMY2002 daratumumab PFS versus PANO+BORT+DEX (lognormal), 8 characteristics matched

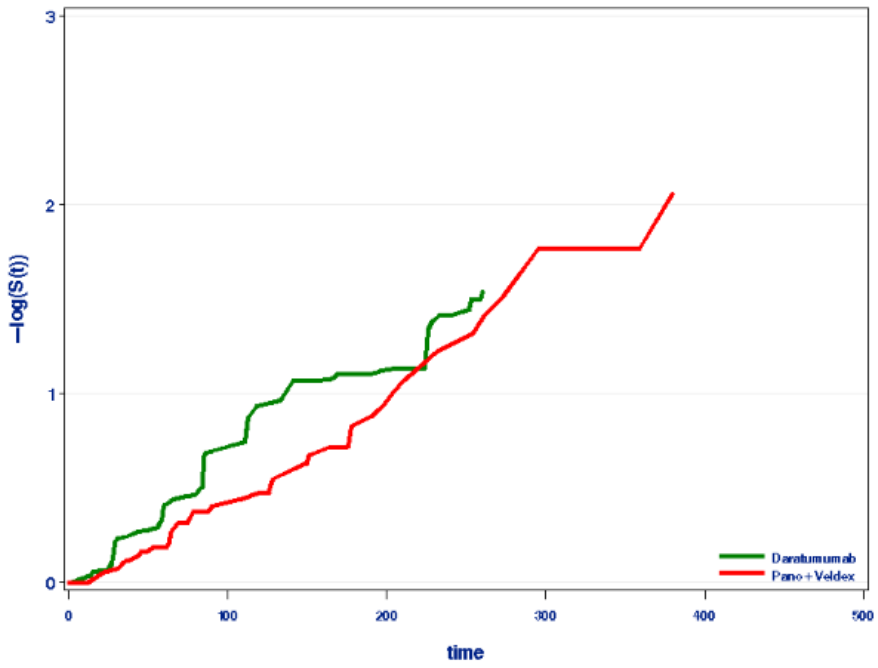


Figure 53. Diagnostic plot of adjusted MMY2002 daratumumab PFS versus PANO+BORT+DEX (Gompertz), 8 characteristics matched

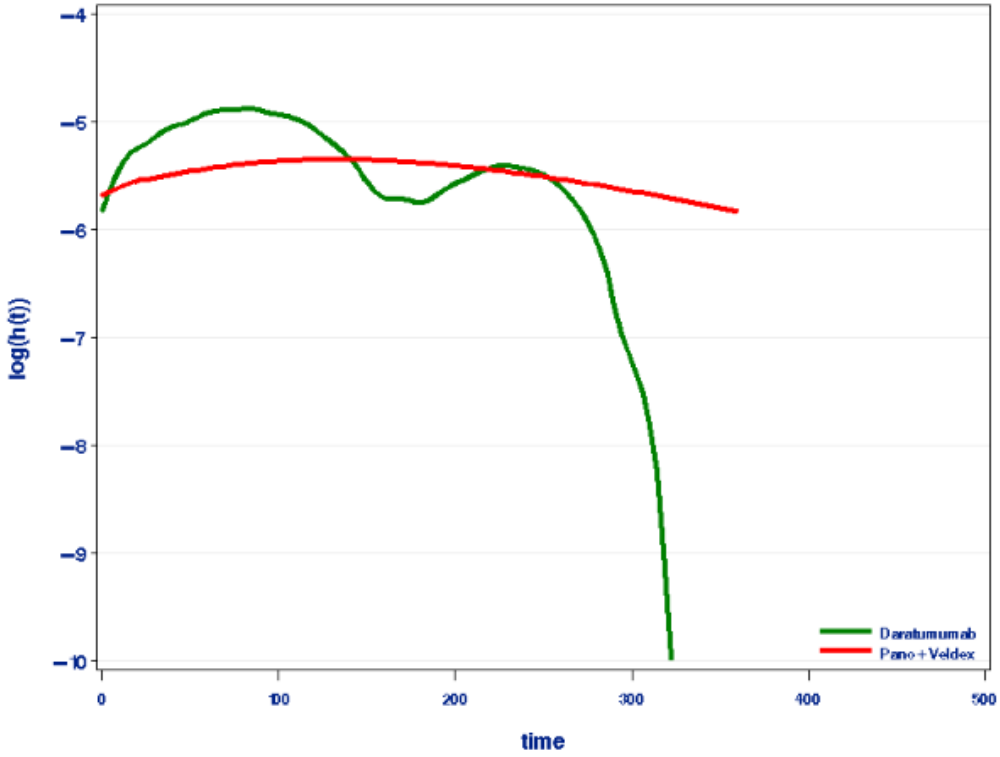


Figure 54. Log-cumulative hazard plots of adjusted MMY2002 daratumumab PFS versus PANO+BORT+DEX, 8 characteristics matched

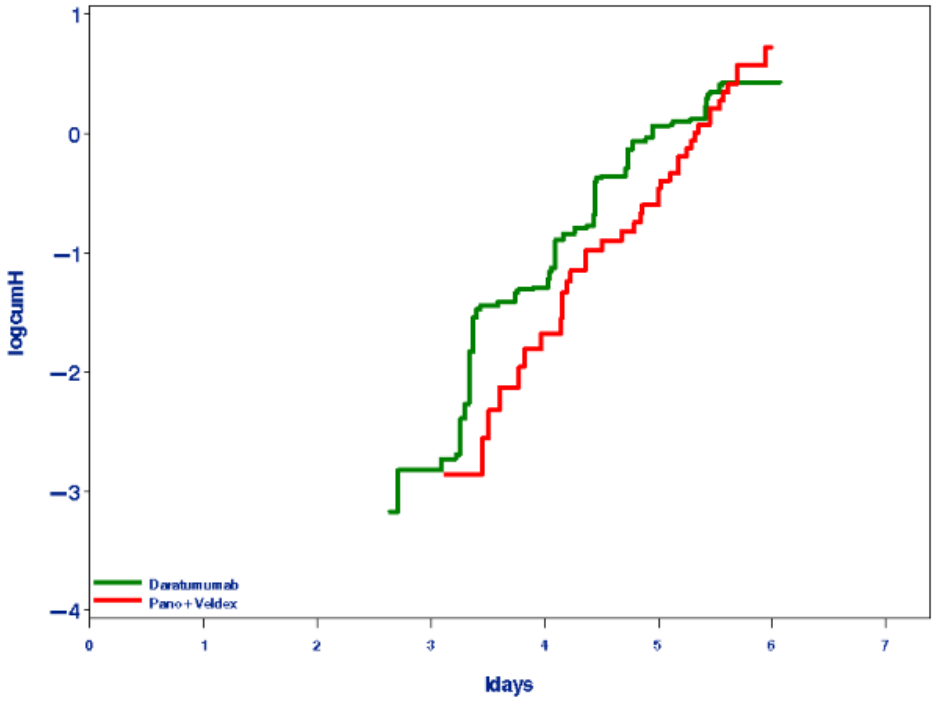


Figure 55. Diagnostic plot of adjusted GEN501 daratumumab OS versus POM+DEX (exponential), 11 characteristics matched

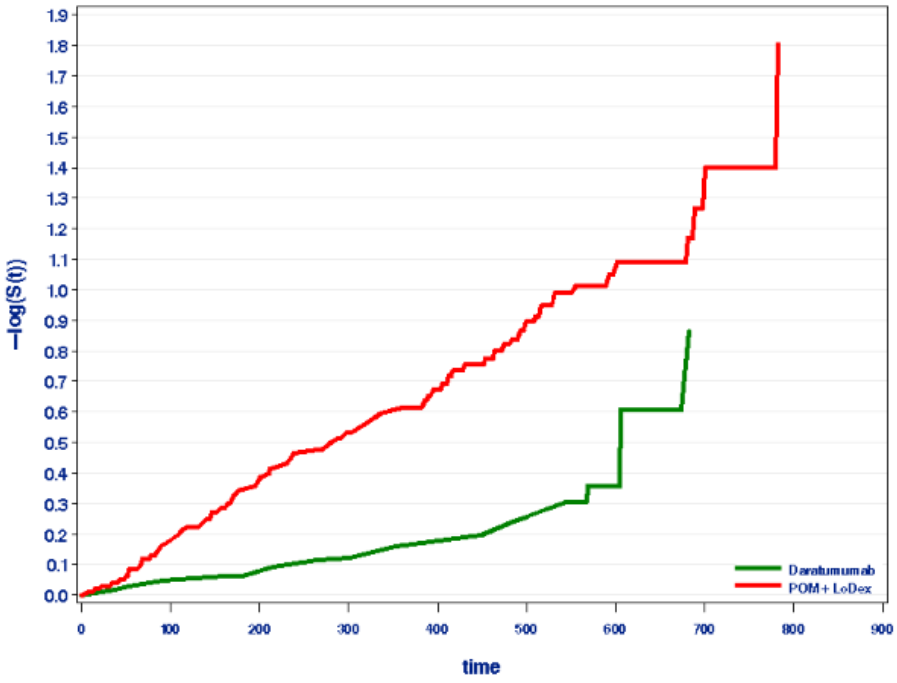


Figure 56. Diagnostic plot of adjusted GEN501 daratumumab OS versus POM+DEX (Weibull), 11 characteristics matched

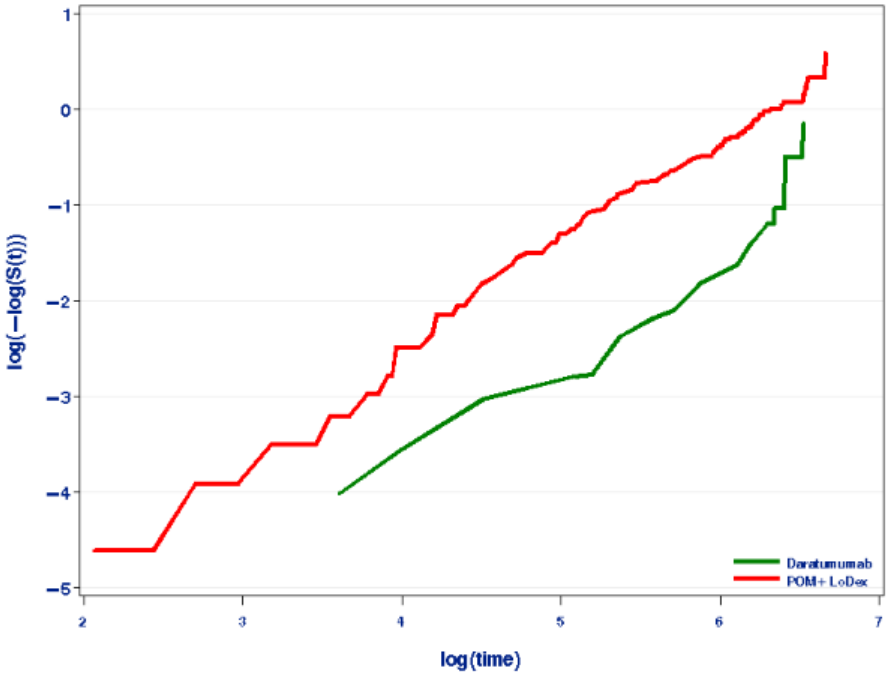


Figure 57. Diagnostic plot of adjusted GEN501 daratumumab OS versus POM+DEX (loglogistic), 11 characteristics matched

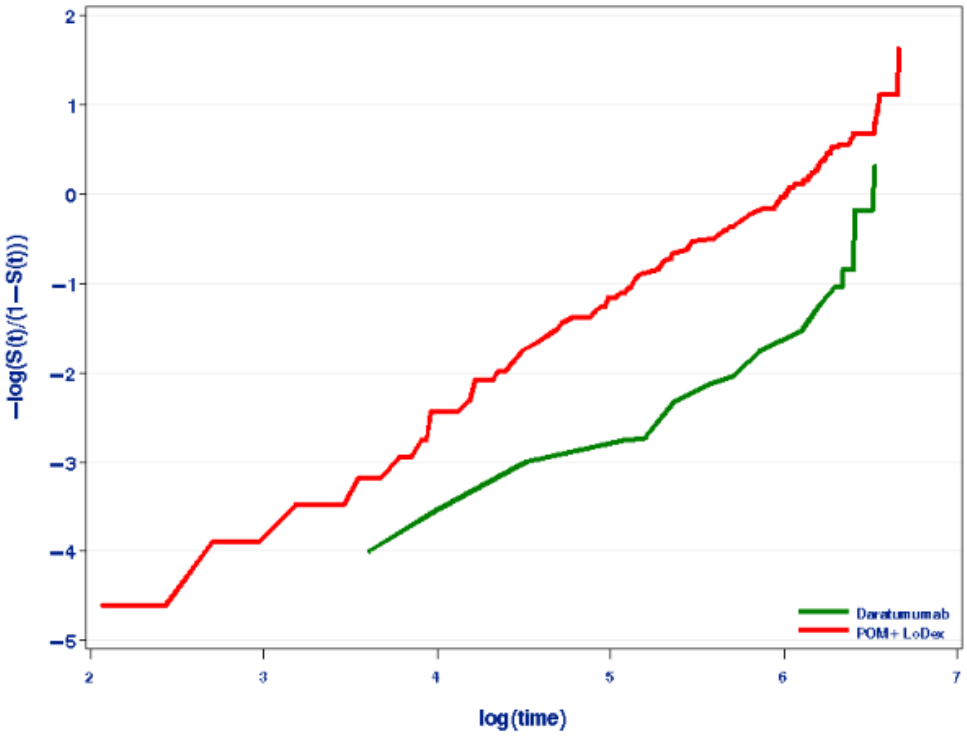


Figure 58. Diagnostic plot of adjusted GEN501 daratumumab OS versus POM+DEX (lognormal), 11 characteristics matched

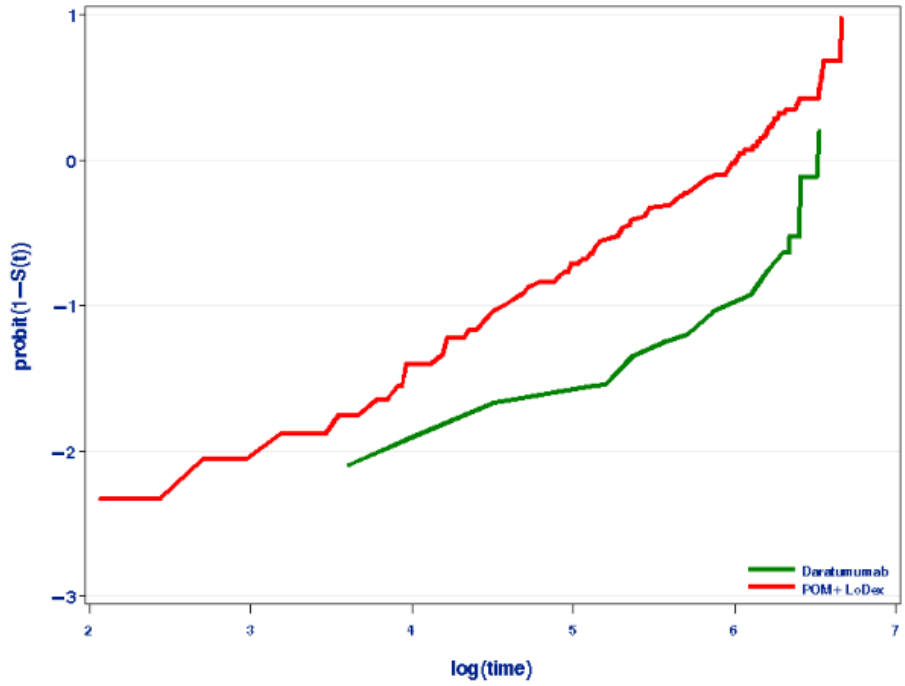


Figure 59. Diagnostic plot of adjusted GEN501 daratumumab OS versus POM+DEX (Gompertz), 11 characteristics matched

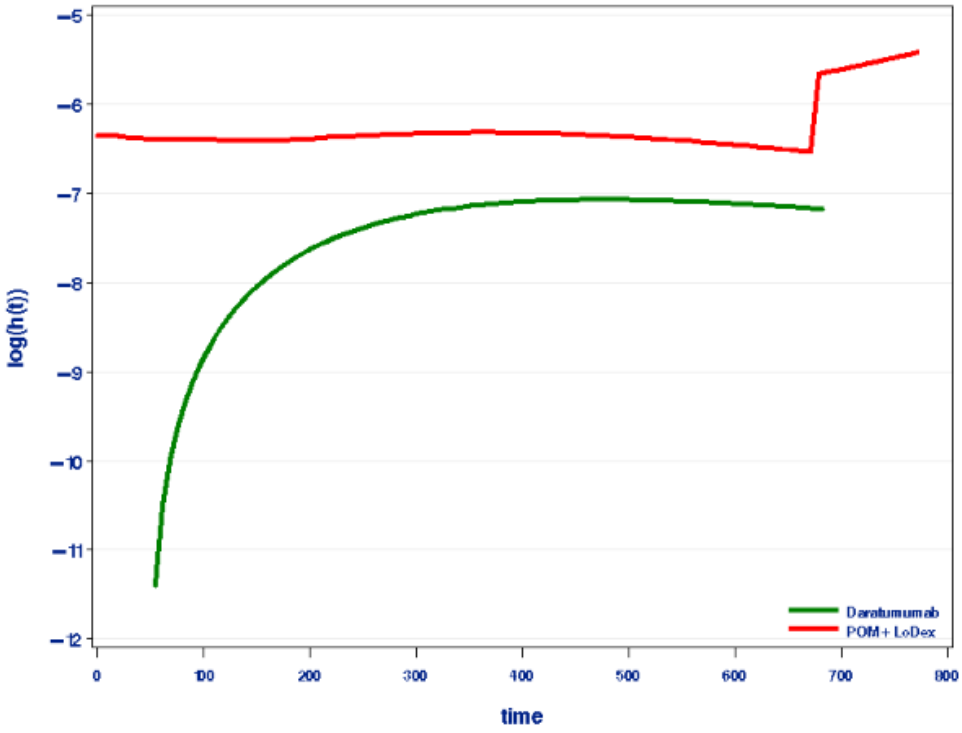


Figure 60. Log-cumulative hazard plots of adjusted GEN501 daratumumab OS versus POM+DEX, 11 characteristics matched

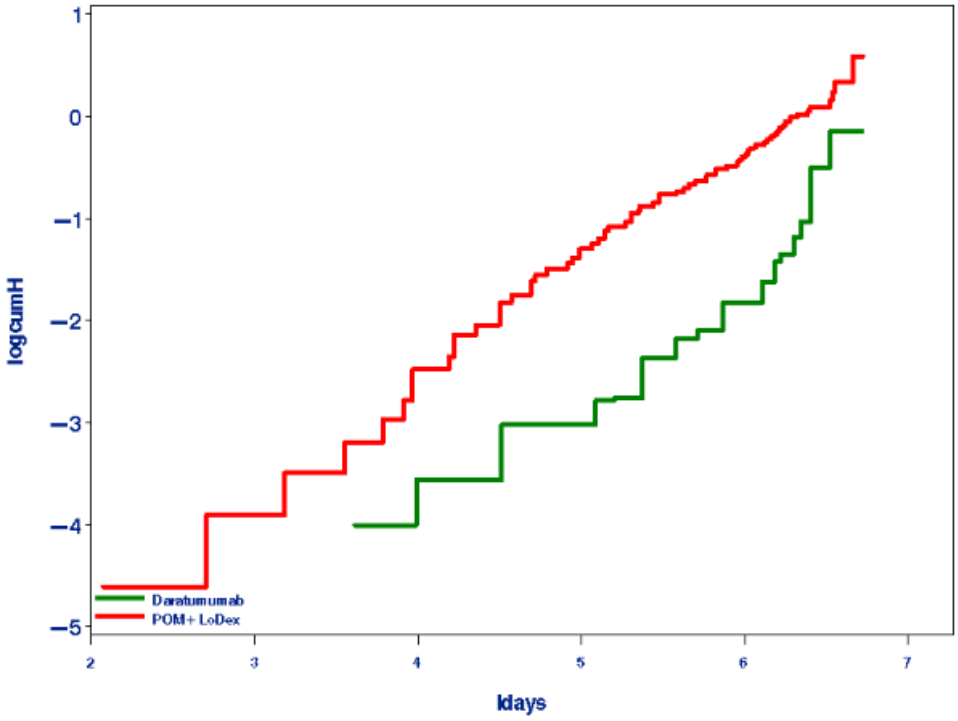


Figure 61. Diagnostic plot of adjusted GEN501 daratumumab PFS versus POM+DEX (exponential), 11 characteristics matched

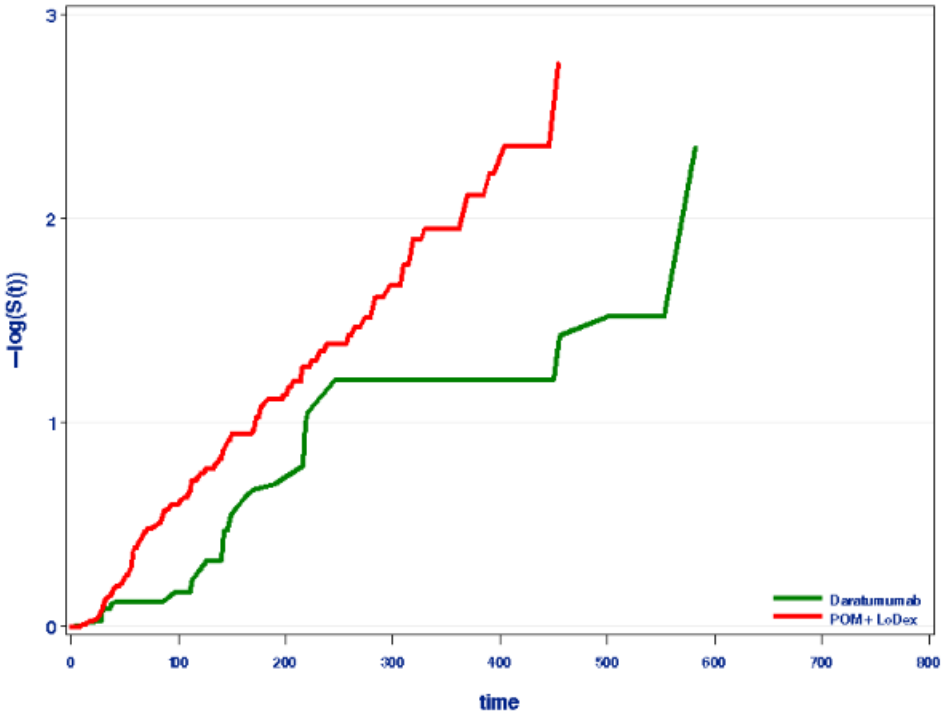


Figure 62. Diagnostic plot of adjusted GEN501 daratumumab PFS versus POM+DEX (Weibull), 11 characteristics matched

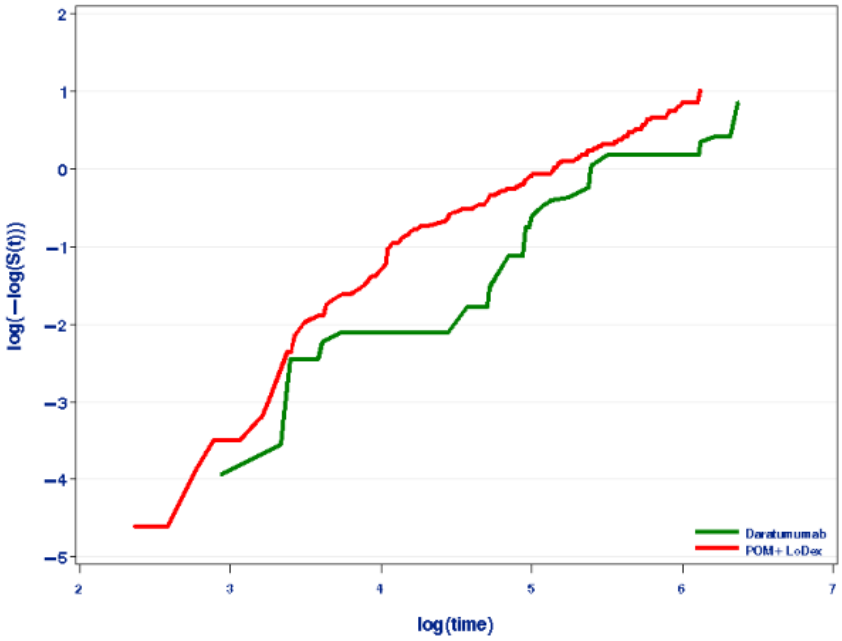


Figure 63. Diagnostic plot of adjusted GEN501 daratumumab PFS versus POM+DEX (loglogistic), 11 characteristics matched

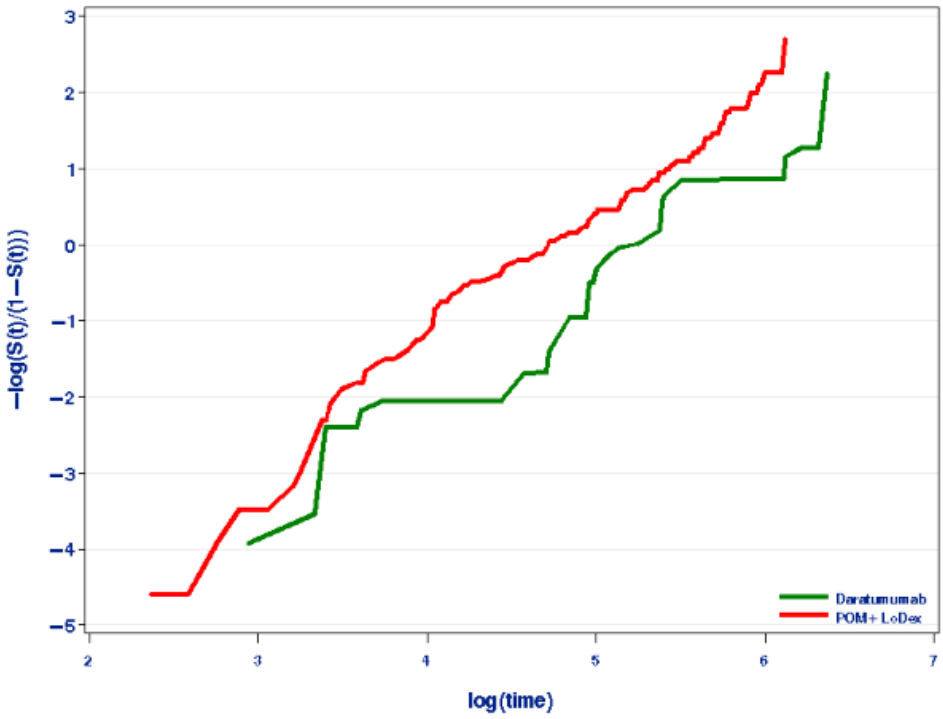


Figure 64. Diagnostic plot of adjusted GEN501 daratumumab PFS versus POM+DEX (lognormal), 11 characteristics matched

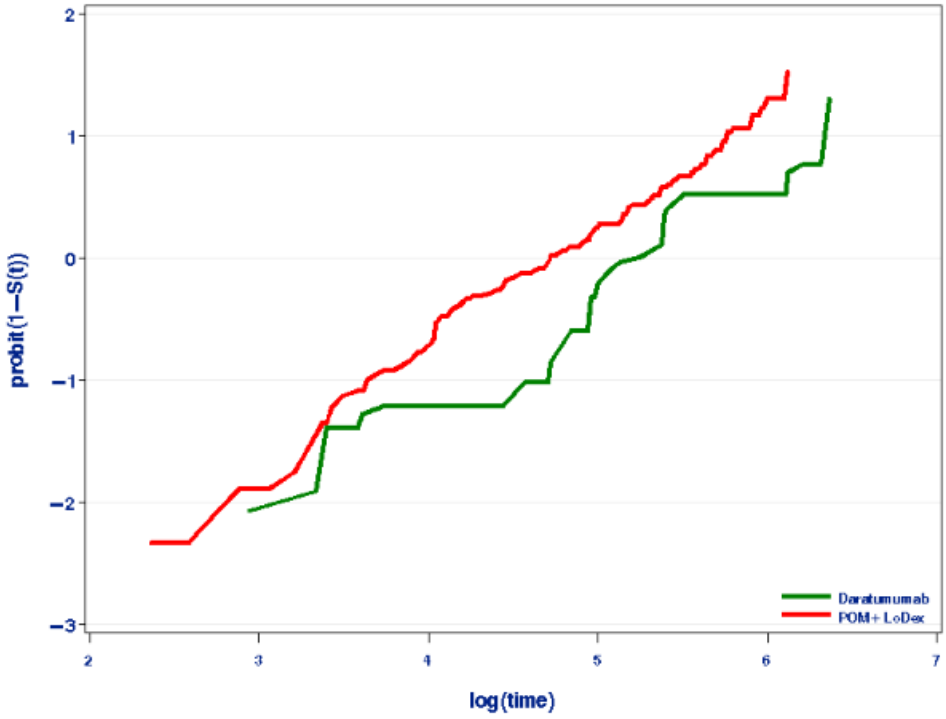


Figure 65. Diagnostic plot of adjusted GEN501 daratumumab PFS versus POM+DEX (Gompertz), 11 characteristics matched

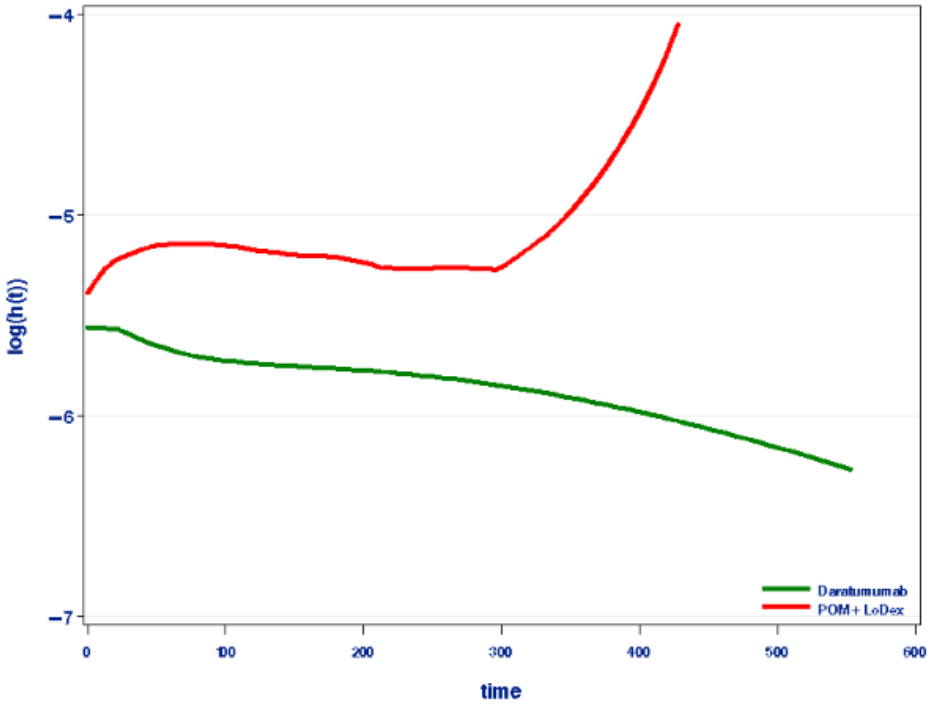


Figure 66. Log-cumulative hazard plots of adjusted GEN501 daratumumab PFS versus POM+DEX, 11 characteristics matched

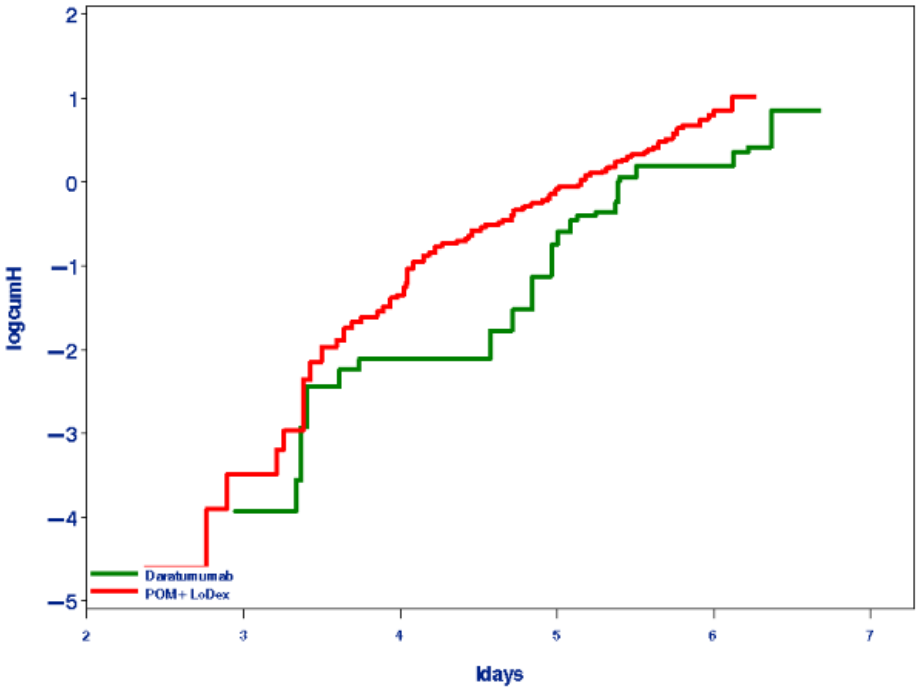


Figure 67. Diagnostic plot of adjusted GEN501 daratumumab OS versus PANO+BORT+DEX (exponential), 5 characteristics matched

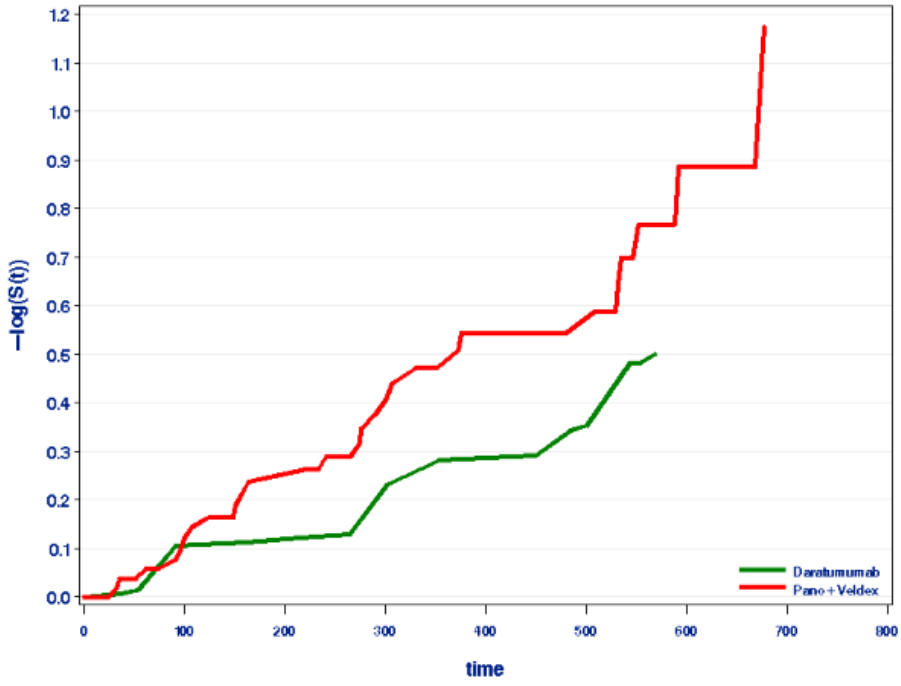


Figure 68. Diagnostic plot of adjusted GEN501 daratumumab OS versus PANO+BORT+DEX (Weibull), 5 characteristics matched

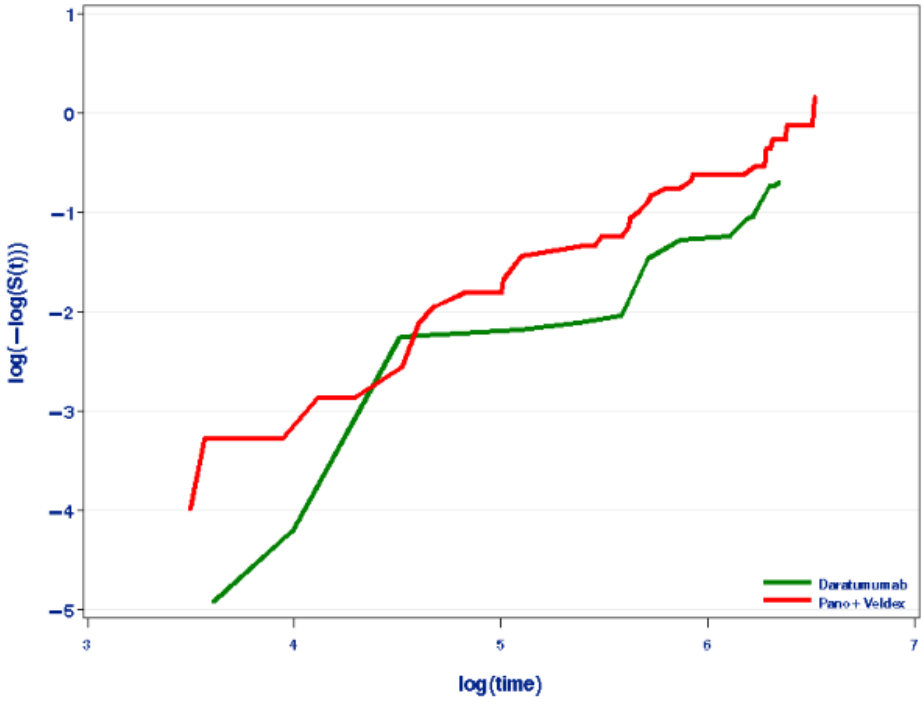


Figure 69. Diagnostic plot of adjusted GEN501 daratumumab OS versus PANO+BORT+DEX (loglogistic), 5 characteristics matched

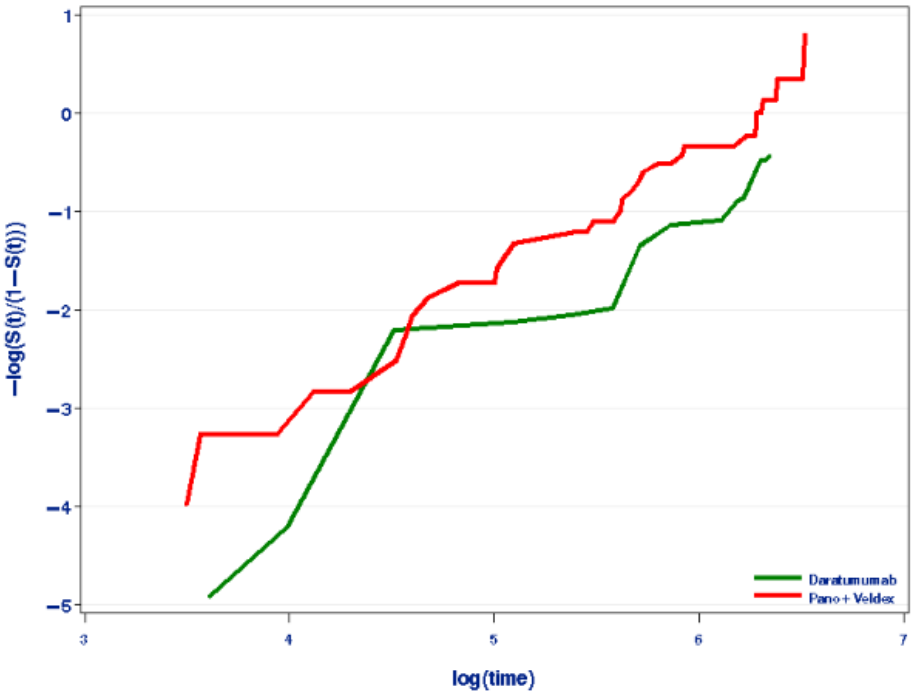


Figure 70. Diagnostic plot of adjusted GEN501 daratumumab OS versus PANO+BORT+DEX (lognormal), 5 characteristics matched

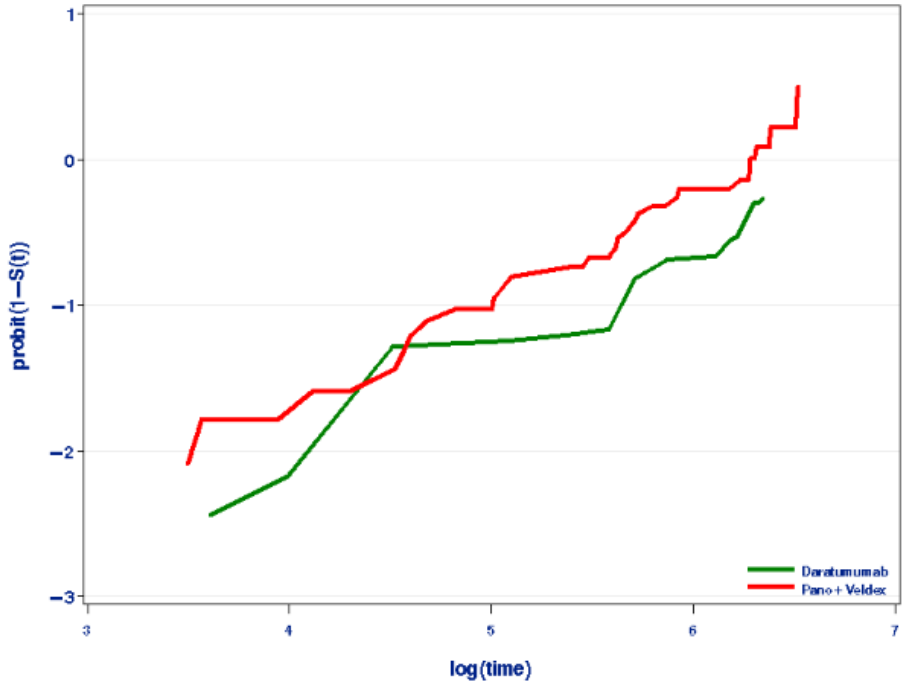


Figure 71. Diagnostic plot of adjusted GEN501 daratumumab OS versus PANO+BORT+DEX (Gompertz), 5 characteristics matched

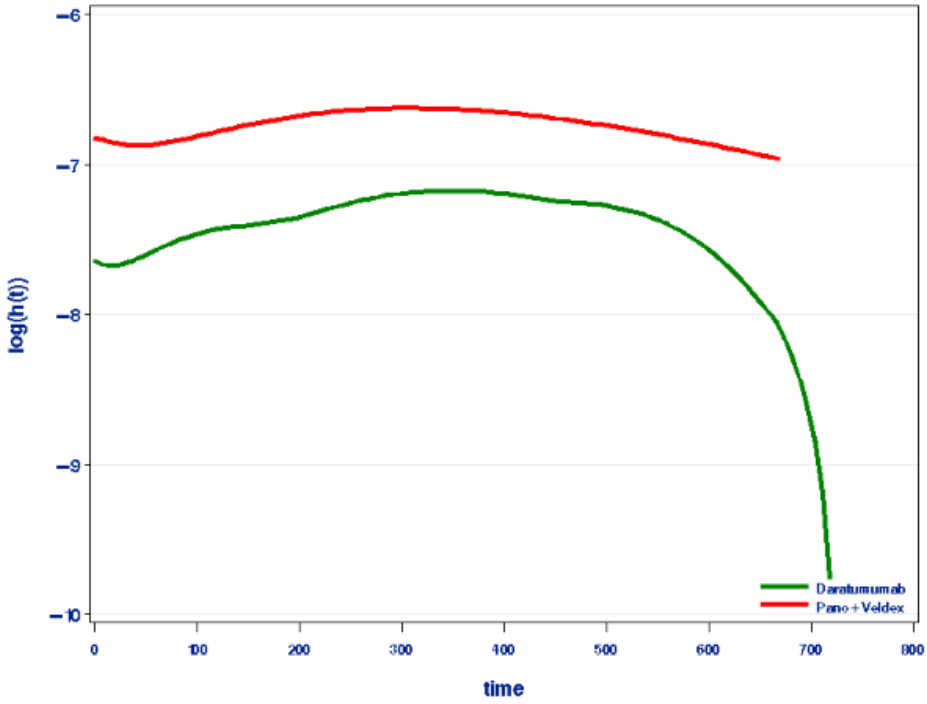


Figure 72. Log-cumulative hazard plots of adjusted GEN501 daratumumab OS versus PANO+BORT+DEX, 5 characteristics matched

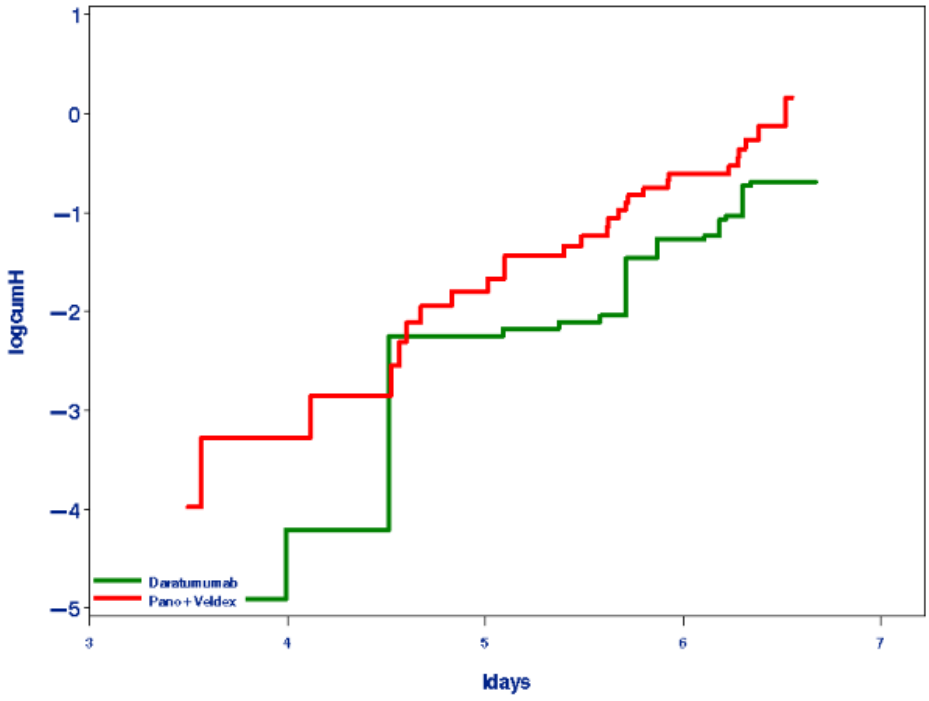


Figure 73. Diagnostic plot of adjusted GEN501 daratumumab PFS versus PANO+BORT+DEX (exponential), 5 characteristics matched

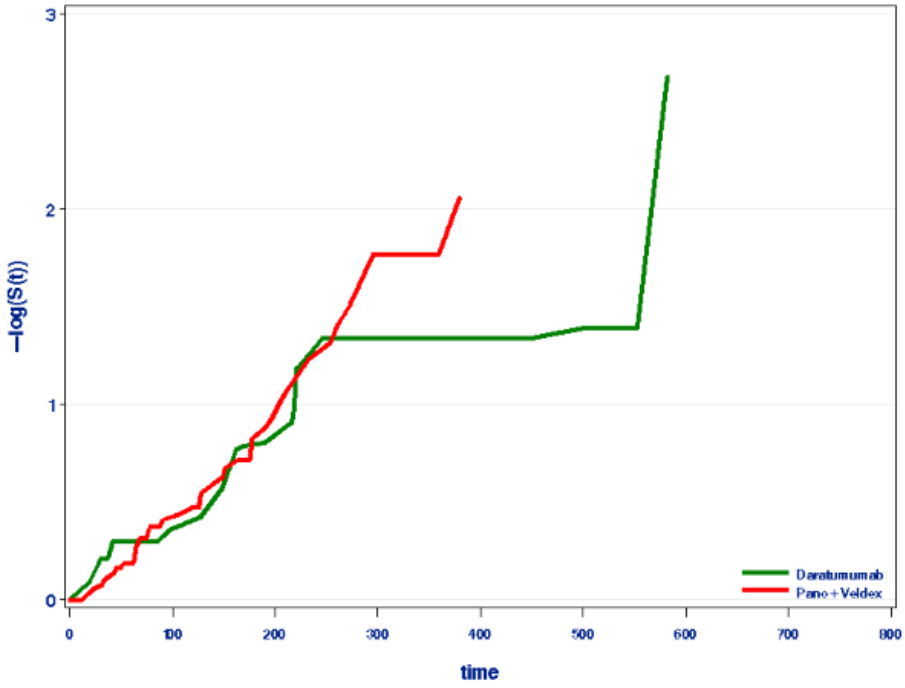


Figure 74. Diagnostic plot of adjusted GEN501 daratumumab PFS versus PANO+BORT+DEX (Weibull), 5 characteristics matched

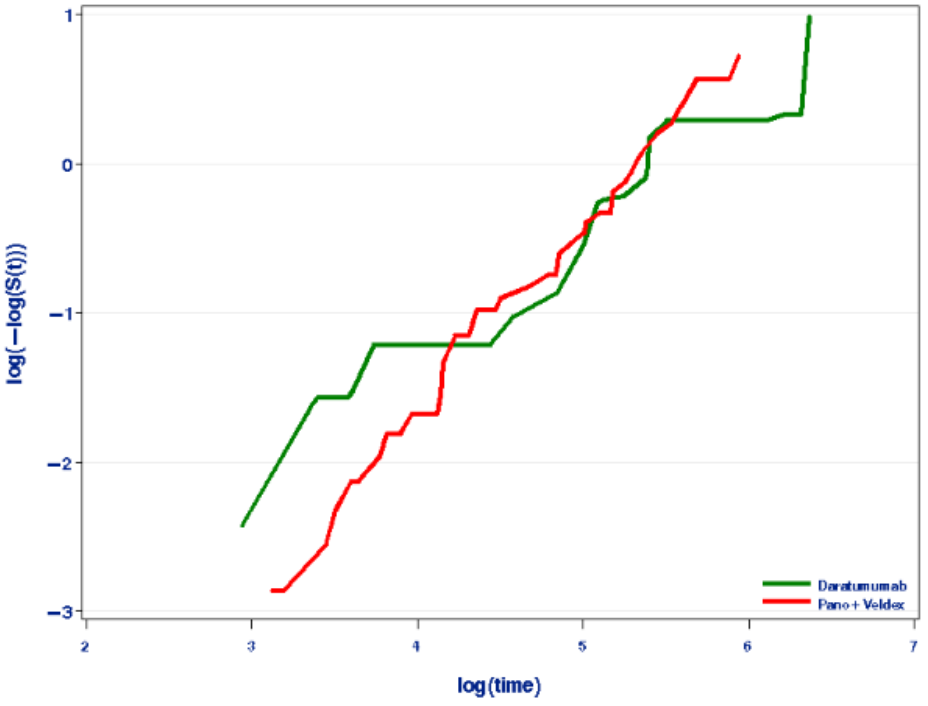


Figure 75. Diagnostic plot of adjusted GEN501 daratumumab PFS versus PANO+BORT+DEX (loglogistic), 5 characteristics matched

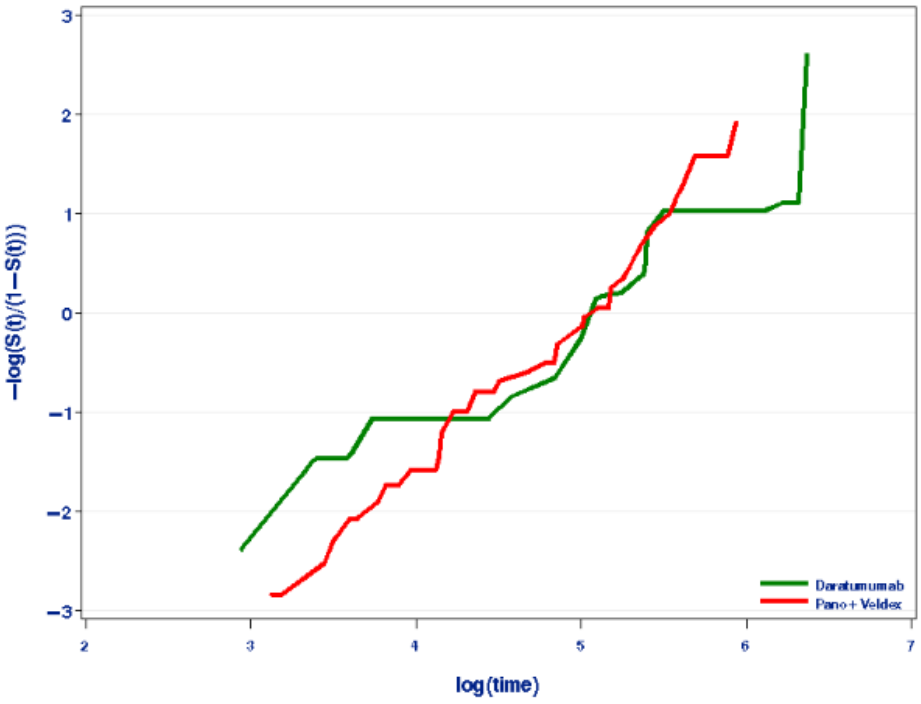


Figure 76. Diagnostic plot of adjusted GEN501 daratumumab PFS versus PANO+BORT+DEX (lognormal), 5 characteristics matched

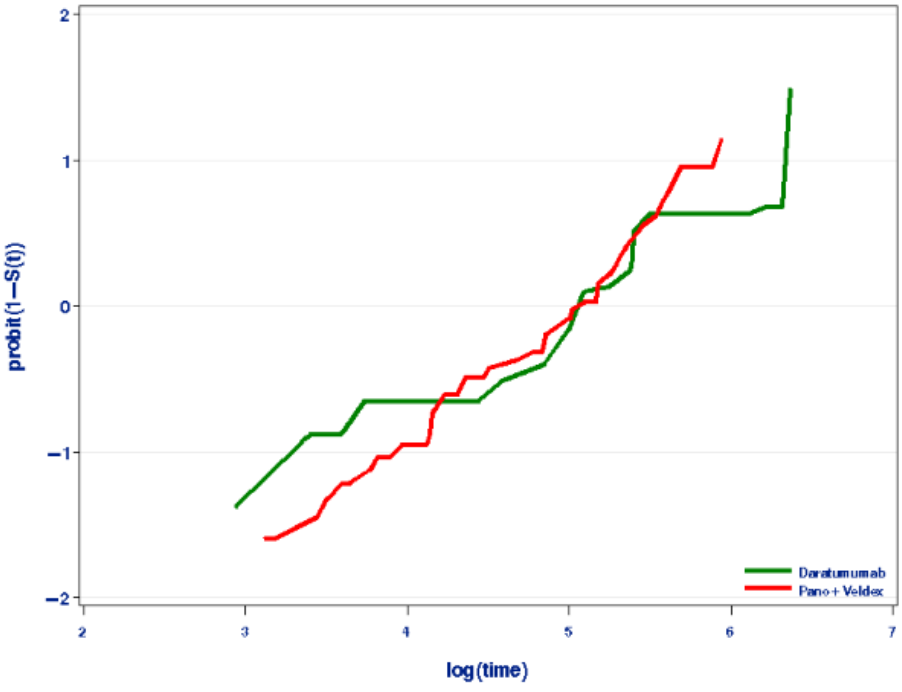


Figure 77. Diagnostic plot of adjusted GEN501 daratumumab PFS versus PANO+BORT+DEX (Gompertz), 5 characteristics matched

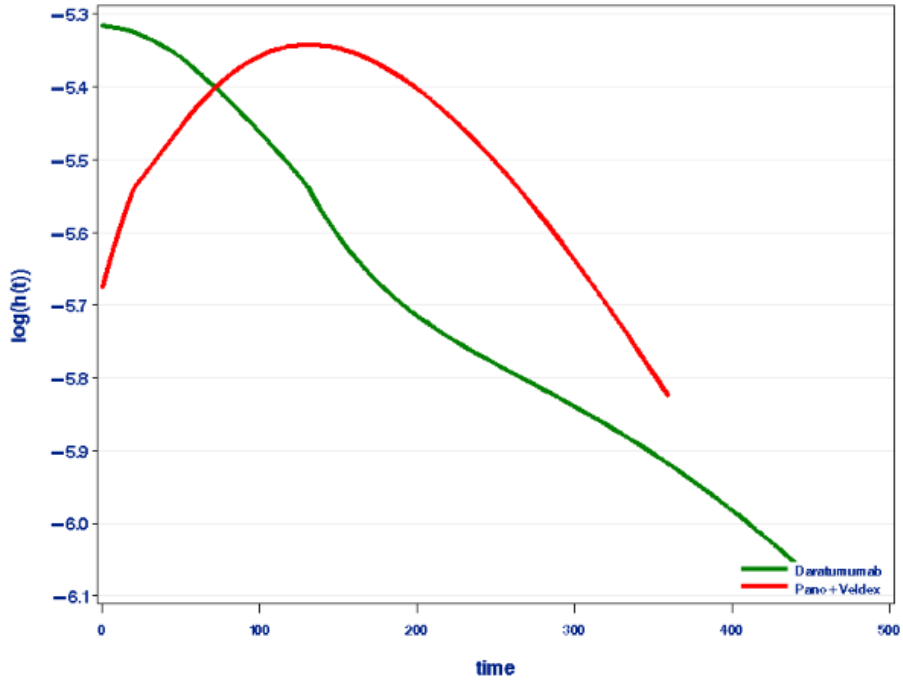
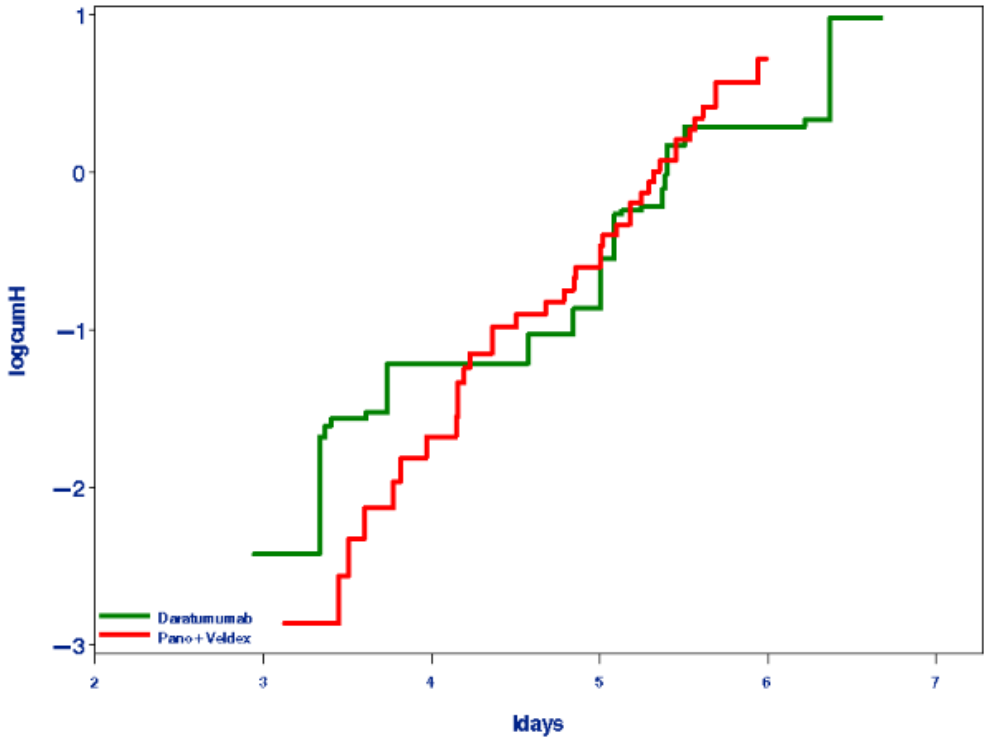


Figure 78. Log-cumulative hazard plots of adjusted GEN501 daratumumab PFS versus PANO+BORT+DEX, 5 characteristics matched



B11. **Priority question**: In appendix 11 of the company submission, the company assessed if the proportional hazards (PH) assumption holds for OS data across the daratumumab integrated data compared with pomalidomide plus dexamethasone, and compared with panobinostat plus bortezomib plus dexamethasone. Please:

a) Undertake the same assessment process with regards to a proportional odds and accelerated failure time assumption based on the plots requested in B7b and B7c.

This question is highly unclear, as no plots are requested in B7b) and there is no B7c). Furthermore, since OS is extrapolated with an exponential distribution (a proportional hazards model) in the base case it is not necessary to assess proportional odds or the accelerated failure time assumption (TSD 14).

b) Provide the same analysis for PFS and TTD data, including the assessment requested in B11a.

Janssen assumes the ERG is requesting assessment of the accelerated failure time assumption for the lognormal model used to extrapolate PFS. Whilst assessment of the accelerated failure time assumption is technically correct, Janssen have taken the commonly used pragmatic approach of applying HRs to an accelerated failure time model. Furthermore, upon request of the ERG, Janssen have also relaxed the proportional hazards assumption by fitting separate curves to the MAIC adjusted data. As such, Janssen consider that it is superfluous to conduct full assessment of proportional odds and accelerated failure time assumptions.

e) Provide the same assessment requested in B11a and B11b for the adjusted MMY2002 versus pomalidomide plus dexamethasone; adjusted MMY2002 versus panobinostat plus bortezomib plus dexamethasone; adjusted GEN501 versus pomalidomide plus dexamethasone; and adjusted GEN501 versus panobinostat plus bortezomib plus dexamethasone combinations.

Data from the individual trials are used as scenario analyses rather than the base case and so the PH assumption has not been tested.

B12. **Priority question**: To estimate PFS for the comparator curves in the model, HRs from a Cox proportional hazard model were applied to an accelerated failure time model. Furthermore, the proportional hazard assumption has not been assessed with regards to the PFS data. Therefore, please include the option to independently fit PFS curves in the

model (similar to the option given for OS in the “Controls.Comp_Method_POM” cell of the model).

This is included in the updated model. There are now 3 options for comparison to POM+DEX and PANO+BORT+DEX.

- Scenario analysis – Independent curve fit to OS MAIC (independent curves for post MAIC OS, MAIC HR for PFS) – as in original submission
- Scenario analysis – Independent curve fit to PFS MAIC (independent curves for post MAIC PFS, MAIC HR for OS)
- Scenario analysis – Independent curve fit to OS and PFS MAIC (independent curves for post MAIC OS and PFS)

Please note that due to that fact that the daratumumab data are MAIC-adjusted in these scenarios, the comparisons to PANO+BORT+DEX and POM+DEX need to be viewed independently. Daratumumab OS and PFS data from the MAIC vs POM+DEX and PANO+BORT+DEX will be different and so these comparisons, using this method, cannot be viewed at the same time. Setting the method used for POM+DEX comparison will change the ICER for PANO+BORT+DEX but this is due to the daratumumab data changed (to adjust for patients in MM-003) and a HR being applied to this.

The ICERs for each of the scenarios described above, vs POM+DEX and PANO+BORT+DEX are reported in Table 39.

Table 39: Results of Independent curve fits, post MAIC scenario analyses

	ICER DARA vs POM+DEX	ICER DARA vs PANO+BORT+DEX
Scenario analysis – Independent curve fit to OS MAIC (independent curves for post MAIC OS, MAIC HR for PFS) – as in original submission	£56,692	£32,271
Scenario analysis – Independent curve fit to PFS MAIC (independent curves for	£46,181	£762

post MAIC PFS, MAIC HR for OS)		
Scenario analysis – Independent curve fit to OS and PFS MAIC (independent curves for post MAIC OS and PFS)	£45,744	£661

B13. **Priority question**: Please provide a list of the parameters/data ranges that changed in the economic model when individual daratumumab trials (MMY2002 and GEN501) are used instead of the integrated data.

Changing the population in “Controls.Population” to MMY2002 and GEN501 changes the inverse HR applied to daratumumab survival data. (Sheet Survival and Progression: Cells N29:P29, N32:P32, N38:P38, N41:P41). It also determines which curve is selected for daratumumab OS and PFS (See sheets PFS Curve_DARA, Columns G and H and Sheet OS Curve_DARA Column F).

B14. **Priority question**: Please explain why the tab “Survival and Progression” of the Excel model had no HRs provided for GEN501 but only for MMY2002 and the integrated analysis. When cell “Controls.Population” in tab “Controls” is changed from MMY2002 to GEN501, the HRs given in the “Survival and Progression” do not change (they still reflect the HRs for MMY2002). Please correct this in the model.

A GEN501 MAIC was not included in the company submission. Having since been performed, MAIC HRs for OS and PFS for GEN501 vs (i) POM+DEX and (ii) PANO+BORT+DEX are reported in Table 40 and have also been added to the model. These results are associated with uncertainty due to the small patient numbers available after matching (n=22 vs POM+DEX, n=18 vs PANO+BORT+DEX), and economic analyses using these should as such be interpreted with caution.

Table 40: MAIC results for GEN501

	Mean	Lower Bound	Upper Bound
MAIC Daratumumab versus POM+DEX			
OS	0.40	0.23	0.69
PFS	0.56	0.32	1.00
MAIC Daratumumab versus PANO+BORT+DEX			
OS	0.55	0.24	1.27
PFS	0.86	0.45	1.67

B15. **Priority question:** A Cox proportional hazard model was used to analyse the reweighted daratumumab individual patient-level data (IPD) data together with the simulated IPD data from pomalidomide plus dexamethasone and panobinostat plus bortezomib plus dexamethasone. Please explain why this was used since it is theoretically incorrect to apply a HR derived from a different parametric model, or one derived from a Cox proportional hazard model (DSU 14).

The application of HRs derived from MAIC to parametric extrapolations of daratumumab trial data is a pragmatic approach and assumes a consistent relative treatment effect.

B16. **Priority question:** An exponential distribution is used to model OS in the model. This has a strong underlying assumption of not only proportional hazard, but also a constant HR throughout the model time horizon. Please justify this assumption as fully as possible.

Janssen followed DSU TSD 14 guidance for parametric curve fitting in using both statistical fit and clinical plausibility to select the most appropriate curve. As described in the submission dossier, the exponential curve was shown to have the best statistical fit and was deemed the most clinical plausible by a practicing haematologist, Kwee Yong, and was selected on this basis.

Furthermore, given that current OS estimates suggest that patients with good response to daratumumab have an extended period of both PFS and OS, the ‘true’ curve is likely to plateau over time (e.g. lognormal/loglogistic). However, the shape of the exponential distribution does not allow this and as such is likely to be conservative.

B17. **Priority question:** Page 182 of the company submission mentions that, "based on statistical fit and clinical plausibility the log-normal curve was deemed most appropriate for use". Based on the AIC and BIC statistics in Table 52 (page 183), the Generalised Gamma function fits the PFS data better. Please explain why the Generalised Gamma was not used in the base-case analysis.

Generalised gamma and gompertz model fits to the integrated daratumumab PFS data project a plateau in PFS for around 5% of patients, from around 5 years onwards, as illustrated by Table 41. The clinical plausibility of this has been verified by the Consultant Haematologist consulted prior to company submission, Professor Kwee Yong, who has confirmed that these projections are not clinically robust. The log-normal model, while providing good statistical fit to the trial data, provides plausible long-run projections for the patient group, as described in the submission dossier.

Table 41: Projections from selected parametric curve fits to daratumumab overall survival data from the Integrated Dataset

Time (Years)	Proportion of daratumumab patients progression-free (and alive)		
	Log-normal	Gompertz	Gamma
1	19%	21%	22%
2	7%	10%	13%
3	4%	7%	10%
4	2%	6%	8%
5	1%	6%	6%
10	0%	6%	4%

B18. Please clarify why the same resource use was assumed for administering the first dose of bendamustine and daratumumab (i.e. SB14Z Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance) as specified in Table 65 on page 212.

This was a typo in the submission document. The administration cost for bendamustine used in the model was £329 (SB13Z Deliver more complex Parenteral Chemotherapy at first attendance). No changes have been made in the model.

B19. The dosing schedule for bortezomib (with PANO) in cycles 8 to 16 (i.e. Days 1, 2, 8 and 9) reported in Table 64 (page 211) does not reflect what is reported in the European Public Assessment Report for panobinostat, which is cited as the source of the schedule. Please justify the dosage used.

This was a typo in the submission document. The correct dosing schedule used, and reported in the European Public Assessment Report for panobinostat, is shown in Table 42.

Table 42: Dosing Schedule for bortezomib (with PANO)

Drug	Dose per administration	Administration method	Dosing cycle	Dosing schedule	Treatment duration
Bortezomib (with PANO)	1.3mg/m²	Injection	21 days	Days 1, 4, 8 and 11 for cycles 1 - 8. Days 1, and 8 for cycles 9-16	Maximum of 16 treatment cycles or until progression

B20. Please clarify whether the UK EQ-5D-5L value set was used to estimate the utility values reported in Table 55 (page 193) of the company submission.

Janssen can confirm that the UK EQ-5D-5L value set was used to estimate the utility values reported in Table 55 (page 193) of the company submission

B21. Please clarify why the systematic literature review of economic evaluations was limited to the intervention (i.e. cost-effectiveness studies of daratumumab in multiple myeloma).

The methodology of this systematic literature review followed Section 3.3.9 of the NICE *Guide to the methods of technology appraisal*, which states:

3.3.9 "Evidence on cost effectiveness may be obtained from new analyses performed according to the NICE reference case; however, a systematic review of published, relevant evidence on the cost effectiveness of the technology should also be conducted."

B22. The equation used to estimate the proportion of patients assumed to experience nausea (all grades) in the model ('Adverse events'! E31) is as follows = ((4%*124)+ (12.5%*32))/ (124+32). Please clarify where the 4% for the MMY2002 was obtained from, as according to Table 28 on page 96 of the MMY2002 CSR this value should be 28.2%.

The 4% estimate has been taken from "Transfusion related reactions" data. This is an error and should have been taken from "Treatment-emergent adverse events" data. This has been corrected in the model to 28.2% as suggested by the ERG and has minimal impact on cost-effectiveness results.

B23. Please clarify whether a weighted average from the GEN501 and MMY2002 trials was used to estimate the proportions of patients experiencing lymphopenia and leukopenia in the tab 'Adverse events'! E21:E22. If so, please provide the equation used.

The values used for leukopenia and lymphopenia are from MMY2002 only as these adverse events are not reported in Table 10 (page 72) of the GEN501 CSR.

B24. Please provide the summary results as reported in Table 76 (page 225), but for mean estimates instead of median.

We have used a restricted means approach to address this. The cut-off point used for PFS was 19.3 months and 22.42 months for OS which was at the point of the last observed event. The same cut-off point was used for both the trial KM data and the modelled data for comparability. The results are reported in Table 43.

Table 43: Comparison of restricted means from the trial and model for daratumumab.

Outcome	Clinical trial result	Model result
PFS – daratumumab	Mean 6.82 months	Mean 6.56 months
OS – daratumumab	Mean 15.73 months	Mean 15.90 months

Key: PFS, progression-free survival; OS, overall survival.

B25. When cells “Controls.Comp_Method_POM” and “Controls.Comp_Method_PANO” in tab “Controls” are changed to a naïve comparison, the survival curves on tab “Survival and Progression” do not seem to change. Please provide more details on the naïve analysis.

The Naïve comparison compares the unadjusted daratumumab data to digitised POM+DEX data from MM-003 and digitised PANO+BORT+DEX data from PANORAMA2. Changing “Controls.Comp_Method_POM” to naïve comparison allows the model to use columns AK and AM in the “Survival and Progression” Sheet (curve fits to the digitised MM-003 data) for the POM+DEX arm rather than AL and AN (Inverse HR from the MAIC applied to the daratumumab PFS and OS data.

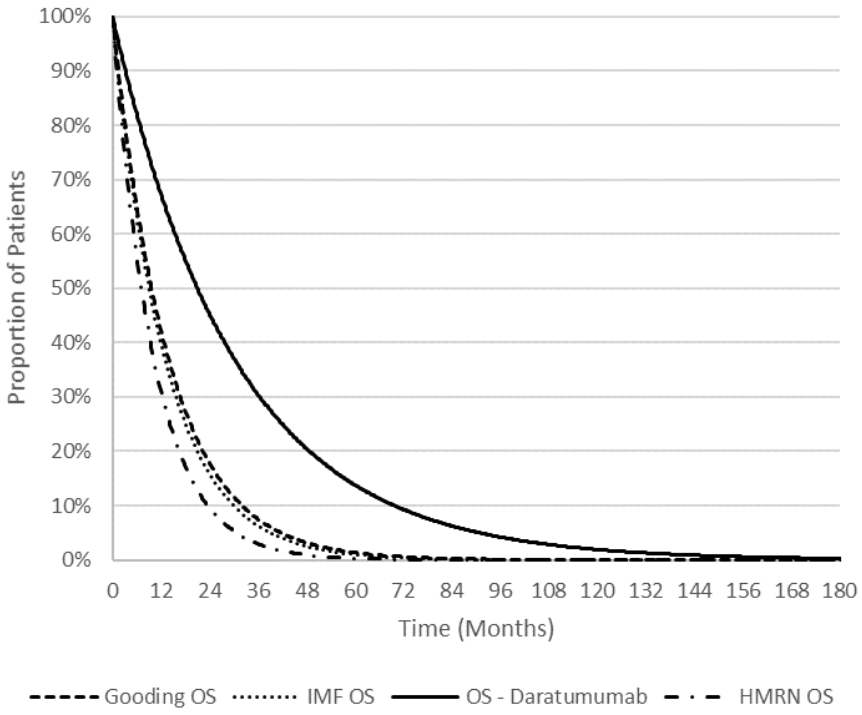
B26. Please clarify why the utility decrements in the model for hypotension, septic shock, syncope, peripheral neuropathy, flatulence, abdominal distention and hypokalaemia are positive while those for the remaining adverse events are negative. This question refers to 'Utility'! G57: G61 and 63:G66.

This was an error in the model. This has been corrected in Cells P361: 366 on the “Parameters” sheets to transform values back into negative values as has been done for the other adverse events. This has very little impact on the results

B27. The OS curve from Gooding *et al.* is missing from Figure 36 (page 182). Please provide Figure 36 including this curve?

The amended figure is shown in Figure 79 below.

Figure 79: Comparison of OS of daratumumab with RWE from the HMRN, Gooding et al and IMF chart review



B28. The ERG could not replicate the results of the scenario analysis in which utility values from TA380 are used as reported in Row 6 of Table 8 of the Addendum to company evidence submission for any of the comparisons. The resulting ICERs from this scenario in the model are £30,097, £50,470 and £50,048 per QALY gained for daratumumab compared with panobinostat plus bortezomib plus dexamethasone, bendamustine-based therapy, and pomalidomide plus dexamethasone respectively. Please clarify this discrepancy or update the model as appropriate.

This appears to be a typo in addendum document and we agree with the ERG that the correct ICERs are £30,097, £50,470 and £50,048 per QALY gained for daratumumab compared with

panobinostat plus bortezomib plus dexamethasone, bendamustine-based therapy, and pomalidomide plus dexamethasone respectively. This is presented in the model in Cells AG21: AI21 on “Scenarios” sheet. No changes have been made to the model.

B29. Please clarify why treatment-emergent adverse events were used in the model rather than treatment-related adverse events.

The use of treatment-emergent adverse event data was consistent with the safety assessment presented in Section 4.12 of the submission dossier, and incorporates a broader range of adverse events than those defined as treatment-related.

B30. Please clarify why the cost-effectiveness model is described as a semi-Markov partitioned survival structure as opposed to a partitioned survival model.

The cost-effectiveness model assumes independence of clinical events; as such, please do describe the model as a “partitioned survival model”.

B31. Please provide the p values and respective confidence intervals associated with the scale parameter of the Weibull distribution used to fit the adjusted and unadjusted integrated OS curves for daratumumab and for the MMY2002 and GEN501 OS curves when the trial data for the 2 trials are analysed separately.

Statistics around the Weibull shape parameter are presented in Table 44

Table 44. Statistics for OS Weibull curves

Daratumumab data	**Scale (SE)**	**95% CI**
Integrated unadjusted	0.938 (0.0997)	-
Integrated MAIC adjusted versus POM+DEX, 11 characteristics	1.0425 (0.1139)	(0.8415, 1.2915)
Integrated MAIC adjusted versus PANO+BORT+DEX, 5 characteristics adjusted	0.9175 (0.1050)	(0.7333, 1.1481)
MMY2002 unadjusted	0.942 (0.1117)	-
MMY2002 MAIC adjusted versus POM+DEX, 13 characteristics	1.2950 (0.1652)	(1.0085, 1.6627)

MMY2002 MAIC adjusted versus PANO+BORT+DEX, 8 characteristics	0.8516 (0.1061)	(0.6670, 1.0872)
GEN501 unadjusted	0.848 (0.1990)	-
GEN501 MAIC adjusted versus POM+DEX, 11 characteristics	0.5378 (0.1234)	(0.3430, 0.8434)
GEN501 MAIC adjusted versus PANO+BORT+DEX, 5 characteristics	0.7974 (0.2175)	(0.4672, 1.3611)
Key: CI, confidence interval; MAIC, matched adjusted indirect comparison; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; POM+DEX, pomalidomide plus dexamethasone; SE, standard error.		

Section C: Textual clarifications and additional points

C1. Is the cost per week for bortezomib presented in Table 73 (page 221) correct? The ERG could not replicate this value based on the unit costs and doses assumed per week.

The calculations for the weekly cost of bortezomib can be seen in cell Z184 on the "Costs" sheet. Subsequent treatment duration is 94 days. Bortezomib has a 21 day cycles with 4 administration required per cycle. This results is an average of 1.33 doses a week.

The weekly cost presented in this table is not used in the model, and was provided for reporting purposes only. The cost of subsequent treatment is applied as a one-off cost upon progression, as described in Section 5.5.5.1 of the submission.

C2. Please clarify this sentence from page 54 of the company submission: "Terms for principal interventions were included in the systematic searches with terms for interventions only used in combination with principal interventions not required."

Search terms for treatments that are only used alongside one of the treatments listed below (termed principal interventions in the original text) were not included in the search strategy. This is because any studies investigating concurrent administration of one or more treatments would be identified through search terms for the individual treatment components. Of note, all treatments of interest to the decision problem for NHS England were included in this list of principal interventions (highlighted in bold).

- **Bendamustine**
- **Bortezomib**
- Carfilzomib
- Cyclophosphamide
- **Daratumumab**
- **Dexamethasone**
- Elotuzumab
- Ixazomib
- Lenalidomide
- Melphalan
- **Panobinostat**
- **Pomalidomide**
- Thalidomide

The ERG has found an error in the curves included in Figure 37 of the CS (page 183) replicated in Figure 1 below. The PFS data used in the base case analysis is reported to be based on the IRC assessed dataset. However the Gamma curve in Figure 1 (and in tab "PFS Curves_DARA") uses data from the INV assessed PFS dataset. When the ERG replicates Figure 1, using the company's data from tab "PFS Curves_DARA" BD19:BI4039 we get the graph shown in Figure 2. When the ERG uses the company's data from tab "PFS Curves_DARA" BM19:BR4039 to produce the equivalent graph for the INV assessed PFS data we get the graph shown in Figure 3.

Can the company please:

1. Clarify if the data ranges BD19:BI4039 and BM19:BR4039 in tab "PFS Curves_DARA" of the model correctly labelled?

Yes, BD19:BI4039 refers to PFS defined by IRC and BM19:BR4039 by INV.

2. Clarify why does Figure 1 (Figure 37 in the CS) include the Gamma distribution taken from the INV dataset?

This is a correctly identified error addressed in the updated model.

3. Correct/explain the AIC and BIC statistics for the Gompertz distribution. Figure 2 shows the Gompertz distribution included in the model but excluded from Figure 37. According to visual inspection, the Gompertz distributions seems a good fit (if not the better fit) to the KM curve. Therefore the AIC and BIC statistics shown in "PFS Curves_DARA" tab of the model (cell BH14 and BH15 for IRC and BQ14 and BQ15) do not seem correct.

Apologies, there is a discrepancy in the AIC/BIC statistics submitted, due to different SAS procedures being used to derive these estimates. The AIC/BIC statistics for the Gompertz distribution are on the original scale whereas; the AIC/BIC for other distributions tested are on the log scale. As noted by the ERG the Gompertz distribution is indeed a better statistical fir to the PFS data than the lognormal. However, as noted in B , clinical validation of the extrapolations resulted in the lognormal being chosen as the base case.

4. Clarify why the time unit for the Gompertz distribution is months when the time unit for all other distributions is days and adjust the time unit in the Gompertz curve to match the other curves. The same issue is found for OS and TTD data in the "OS Curves_DARA" and TTD Curves_DARA" tabs of the model, respectively. Please correct this in the OS and TTD tabs as well.

The time unit of months was used for the Gompertz distribution as convergence was problematic when using time in days.

5. Provide the KM data in Excel format to derive the curve for the KM INV PFS curve for superimposition with the derived curves in Figure 3. The ERG notes that these data were used to derive the curves, so there is no need for additional analysis but simply providing the KM data.

Figure 1. Replication of Figure 37 in CS

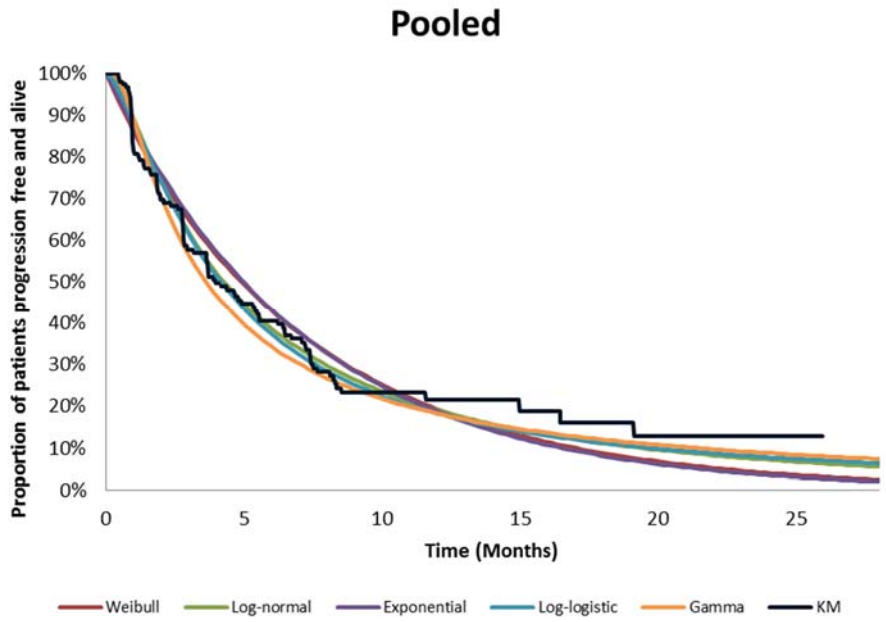


Figure 2. IRC PFS curves

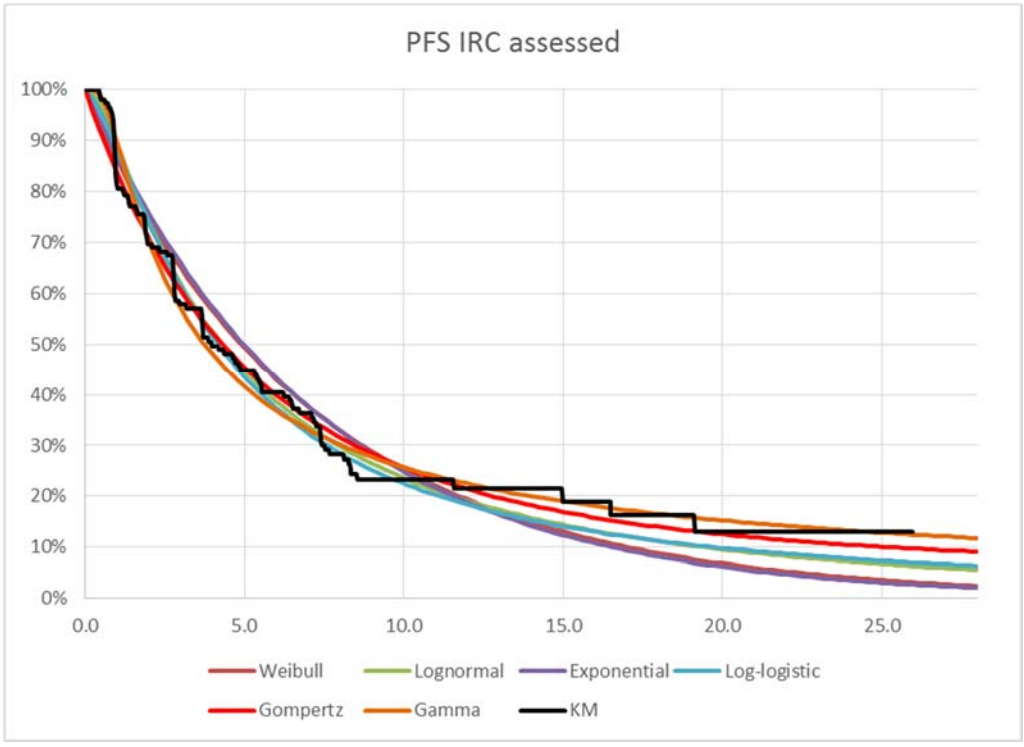
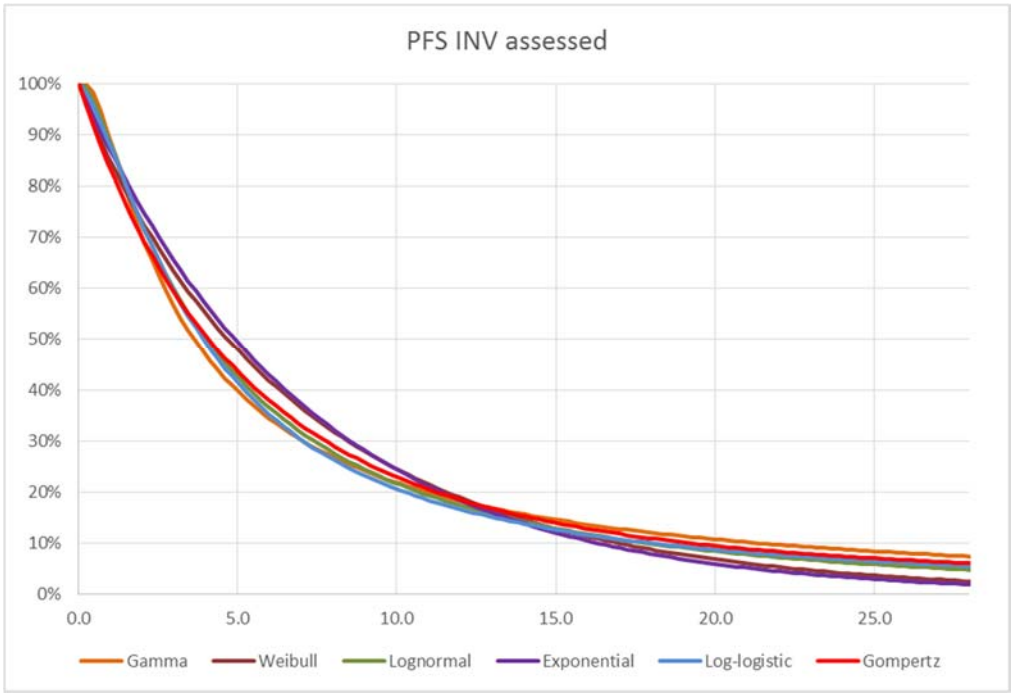


Figure 3. INV PFS curves


PFS INV assessed
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0.0
5.0
10.0
15.0
20.0
25.0
Gamma
Weibull
Lognormal
Exponential
Log-logistic
Gompertz

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: Shelagh McKinlay
Name of your organisation: Myeloma UK
Your position in the organisation: Policy and Public Affairs Officer

Brief description of the organisation:

Myeloma UK is the only organisation in the UK dealing exclusively with myeloma. Our broad and innovative range of services cover every aspect of myeloma from providing information and support, to improving standards of treatment and care through research and campaigning. We receive no government funding and rely entirely on the fundraising efforts of our supporters and unrestricted educational grants from a range of pharmaceutical companies.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: We do not have any links with the tobacco industry.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

"Myeloma creeps up on you, engulfs you, and if you win the battle, leaves you wondering when it will come back."

Myeloma is an incurable and complex cancer originating from abnormal plasma cells in the bone marrow. There is currently no cure, but treatment can halt its progress and improve quality of life.

Due to increasing treatment options, survival in myeloma has improved greatly, but it remains a challenging cancer to treat with high mortality rates. There is an urgent and continual need for new treatments to ensure that patient survival rates keep improving.

Myeloma is a highly individual, relapsing and remitting cancer which evolves over time and becomes resistant to treatment. This takes a considerable toll on patients' physical and emotional wellbeing and can be particularly acute for the relapsed and refractory patient population, eligible to receive daratumumab as a monotherapy. Patients report an increasing sense of despair and resignation as they experience repeated relapses and see their treatment options reduce.

The complications of myeloma can be significant, debilitating and painful and include: severe bone pain, bone destruction, kidney damage, fatigue and a depleted immune system. Given the non-specificity of symptoms, research highlights that myeloma patients are more likely to be diagnosed late and often present in secondary care with bone lesions, fractures and in the worst cases collapsed vertebrae. This compounds the distress of their diagnosis,

presents treatment challenges and impacts negatively on pain levels, mobility and their ability to complete everyday tasks.

Treatment side-effects and frequent hospital visits can have a social and practical impact on patients' lives, including significant financial implications. Reduction in mobility over time and a perceived increase in reliance on carers and family members, also impacts on patients' sense of control.

Impact on myeloma carers

"*Everybody is affected and just because we don't have the illness doesn't mean our lives are not just as much turned upside down."*

A recent Myeloma UK study[1] into the experiences of carers and family members found that looking after someone with myeloma has a significant emotional, social and practical impact.

- Carers and family members can carry a heavy emotional burden: 94 percent of carers reported that caring impacted on their emotional life; 84 per cent always put the needs of their relative or friend with myeloma before their own; and 52 per cent of all carers find emotional support the hardest type of support to give. "*You're trying to support them and your heart's breaking too"*

- Carers' lives can change dramatically because of their caring responsibilities: 60 per cent of carers reported that their social life had changed for the worse and 25 per cent of those in work had been unable to work or had to retire early to care for the person with myeloma. *"I feel angry that I'm not going to get the future I wanted, but the hardest thing to feel is how my life at the moment is in limbo"*

- The impact of myeloma on the well-being of carers is often overlooked; 42 per cent of carers were not given enough information at diagnosis about how myeloma may affect them and only 6 per cent of carers are asked how they are by healthcare professionals when attending appointments with their relative or friend

Living with myeloma is therefore often extremely challenging emotionally and physically for patients, carers and family members. The negative impact of myeloma can be particularly acute for patients and carers in the relapsed and refractory setting. However, even multiply relapsed myeloma patients can have durable and deep responses to treatment and can experience good quality of life and meaningful extended survival – if they have access to new, effective and innovative treatments.

[1] The study, conducted between May and June 2016, was designed with the input of carers and involved a survey of 374 carers and a second stage of interviews to explore issues in more depth.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Through our regular programme of health services research, Myeloma UK continually asks patients about what they value from new treatments. In addition, to inform our response to this NICE appraisal Myeloma UK conducted a number of informal interviews with patients about what it would mean to them to have daratumumab approved in this setting.

Myeloma patients and their carers place a very high value on treatments that put their myeloma into remission for a long time and prolong their life. It is also very important to them that treatments allow them to enjoy normal day-to-day life doing the things they enjoy.

In particular, patients and carers tell us:

- Treatment outcomes they value most are those to do with length and quality of life, including progression free (PFS) and overall survival (OS). This is incredibly important to multiply relapsed patients, enabling them to spend more quality time with loved ones. *"Daratumumab gives you time and it gives you hope."*

- They want treatments that increase remission (i.e. disease free periods) for the longest possible time and reduce their paraprotein to stable or non-detectable levels. Effectively controlling patients' myeloma improves quality of life for patients, and also reduces the impact on carers. "*For me getting the myeloma under control is the most important thing. I think it is for many people"*

- Treatments with minimal negative impact on quality of life are very important, particularly those with as few side effects as possible and of low severity. Again, this is of particular importance to this patient population who may suffer from the cumulative effects of previous treatments

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Given that daratumumab would be prescribed after patients had shown disease progression on treatment with a proteasome inhibitor and an immunomodulatory agent, it would be given after Velcade and Revlimid. Depending on final NICE guidance, our understanding is that it would also be likely to be prescribed following pomalidomide; particularly because, as a monotherapy, its single agent action would be of benefit in heavily pretreated patients.

However, the individual and heterogeneous nature of myeloma means that it is difficult to compare treatments in head-to-head terms as some patients may tolerate a treatment well and others may not.

It is therefore essential to have a range of treatments and treatment combinations available to ensure that doctors can treat myeloma flexibly and improve outcomes.

There are limited treatment options available to patients in this setting who may have received several prior lines of treatment and become refractory to key “backbone” myeloma treatments – including a proteasome inhibitor and immunomodulatory agent.

There is a continuous need to develop and bring new drugs and drug combinations to market that prolong progression-free and overall survival in myeloma. There is also a need to use NICE approved treatment in increasingly innovative ways.

Below we cover our experience of each of the comparators mentioned in the final scope for the appraisal. We cover the advantages and disadvantages of each. We cannot state which are preferred by patients, as this varies on a patient-by-patient basis.

Revlimid® (lenalidomide) with dexamethasone

Myeloma doctors in England and Wales are used to prescribing Revlimid for patients at third line (second relapse) (TA 171), having received NICE approval in 2009. Whilst only approved by NICE for use in this setting, it is known to be an effective treatment in all stages of myeloma and is largely well tolerated.

Whilst Revlimid plus dexamethasone is listed as a comparator in the final scope of the appraisal, we do not think it should be considered a comparator as patients will have previously received treatment with and shown disease progression on this combination.

Farydak® (panobinostat) in combination with Velcade® (bortezomib) and dexamethasone

NICE guidance (TA380) recommends Farydak in combination with Velcade and dexamethasone as an option for treating relapsed or refractory myeloma patients who have received at least two prior regimens, including Velcade and an immunomodulatory agent.

Advantages

A major advantage of Farydak is that it offers an entirely new mechanism of action to other treatments that are approved for use in the disease. Adding drugs with new mechanisms of action into treatment combinations can help to treat underlying myeloma clones, improving a patient’s response to treatment.

Published data has also highlighted that patients who have become refractory to Velcade, are able to respond again when it is given in combination with panobinostat.

Patients report that it improves symptoms associated with myeloma and their quality of life in the longer term and that the oral formulation is easy and convenient to take (although Velcade is administered subcutaneously or intravenously and requires hospital visits).

Disadvantages

The main disadvantage of the Farydak combination treatment is gastrointestinal problems, in particular diarrhoea. Other side effects include neuropathy, fatigue, low blood counts and nausea. However, patients and doctors report that these have been adequately managed through communication and supportive care.

Imnovid® (pomalidomide) in combination with dexamethasone

We are currently awaiting a decision from NICE in relation to the appraisal of Imnovid for patients who have received prior treatment with both bortezomib and Revlimid. It specifically relates to patients who have become refractory to their last treatment, which is usually Revlimid. We understand that in practice, daratumumab would be likely to be used after pomalidomide, but for completeness we have recorded patients' experience of its advantages and disadvantages.

Advantages

Until recently, myeloma patients were able to receive Imnovid on the NHS via the CDF. Given there are relatively few treatment options available for this stage in myeloma, Imnovid did reach an unmet need for multiply relapsed patients. Patients and doctors report it is well tolerated in the majority of patients and has a good anti-myeloma affect.

Compared to other IMiDs, pomalidomide has a reduced side-effect profile. This is beneficial to multiply relapsed patients in general and would be particularly welcome for patients who experience the cumulative effect of previous treatments on their body.

Disadvantages

As patients eligible for pomalidomide are multiply relapsed, some will have a very poor prognosis and issues relating to quality of life from previous lines of treatment. There is a risk that even minor side-effects will have a big impact in this group of patients if treated with pomalidomide.

Poor patient experience on treatments can be negated by appropriate clinician decision-making to determine which patients are likely to have a good outcome from pomalidomide treatment and trial evidence suggests that side-effects can be reduced with effective dose moderation.

As with all myeloma treatments, due to the individual and complex nature of the disease not all patients will respond well to pomalidomide. However, it is important that pomalidomide is made available to allow clinicians the flexibility to prescribe pomalidomide to patients they think will benefit clinically.

Bendamustine

Bendamustine is only routinely approved for myeloma patients living in England and is usually prescribed in combination with thalidomide and dexamethasone. In Wales, bendamustine is only available via an individual patient funding request.

Advantages

Usually bendamustine is used in multiply relapsed patients where approved treatment options are nearly exhausted, bendamustine offers patients a further treatment option with a good anti-myeloma effect, particularly when given in combination with thalidomide and dexamethasone.

It also offers a different mechanism of action to other alkylating agents.

Disadvantages

Whilst effective in some patients, bendamustine has a big impact on the bone marrow in patients. As it is given in a heavily pre-treated population, some patients will not be able to receive it given that they may be immunosuppressed.

Conventional chemotherapy options

Whilst these are not included in the official list of comparators, these may be used following patients exhausting NHS approved treatment options and consist of a range of different options, including melphalan, cyclophosphamide and other treatments such as DTPACE and ESHAP. Unlike daratumumab, these types of chemotherapy are used in the “salvage setting” and there is no one standard chemotherapy option. Decisions usually come down to doctor preference and the patient’s previous exposure and response to anti-myeloma treatment. Treatment outcomes in the salvage setting are not associated with long-term outcomes and given the toxicities associated with some treatments and the heavily pre-treated nature of the patient population, they often have a poor impact on quality of life.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Myeloma UK, patients and carers agree that access to daratumumab would improve the treatment pathway of patients in England and Wales. Daratumumab:

- **Prolongs life.** Daratumumab has been shown to give an additional overall survival of almost 18 months; an incredibly important benefit to multiply relapsed patients, enabling them to spend more time with loved ones. *"I am all about survival. Where there is longevity there is hope."*

- **Treats underlying disease, thereby addressing symptoms and preventing complications.** Effectively controlling myeloma prevents the progressive damage that it does to the body, leading to complications such as bone fractures and renal impairment. This has a positive impact on quality of life enabling patients to take part in day to day activities they enjoy and find fulfilling. "*Just knowing a treatment is working and you're not hitting that brick wall and seeing your condition deteriorate; that really helps"*

- **Addresses an unmet need.** Daratumumab is effective in patients who are refractory to all other available treatments. It offers a lifeline for patients who have exhausted all other NICE approved treatments and have no other option which can effectively treat their myeloma. It enables doctors to treat patients on a more personalised basis. *"It is so encouraging that it is successful for people with limited options"*

- **Is well tolerated**. It is extremely well tolerated and can deliver major benefits over other treatments in terms of its side-effect profile. It also demonstrates good responses in patients as a monotherapy, which is rare in myeloma and is also associated with lesser side-effects. This is very important to patients who are heavily pre-treated, for whom cumulative toxicities are a concern. *"Daratumumab feels like a much 'cleaner' treatment than anything else I've been on. You really do feel it's less toxic, you feel better in yourself"*

- **Improves emotional wellbeing.** Patients often feel an increasing sense of despair on each relapse; this is particularly acute for this patient population who may have to face the fact that there are no other treatments out there for them. Knowing an effective treatment, with a good survival benefit, is available at this stage is very important psychologically – not just for this patient population but for all myeloma patients. "*Given that treatments at this stage can be so limited it was a boost psychologically to get daratumumab"*

- **Is innovative.** As a first-in-class monoclonal antibody, daratumumab is a highly innovative development. The myeloma community is extremely hopeful and excited about the potential of immunotherapies. It is very important that this innovation is made widely available for patients. *"It is an innovative treatment. You never know when a new treatment might be the one – that is what we are all looking and striving for"*

These benefits also apply to carers and family members, for example:

- Improved psychological and emotional wellbeing knowing that the patient has effective treatment options

- Alleviation of symptoms and prevention of complications enables patients to be more independent and reduces day-to-day reliance on carers

- A good side-effect profile improves quality of life and improves patients' ability to live a fuller life, participating in and enjoying more activities with family and friends

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

Not applicable.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Please list any concerns patients or carers have about the treatment being appraised.

Giving the treatment by IV infusion does mean taking time out of the day to attend hospital and may involve an overnight stay for the first infusion, due to a risk of infusion-related reactions. (The risk of reactions reduces significantly after the first infusion.) For some patients there are cost/capability issues associated with this and it may lead to anxiety issues. In addition, it can place an additional burden on carers who have to accompany the patient to hospital.

However, in a patient survey we found that views are fairly evenly divided on the advantages and disadvantages of oral treatments (taken at home) and IV subcutaneous treatments. Some patients actively prefer the safety and community of the hospital setting, being reassured by interaction with health care professionals while having their treatment administered.

Infusion related reactions of low severity occur in a relatively high percentage of patients on first infusion, but patients we interviewed said that they had been warned in advance and that any reactions were dealt with swiftly and professionally by clinical staff. It did not dissuade patients from continuing with the treatment. Patients saw receiving infusions as a small price to pay for the benefits that daratumumab could deliver when their treatment options are limited.

> *"I did have a reaction to my first infusion but the specialist nurses were brilliant."*

> *"My reaction happened after the first hour. It was quite scary at the time but it helped a lot to have been forewarned and I was well monitored. The main thing is I am glad that my myeloma is under control and not progressing."*

> *"I don't have a problem with infusions. Would you prefer to go for an infusion once a month or be dead? That's a normal decision for me and it's an easy one to make."*

Like all myeloma drugs in the relapsed setting, particularly given the heavily pretreated population, not all patients will achieve a good response to daratumumab. There is a chance that multiply relapsed patients will have a compromised immune system which could reduce the effectiveness of the treatment. This is negated through appropriate patient selection by myeloma clinicians.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Not applicable.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Not applicable.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Not applicable.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐X Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

We currently are not in a position to answer this question with specific reference to daratumumab since it has not been available to patients outside a clinical trial setting.

However, from our general experience, myeloma patients do better on treatments outside of the clinical trial setting. For example, adjusting dosage for patients who experience severe side-effects is easier in clinical practice than in trials.

> "*My main issue with taking daratumumab is that I am in a long-term trial and it is frustrating not to be able to cut down on other drugs. I am starting to get increased side effects from those drugs."*

Patients we spoke to also commented that if daratumumab were available on the NHS then hospital visits to receive infusions would be more convenient since their treatment would be delivered locally.

> *"One major benefit of making it available on the NHS is that patients won't have to travel to receive it. If I could get it at my local hospital that would be a real benefit."*

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

We are not aware of any limitations in how the treatment has been assessed in clinical trials. Clearly this is a Phase II trial and therefore does not include the comparator or quality of life data that would be part of a Phase III trial. However, we believe that that the quality of the Phase II data, particularly given daratumumab's innovative mechanism of action, is sufficient to demonstrate meaningful clinical benefit for this patient population for whom, in practice, there may be no other active treatment option. This appraisal is a good example of how the drug approval process can evolve to deliver faster access to the most promising treatments.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not applicable

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

X Yes ☐ No

If yes, please provide references to the relevant studies.

Muhlbacker et al. Evaluating patients' preference for multiple myeloma therapy, a Discrete Choice Experiment (2008)

Raven D et al. Comparison of generic, condition-specific and mapped health state utility values for multiple myeloma (2012)

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Not applicable.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Not applicable.

9. Other issues

Do you consider the treatment to be innovative?

X Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

As a first-in-class monoclonal antibody, daratumumab, is a highly innovative effective new treatment with a new mechanism of action. This is particularly significant given that myeloma is a relapsing and remitting cancer which evolves and becomes resistant to treatment. Patients who are refractory to all other existing standard treatments could have deep and durable responses to daratumumab, since its mechanism of action harnesses the body's own immune system in a way that is entirely different to all other standard treatments. It has also demonstrated strong responses as a monotherapy, which is unusual in myeloma and of benefit in reducing toxicities for a heavily pretreated patient population.

"Daratumumab has given me a psychological boost because it is the treatment of the future."

Are there any other issues that you would like the Appraisal Committee to consider?

No.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Myeloma is a highly individual, relapsing and remitting cancer which evolves and becomes resistant to treatment and it is therefore particularly important that there are a range of treatments available at all stages of the disease pathway
- As a first-in-class monoclonal antibody daratumumab is a highly innovative development in the exciting field of immunotherapy. It is important, given the efficacy that has been demonstrated, that this innovation is made widely available for patients
- Treatment options for this patient population are extremely limited and daratumumab therefore addresses a significant area of unmet need
- Adding another treatment option to the pathway, particularly with such a new and innovative mechanism of action, increases doctors' ability to provide treatment suited to the patient's individual circumstances and helps alleviate the psychological burden of patients who are refractory to other treatments. This also improves the emotional well-being of myeloma carers and family members
- Daratumumab delivers patient responses and survival benefit in a heavily pretreated, refractory patient population and is well tolerated; an important benefit in this patient population who may be unwell and suffering from cumulative toxicities

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation:UK Myeloma Forum
Are you (tick all that apply):

- other? (please specify)
- Healthcare professional / Consultant Haematologist / Advocacy Lead UK Myeloma Forum

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: Nil

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933]

What is the expected place of the technology in current practice?
This is the first monoclonal antibody with significant anti-myeloma effect. It is considered a game changing therapy with significant activity in extremely heavily pre-treated patients and has had a rapid approval pathway in both the USA and Europe as a result of its obvious efficacy. Myeloma patients who relapse after 3 lines of therapy that usually includes bortezomib, thalidomide and lenalidomide have a dire prognosis. Overall survival was observed to be 6 -12 months in this group of patients. There is therefore an unmet need for relapsed and refractory myeloma patients.
The place of the technology reflects the marketing authorisation for patients with relapsed and refractory myeloma who have previously been treated with a proteasome inhibitor and an immunomodulatory agent. According to the current NICE approved "pathway" patients are eligible to receive bortezomib based treatment at 1st line therapy and 2nd line therapy (TA129) and lenalidomide / dexamethasone or bortezomib / panobinostat / dexamethasone therapy as 3rd line treatment (TA380). In practice lenalidomide / dexamethasone is more likely to be used at 3rd line than panobinostat / bortezomib / dex (PVd) due to improved efficacy and reduced toxicity with lenalidomide / dexamethasone for most patients. The technology would be considered a treatment option at 4th line therapy and beyond ie. Following progression on or after lenalidomide. PVd is the only NICE approved choice at this stage of the pathway but is not suitable for all patients due to prior lack of response or excessive toxicity experience with previous bortezomib therapy.

We note the suggestion of lenalidomide / dexamethasone as a comparator. This would be inappropriate as the technology is aimed for treatment beyond 3rd line therapy. We also note that Bendamustine, although available on the CDF, is currently authorised (on CDF) as a last line therapy and that there is no specific suggested combination treatment. There is an acknowledged paucity of data for bendamustine efficacy in this setting. It should also be noted that the evidence underpinning approval of PVd for >2 prior lines of therapy is based on a much less heavily treated patient group than that described in the daratumumab monotherapy trials. PVd would be considered a suitable comparator. Pomalidomide / dexamethasone if approved by NICE would be a suitable comparator.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933]

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

This technology is administered as an intravenous infusion. It can be given in the outpatient setting but necessitates hospital attendance for treatment (e.g. to chemotherapy day unit). Treatment is initially given weekly for 8 weeks, fortnightly for 16 weeks then monthly. In common with many other monoclonal antibody therapies there is the potential for first dose infusion related reactions (48%), these are unlikely to recur with subsequent doses. Pre-medication is required and the first infusion may last up to 8 hours. Subsequent infusions are shorter. All concomitant mediations are standard generic drugs. There are no additional clinical requirements. Exposure to daratumumab can interfere with blood transfusion testing and pre-treatment transfusion panel testing is required. There are no other disadvantages to the therapy. In practice following the first infusion subsequent infusions are straightforward with few drug associated adverse events.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

There are no identified patient subgroups more or less likely to respond to treatment. Response assessment is a standard aspect of myeloma monitoring / treatment and is not additional. It is noted that having stable disease is associated with significant overall survival benefit. The major stopping rules would be severe infusion related reactions (extremely uncommon) or progressive disease on therapy.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Patient overall survival following relapse after bortezomib and lenalidomide is extremely poor and was reported in both UK and international studies to be 6-12 months. A median of 4 prior lines of therapy was reported in the daratumumab supportive evidence but with 55% of patients having had pomalidomide exposure and 40% of patients having had carfilzomib exposure (neither of these drugs are

available outside of the clinical trial context in the UK) in addition to bortezomib / lenalidomide / thalidomide. The reported population is therefore much heavier pre-treated group than the proposed UK population. In common with most clinical trials for relapsed / refractory myeloma the median age of 64y at entry is younger than the median age at diagnosis for myeloma in the UK the range of patients treated did however extend up to 84y. It is unlikely that the younger age leads to a positive bias in terms of reporting compared with expected UK patient response. Otherwise the reported data reflects the UK population.
The most important outcomes measured are both the effects on progression free survival but more significantly the dramatic improvements seen on overall survival even in those patients with stable disease or minimal response. This is unprecedented in the relapsed / refractory myeloma setting and suggests a clinically beneficial effect in most treated patients. The reported overall survival rates are far in excess of those expected for such a heavily pre-treated patient group. UK experience with daratumumab monotherapy via the compassionate use programme and MMY3010 Expanded Access programme is anecdotally associated with a similar effect.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

As discussed above the main adverse reaction is infusion related reaction. This occurs in 48% of 1st dose patients. It is manageable by altering rate and length of infusion and is rarely associated with cessation of therapy. Reactions with subsequent infusions occurs in <5% of patients at 2nd or 3rd dose. Infusion reactions appear to be the only major adverse event attributable to daratumumab and are manageable. No additional adverse effects have come to light subsequent to these trials.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933]

Nil

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

There are many monoclonal antibodies in clinical practice and a similar approach to infusions is required for Daratumumab. No additional resource for staff or training, facilities or equipment would be needed.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Nil

NHS England submission for the NICE appraisal of daratumumab in the treatment of myeloma February 2017

1. Daratumumab has a marketing authorisation (MA) as monotherapy in adults with relapsed/refractory myeloma whose prior therapy has included both a proteasome inhibitor and an immunomodulatory agent and who have demonstrated progressive disease on their last treatment.

2. The evidence base for the benefit and toxicity of single agent daratumumab that led to it gaining a MA comes from 2 open label and in effect phase 2 studies, MMY2002 and GEN501.

   MMY2002 study

3. The main part of MMY2002 is a 106 patient study in which the all following criteria were satisfied: patients had to have responded to at least one previous regimen; previous treatment had to include an alkylating agent, alone or in combination; patients had to either have received at least 3 lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (iMiD) or be doubly refractory to a PI and an iMiD; and patients had to be of performance status (PS) 0-2.

4. Patients in MMY2002 had the following characteristics:
   - Median time since diagnosis of 5.2 years
   - PS 0 27%, PS 1 65% and PS 2 8%
   - ≤3 lines of treatment in 18%, >3 lines of treatment in 82%
   - The median number of lines of treatment was 5
   - 80% of patients had previous high dose chemotherapy and autologous stem cell transplantation
   - Prior bortezomib treatment was in 99%
   - Prior lenalidomide therapy was in 99%
   - Prior thalidomide treatment was in 47%
   - Prior pomalidomide therapy was in 63%
   - Prior carfilzomib treatment was in 50%
   - Refractoriness to last line of treatment was in 97%
   - 95% were refractory to both a PI and an iMiD (82% were refractory to both bortezomib and lenalidomide)
   - 77% were refractory to an alkylating agent, 63% to pomalidomide and 48% to carfilzomib.

5. The median duration of follow-up in MMY2002 was 14.7 mo. The overall response rate was the primary endpoint and was 29%. The median duration of response was

7.4 mo. The median progression free survival (PFS) was 3.7 mo (73/106 events) and the median overall survival (OS) was 17.5 mo (47/106 events). At an analysis 6 months later, the median duration of OS was 18.6 mo.

6. In terms of subsequent systemic therapies after daratumumab in MMY2002, 71% of patients are reported to have received further treatment with the present durations of follow-up: 32% with pomalidomide, 31% with cyclophosphamide, 29% with carfilzomib, 26% with bortezomib and 8% with lenalidomide. The fact that 95% had disease that had previously been refractory to both a PI and an iMiD yet further treatment with a PI and an iMiD was being used reflects the fitness and motivation of this population of patients. Of additional note is that the overall response rate to these further post-daratumumuab therapies was 40%, a figure which compares with the 29% achieved with daratumumab itself. This noteworthy response rate to post-daratumumab treatment can thus safely be assumed to have had a significant effect on the OS of the trial population in MMY2002.

<u>GEN501 study</u>

7. The main part of the second study (GEN501) is a 42 patient trial in which the following criteria had to be met: patients had to have relapsed/refractory myeloma to 2 or more different prior therapies which included a PI, an iMiD, conventional doses of chemotherapy and high dose treatment; patients had to be of performance status (PS) 0-2; and patients had to be without further established treatment options in the countries concerned (this latter criterion is stated in the company's submission on p66 but is not mentioned in the NEJM publication of the GEN501 study).

8. Patients in GEN501 had the following characteristics:
   - Median time since diagnosis of 5.8 years
   - PS 0 29%, PS 1 67% and PS 2 5%
   - ≤3 lines of treatment in 38%, >3 lines of treatment in 62%
   - The median number of lines of treatment was 4
   - 74% of patients had previous high dose chemotherapy and autologous stem cell transplantation
   - Prior bortezomib treatment was in 100%
   - Prior lenalidomide therapy was in 95%
   - Prior thalidomide treatment was in 45%
   - Prior pomalidomide therapy was in 36%
   - Prior carfilzomib treatment was in 19%
   - Refractoriness to last line of treatment was in 76% (Of note is that this requirement for refractoriness to the last line of treatment is in the MA)
   - 64% were refractory to both a PI and an iMiD

- 60% were refractory to an alkylating agent, 30% to pomalidomide and 17% to carfilzomib.

9. The median duration of follow-up in GEN501 was 15.2 mo. The overall response rate was the primary endpoint and was 36%. The median duration of response was not estimable (95% CI 5.5 mo to not estimable), the median progression free survival (PFS) was 6.2 mo (27 /42 events) and the median overall survival (OS) was not estimable (95% CI 18.7 mo to not estimable) [16/42 events].

10. In terms of subsequent systemic therapies after daratumumab in GEN501, 76% of patients are reported to have received further treatment with the present duration of follow-up: 38% with pomalidomide, 33% with cyclophosphamide, 26% with carfilzomib, 21% with bortezomib and 36% with lenalidomide. These treatments occurred despite the company stating that the clinical trial stipulated that there were no further treatment options prior to entry into the study (p66 of the company's submission although this criterion is not mentioned in the NEJM publication of GEN501). Of additional note is that the overall response rate to these further therapies was 38%, a figure which compares with the 36% achieved with daratumumab itself. This noteworthy post-daratumumab response rate can thus be safely assumed to have had a significant effect on the OS of the trial population.

Toxicities of daratumumab

11. The main toxicities of daratumumab were infusion reactions, fatigue, pyrexia, cough, nausea, infections, anaemia (grade 3/4 in 17%), neutropenia (grade 3/4 in 12%) and thrombocytopenia (grade 3/4 in 14%). Daratumumab can interfere with Indirect Coomb's tests and thus may mask detection of antibodies to minor antigens (of relevance particularly for blood transfusions). As daratumumab is a human igG Kappa antibody, it can interfere with estimations of myeloma protein levels in patients with IgG Kappa myeloma. NHS England regards daratumumab as being a generally well tolerated treatment by patients although its frequency of administration (weekly for 8 weeks, 2-weekly for 16 weeks and then monthly) imposes significant burdens on patients and NHS treatment facilities.

Conclusion on efficacy and toxicity of daratumumab

12. NHS England concludes that the (in effect) phase 2 trials of daratumumab have shown modest efficacy in myeloma with a response rate of about 30%, a relatively short median PFS but nevertheless a noteworthy median OS. The follow-up is still immature in both MMY2002 and GEN501 studies for OS but also to a lesser extent for treatment duration. Toxicity is tolerable. NHS England notes the high rates of subsequent treatments in both studies and is thus aware that the median OS could just reflect a high degree of selection and motivation of patients recruited into these

studies ie there is a significant contribution to the duration of OS from these post-daratumumab treatments. It is also possible that the relationship between modest median PFS figures and the effect on OS in these groups of patients may be an effect of the daratumumab but the former explanation as to patient selection is highly likely to be playing a significant part. In conclusion, the relatively small numbers of patients treated in these 2 studies, the immaturity of these trials and the post-daratumumab therapies (see later) result in caution in NHS England's interpretation as to how assuredly these results can be expected to translate into benefits to NHS patients.

Myeloma treatment pathway and comparators for relapsed/refractory disease

13. NHS England notes that the EPAR for daratumumab states that pomalidomide and panobinostat are in the same position in the myeloma treatment pathway (ie for patients with relapsed/refractory disease with at least 2 previous treatments including bortezomib and an iMiD). However these two drugs (unlike daratumumab) have no stipulation in their MAs as to their use necessitating disease progression on the immediately previous therapy. The daratumumab EPAR also notes that carfilzomib (currently undergoing NICE appraisal) and elotuzumab (licensed but NICE appraisal deferred to 2018) have marketing authorisations in the 1-prior group of patients. The EPAR thus concludes that because the MA for daratumumab includes the stipulation that patients must have had a PI and an iMiD and progressed on their last therapy, this places daratumumab alongside the options of treatment of physician's choice and palliative care. Despite this positioning in the myeloma treatment pathway by the EMA, the further clinical evidence for daratumumab that the EMA wishes to see is in the form of the results of 2 RCTs which randomise daratumuab with or without lenalidomide plus dexamethasone in one study and daratumumab with or without bortezomib plus dexamethasone in the second trial.

14. NHS however regards the use of daratumumab to be in the same potential place in the myeloma treatment pathway as pomalidomide plus dexamethasone and the 3-drug combination of panobinostat, bortezomib and dexamethasone. Bendamustine is currently available via the CDF as an option when all other treatments have failed. NHS England does not regard bendamustine as being a standard of care in myeloma until its funding comes from NHS baseline commissioning. Bendamustine is being used off-label in the CDF for this last-line indication and thus the issue as to potential funding from baseline commissioning will be addressed via the policy prioritisation process in NHS England Specialised Commissioning. In conclusion, NHS England regards the correct comparators for daratumumab in this appraisal as being pomalidomide plus dexamethasone and panobinostat in combination with bortezomib and dexamethasone.

15. NHS England is wary of the numerical specification of the number of lines of treatment. The myeloma treatment pathway is increasingly complex and shifting eg bortezomib was originally both NICE-approved and regarded as '2nd-line' and lenalidomide similarly as '3rd-line'. However, bortezomib now has NICE-approved indications in some 1st-line indications which apply to some but not all patients. NHS England understands the clinical view that in some patients this would shift the use of lenalidomide forward to '2nd-line' treatment (this use is currently being appraised by NICE). It is also aware of carfilzomib currently undergoing NICE appraisal as potential options in the '2nd-line' and '3rd-line' slots. NHS England thus regards it as being more helpful to address the myeloma treatment pathway in terms of previous treatment received, the response to such treatment and past and future treatment-limiting toxicities. Other relevant issues relate to whether treatment was continued to progression or planned to be a defined course of therapy (ie in those patients who are transplant-eligible in which induction treatment is relatively brief) and also whether patients are primarily refractory to previous treatment(s). Once the present flurry of myeloma appraisals is complete, NHS England plans to rationalise all the above issues into a set of myeloma treatment algorithms and commission with them accordingly.

<u>Pooling of MMY2002 and GEN501 analyses</u>

16. NHS England is very circumspect of the pooled analysis of MMY2002 and GEN501 presented by the company. NHS England regards these populations as being different. The populations entered into these 2 studies differ as shown below, MMY2002 figures being first:
    - Median time since diagnosis of 5.2 years vs 5.8 years – despite the greater lines of treatment in MMY2002, patients in this study had a shorter OS duration prior to daratumumab
    - ≤3 lines of treatment 18% vs 38%, >3 lines of treatment 82% vs 62%
    - The median number of lines of treatment was 5 vs 4 ie it is clear that MMY2002 had received more treatment than those in GEN5001
    - Prior pomalidomide was 63% vs 36%
    - Prior carfilzomib was in 50% vs 19%
    - 95% were refractory to a PI and an iMiD in MMY2002 vs 64% in GEN501
    - Refractoriness to PI and an iMiD and an alkylator was observed in 75% in MMY2002 and 50% in GEN501
    - 77% vs 60% were refractory to an alkylating agent, 63% vs 30% to pomalidomide and 48% vs17% to carfilzomib.

    - Thus MMY2002 had a greater proportion of patients treated with drugs potentially positioned before daratumumab (carfilzomib) or in the same place in the treatment pathway (pomalidomide). Since the MA for daratumumab

requires patients to have progressed on their last line of treatment received, it is more likely that daratumumab will be used after pomalidomide, especially because patients in general prefer oral regimens with fewer visits to clinic (eg 6 visits for treatment in the first 6 months for pomalidomide vs 16 visits for treatment in 6 months for intravenous daratumumab with its need for slower infusions at the start of a course of treatment).

- In addition, the MA requires the patient receiving daratumumab to be refractory to the previous line of treatment; this was observed in 97% of patients in MMY2002 but only 76% in GEN501. This and all the above reasons point to the dangers of the pooled analysis of the MMY2002 and GEN501 studies and that NHS England believes that the MMY2002 study offers the patient characteristics that best correspond with the MA.

<u>Indirect comparison between MMY2002 and other trials</u>

17. In an appraisal of a drug which has a very substantial potential budget impact and in which the current evidence base relies entirely on immature single-arm studies of very modest size, NHS England would wish NICE to be assured that the indirect comparisons necessary for the assessments of clinical cost effectiveness are robust and of the highest quality.

<u>Subsequent treatments after daratumumab in MMY2002 and GEN501</u>

18. NHS England wishes to further comment on the subsequent treatments received by patients in the MMY2002 and GEN501 studies after daratumumab. Pomalidomide is recommended by NICE and there is no biological implausibility as to why pomalidomide would not be active after daratumumab (32% of MMY2002 and 38% of GEN501 received pomalidomide). There would therefore be no need to adjust for OS for pomalidomide use. Carfilzomib is currently being appraised but in the absence of an as yet positive recommendation by NICE, it would be appropriate for NICE to at least see a scenario analysis in which an adjustment is made for removal of the OS benefit from use of carfilzomib (as 29% of MMY2002 and 26% of GEN501 received carfilzomib). The use of post-daratumumab bortezomib (26% in MMY2002) and lenalidomide (8% in MMY2002), even though 82% were refractory to both agents prior to daratumumab, reflects that some of these patients must have stopped these drugs previously because of toxicity but also demonstrates their fitness and motivation. The use of post-daratumumab bortezomib (21% in GEN501) and lenalidomide (36% in GEN501), presumably reflects that these patients stopped these agents on account of toxicity. Given that both bortezomib and lenalidomide are not commissioned by NHSE in this even late place in the treatment pathway, adjustment for their benefits in terms of OS would be appropriate.

<u>Other comments</u>

19. NHS England is unaware of any published evidence to suggest that the toxicity profile of daratumumab is one which allows more subsequen treatments to be given. NHS England regards the most plausible explanation for this in terms of MMY2002 and GEN501 is the fitness and motivation of the patients entered into these clinical trials.

20. NHS England is unaware of any published evidence to indicate that previous treatment with daratumumab increases the likelihood of a response to subsequent treatments.

21. NHS England does not regard the impact of daratumumab as assessed on the current evidence base to be a step change in the management of myeloma. The response rate is modest, the median PFS duration is relatively short, the toxicity is significant and the evidence so far is immature and based on single arm studies.

[redacted]

[redacted]

February 2017

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by **UK Myeloma Forum** and consequently I will not be submitting a personal statement.

Name: Dr. Jonty Ancroft

Signed: [redacted]

Date: 9/1/17

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma ID933

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:
Dr Cathy Williams

Name of your organisation
Centre for Clinical Haematology, Nottingham University Hospitals

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NONE

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Multiple Myeloma is a malignant blood disorder characterised by the presence of Myeloma cells (also called plasma cells) in the bone marrow. Through various mechanisms they cause symptoms such as anaemia, recurrent infections, bone pain and fractures and kidney dysfunction. The disease is very heterogeneous in that it may present in different ways in different patients, with each having differing degrees of end organ damage. Cytogenetics can also be abnormal in about a quarter of patients with 17p- or t(4:14) signifying high risk disease with a shorter prognosis.

The condition is treatable but not curable and the aim of therapy is to control the varying myeloma clones for as long as possible during the course of the disease using a variety of anti-cancer agents. This results in periods of remission and subsequent relapses. The median survival is 5 years.

Current practice in the UK in the treatment for multiple myeloma has been largely driven by the clinical trials available (e.g. Myeloma XI), the results of these and which therapies have subsequently been funded. There is a general consensus amongst clinicians and minimal geographical variation within the first 2 to 3 lines of therapy – agents used include immunomodulatory drugs (thalidomide, lenalidomide), proteasome inhibitors (bortezomib) and steroids. Patients are considered for an autologous stem cell transplant as part of first line therapy and again at first relapse if fit enough.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The variation in treatment practice tends to become apparent, both by clinician and geographically, at the point at which the patients have received and relapsed from both bortezomib and lenalidomide. This would normally be at 4th line therapy. There is no standard of care at this point and several options are available. This is where Daratumamab monotherapy would fit well in the treatment pathway.

Current alternatives to Daratumamab are as listed in the final scope document; the decision as to which of these to give will depend on certain aspects including the patient's performance status, comorbidities, disease characteristics and response to previous therapies. This will vary between patients. Some patients who have responded well to a particular type of treatment may do well with an alternate drug with the same mechanism of action whist others may not have responded to or relapsed quickly from all previous therapies. Also, most of the comparators can have significant side effects and are often not well tolerated. All need to be given with large doses of steroids which also cause morbidity.
The fact that the mechanism of action of Daratumamab is different to those therapies previously given, makes it a very logical choice as it will target the myeloma clone in a different way. Also it does not require high doses of steroid to be given alongside it and it is well tolerated with a minimal side effect profile; a huge factor to consider for patients.

I suspect most patients with relapsed myeloma would receive Daratumamab monotherapy as 4th line therapy if it were available. It would not be used outside of its licenced indications.

The decision to use Daratumamab would be taken by a consultant Haematologist in charge of the patients care after discussion in an MDT. It would need to be given in a hospital day-care setting where doctors and nurses have experience of both haematology patients and the administration of monoclonal antibodies. This could be in both district general and teaching hospitals. No extra professional input would be required other than the sufficient day-care nursing staff available to administer the Daratumamab and monitor the patient during this.

Daratumamab has only been available in the UK through clinical trials to date.
The NICE guideline on Myeloma: diagnosis and management (ng35) published 10 Feb 2016 does not mention its use it was not available at that time .

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The response rate of 29% with Daratumamab monotherapy seen in the main phase II clinical trial (MMY2002) in heavily pre-treated patients is impressive and compares favourably to alternate available treatments in this setting. As no direct comparison

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

has been made in the clinical trial setting between Daratumamab and these other treatments it is difficult to interpret but it does appear extremely effective.

Daratumamab has a well-tolerated side effect profile and does not cause many of the serious morbidities such as peripheral neuropathy (bortezomib), GI toxicity (bortezomib, panobinostat and lenalidomide) and thromboembolism (lenalidomide and pomalidomide) seen with the current alternatives. As such it is easier for patients to tolerate. Clinical trial data does report several side effects but the only ones reported as Grade 3 or higher in ≥ 5% of patients were anaemia (13%) and thrombocytopenia (9%).
There most common side effect seen within the clinical trials was an initial infusion reaction in 48% of subjects but this was generally mild and took the form of allergic rhinitis or a cough. This is usually manageable and does not recur with infusions thereafter.

Concomitant medications are limited to a small dose of steroids and antihistamine pre- and post-infusion. Daratumamab is given intravenously and therefore requires cannulation, a day –case chair and monitoring during this. The initial infusion can take up to 8 hours but by the 2nd or 3rd infusion this usually drops to 3-4 hours. The scheduling of treatment (weekly for the first 2 of the4-week cycles), then 2-weekly for Cycles 3-6 and monthly thereafter, is no more onerous on the patients than other comparator therapies that require regular clinic visits, and blood tests. The main issue will be the required increased availably of day-case facilities, chairs and nurses to administer the treatment.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

The rules for starting the technology should be as outlined in the final scope document alongside informed patient consent and a suitable setting for administering the treatment. Stopping would be at evidence of progressive disease as assessed by monthly blood tests and in line with International Myeloma Working Group (IMWG) criteria, or unacceptable toxicity or side-effects.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The evidence base for Daratumamab in this setting comes from 5 phase 1 and II trials, which were mainly undertaken in the USA. The circumstances of these trials does reflect the way in which it would be used in the UK – if anything the patients were more heavily pretreated in the trials than the patient group who would receive it in the UK. Hence one would expect the UK patients to fare at least as well.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The most important outcomes are achievement of response and survival. Stable disease or greater is actually a reasonable aim in this group of patients, although partial response and better is desirable. PFS is also important and was measured though follow up was short at this point. OS should also be looked at but requires longer follow up than is currently available.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The side effect profile and adverse reactions to this drug are limited and manageable. Having treated over 10 patients at our centre with Daratumamab the key feature, apart from response, is how well it is tolerated and how the patients' quality of life is significantly improved compared to previous therapies. The fatigue seen with most other treatments is not apparent and the fact that the enormous doses of steroids required to be given as part of all other comparative therapies is not needed with Daratumamab, has a huge impact. Side effects such as hypertension, glucose intolerance, mood swings and fluid retention see regularly with high doe dexamethasone are no longer a problem.
To date, I have not seen any adverse effects which differ from those mentioned in the clinical trials.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

I do not think any of these are the case

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Barry Neville
Name of your nominating organisation: Myeloma UK
Do you know if your nominating organisation has submitted a statement?

☒ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☒ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☒ Yes ☐ No

- a carer of a patient with the condition?

☐ Yes ☒ No

- a patient organisation employee or volunteer?

☐ Yes ☒ No

Do you have experience of the treatment being appraised?

☐ Yes ☒ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

Life is a continual juggling of conflicting perceptions and ambitions. I have gone through two rounds of treatment, during which I experienced some of the anticipated symptoms, either from the principal (Trial) drug or from one of the support drugs, especially dexamethasone. There have been days when I have not felt very well. There have been days when I have felt remarkably well.

I continually experience bone pain. This fluctuates in severity. It does not prevent me doing things, such as gardening, walking and domestic chores. These can set off more intensive pains. I have to rest. Sometimes I take co-codamol as a painkiller. For me, the worst aspect is that I sometimes have to be very circumspect when playing with my 3-year old grandson. My wife and I waited a long time for him. We will have no other grandchild. The emotional attachment is very strong. Generally, I take a risk that no damage will be done if I play with him at his pace. I worry that as he gets older, faster, fitter and heavier I will not be able to be the grandfather that he deserves

There is a deeper worry associated with him. I have an incurable cancer. I have done well so far but nonetheless face an uncertain future. I know that my time with him may be very limited. A drug with more certainty of a long remission, and which might reduce the cycle of relapse and remission, will be invaluable. I want to survive in good health for as long as possible and with a reduced emotional burden.

My life also tends to be dependent upon monthly blood test readings. Currently, I am slowly relapsing. Can I book a holiday with certainty? Can I become a committee member of my Probus Club again (I had to stand down at short notice five years ago)? If I have a third round of chemotherapy, what will its regime be? Where will it be? Will I have side effects?

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

A long remission before relapse/progression with some certainty that I will be able to ignore some of the issues raised under Q2. Along the way, during treatment, I would wish for a drug combination that was as free of adverse side effects as possible.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

I have been very fortunate in that my treatment, at Royal Berkshire Hospital and The Churchill, Oxford for Myeloma XI and at The Churchill for MUK5 has been excellent.

I tolerated both treatments well. There were more side effects with Myeloma XI – thalidomide arm – and my stem cell transplant was predictably unpleasant but well managed. I have had few problems with carfilzomib. Indeed, I have had a longer and deeper remission with my second round of treatment than my first. In both trials, the principal problem has been coping with the highs and lows of dexamethasone.

At present my myeloma is in remission and the next treatment option I am likely to receive is lenalidomide in line with NICE guidance. However, in the future I am likely to be eligible for daratumumab treatment to which I would greatly value access.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

From my understanding of daratumumab, I would expect to get a prolonged remission, with fewer side effects during treatment and a reduction in the underlying symptoms, particularly bone pain. This will hopefully reduce the emotional burden, as I would be more assured of some foreseeable time without intrusive and debilitating treatment and side-effects.

I would also expect that my family especially would experience a reduced emotional burden as there is less worry and care associated with successful treatment.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

Daratumumab appears to be a drug that will address an unmet need. Whilst I hope that I am a long way from becoming refractory, patients who have reached this stage, with limited options remaining, will have another treatment available to them. This is very valuable to patients and it is heartening to know doctors would have such an effective treatment in their armoury at this stage.

At the stage that daratumumab is likely to be made available, patients will have had a number of previous treatments, so I would appreciate another effective treatment option, which clearly works, becoming available.

From the clinical trials, I understand that daratumumab is currently the only myeloma drug that tackles the under-performing CD38 protein, which seems to be widely regarded as a significant marker for myeloma treatment. From regularly speaking to my healthcare professionals, daratumumab seems to be drug that is highly innovative and patients like me would value access to it.

As daratumumab is a treatment which is given on its own, this would be beneficial to patients as there is no obligation to regularly take tablets. The absence of dexamethasone would be beneficial, as I know only too well the highs and lows of this treatment.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

No.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)

- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

As an individual, I have already been treated with thalidomide and carfilzomib. This seems to disqualify me in the long-term from some of the more innovative drugs (e.g. pomalidomide) because I have not specifically had lenalidomide or bortezomib. I feel that I am compelled to follow a pathway that will not bring me quickly into contact with the newer, more innovative drugs that are now available. I do appreciate the challenges that NICE, the NHS and pharmaceutical companies face with this issue.

Please list any concerns you have about the treatment being appraised.

None, other than the inevitable concerns that precede starting any treatment, irrespective of the drugs involved, i.e. how will this affect me, personally?

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None known to me.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Given that myeloma is increasingly recognised as a very individual cancer, it seems inevitable that some treatments will not be suitable for every patient. There is no perfect solution, no matrix of varieties of myeloma against the most appropriate drug. Daratumumab, with its ability to target CD38, may represent a good, wide-spectrum drug that would cut across this matrix.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

As above. Individual patients may well reject daratumumab.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☒ Yes, some of it ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Have not been treated with daratumumab.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

The SIRIUS trial suggests that daratumumab is well tolerated without the worst of myeloma's adverse side effects. I do not know how the common side effects were distributed amongst trial patients, however. Some patients may have experienced no side effects, others may have experienced multiple impacts.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not known.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☒ Yes ☐ No

If yes, please provide references to the relevant studies.

Myeloma UK's own research on Patients' attitudes to treatment choices and preferred outcomes.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

None

9. Other issues

Do you consider the treatment to be innovative?

☒ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

I understand that this is the first drug which targets CD38 by addressing the impaired immune response of the protein and that there is evidence of significant success with heavily pre-treated and refractory myeloma patients.

Is there anything else that you would like the Appraisal Committee to consider?

The stage(s) at which daratumumab, as a monotherapy, can be introduced into the treatment pathway.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Daratumumab offers a potentially significant opportunity for myeloma patients to receive a well-tolerated drug with a proven track record of delaying progression and prolonging life.
- Daratumumab is the first anti-myeloma drug to target poorly-functioning CD38 proteins, thereby re-energising a patient's immune system.
- Daratumumab appears to have the added benefit of reducing other symptoms, e.g. bone pain and fractures. It can also be used without dexamethasone.
- Daratumumab fills an unmet need, for those patients who have had a number of treatments, and for whom options are limited, to receive another option.

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933]

Personal Details and Timeline.

My name is Barry Neville. I am 71 years of age and live in Berkshire. I am a myeloma patient. A brief summary of my myeloma journey follows.

Autumn 2011	Experienced severe back ache. Initially visited local chiropractor, without success. Went to local GP surgery in late December.
December 2011	Knowledgeable GP was suspicious and requested extensive blood tests.
January 2012	GP advised that blood tests showed evidence of multiple myeloma. Went for x-rays on same day. Admitted to Royal Berkshire Hospital (RBH) on 11/1/2012. X-rays showed fractured T3 and two other compressed vertebrae, plus lytic lesions. Initial treatment with pain killers. Myeloma confirmed.
February 2012	Started Myeloma XI, on thalidomide arm.
August 2012	High Dose Therapy-Stem Cell Transplant at The Churchill Cancer Centre, Oxford.
December 2012	Admitted to RBH with pneumonia. Randomised to "No Support" in Phase 4 of Myeloma XI. Contracted chicken pox.
2013	Monthly monitoring by RBH Haematology staff, plus pamidronate infusions. Slow rise in paraproteins and kappa light chains.
May 2014	Relapsed sufficiently to be transferred to MUK5, trialing Kyprolis (carfilzomib) versus Velcade (lenalidomide). Subsequently randomised to Kyprolis arm.
July 2014	Started MUK5 at The Churchill Hospital, Oxford. Paraproteins at 16.6. Kappa light chains at 340.
December 2014	Final cycle of carfilzomib, cyclophosphamide and dexamethasone. Paraproteins reduced to zero. Randomised to no ongoing support in Phase 2.
February 2015	Diagnosed with Prostate Cancer. Gleason Index 6. Lowest possible level. Monitor only.
March/April 2015	Paraproteins normal. Kappa light chains normal. Complete Response to treatment.
Through 2016	Remission continues with slow rise in paraproteins and kappa light chains. Other blood readings normal. Occasional discussions about next round of treatment. Two bone marrow biopsies at Trial thresholds. Minimal involvement by kappa-restricted plasma cell myeloma – less than 5%.

January 2017 Paraproteins at 10.5
Kappa light chains at 270.
Relapse starting, although neither my paraprotein nor kappa light chain levels have reached the datum level of MUK5.

I have now survived for five years, thanks to superb treatment at Royal Berks and The Churchill, plus support from Myeloma UK staff.
I have generally been well throughout, with few of the anticipated side effects of thalidomide and carfilzomib other than tiredness. Dexamethasone has been disruptive.
Bone pain is an ever-present. Usually at a low level in rib cage and diaphragm with occasional short-term increases, usually treated by rest and, if necessary, co-codamol.
I have had occasional chest infections and keep co-amoxiclav as a prophylactic.
Admitted to RBH in February 2016 after reaction to inhalers – following a mis-diagnosis of COPD.
Prostate cancer is debatable. Not borne out by PSA readings. On six-monthly monitoring.

I am a member of the Reading Myeloma Support Group.
I occasionally attend the Oxford Myeloma Support Group, if my treatment day coincides.
I am a member of the Myeloma UK Patient and Carer Research Panel.

Daratumumab for treating relapsed and refractory multiple myeloma [ID933]

STA REPORT

This report was commissioned by the NIHR HTA Programme as project number 16/10/05

BMJ Technology Assessment Group

Daratumumab for treating relapsed and refractory multiple myeloma [ID933]

Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
Authors:	Steve Edwards, Head of Clinical & Economic Evidence, BMJ-TAG, London Mariana Bacelar, Senior Health Economist, BMJ-TAG, London Samantha Barton, Senior Health Technology Assessment Analyst, BMJ-TAG, London Charlotta Karner, Health Technology Assessment Analysis Manager, BMJ-TAG, London Natalie Masento, Associate Health Technology Assessment Analyst, BMJ-TAG, London Fatima Salih, Health Economist, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ-TAG, BMJ Evidence Centre, BMJ Group, BMA House, Tavistock Square, London, WC1H 9JP.
Date completed:	25/01/2017

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 16/10/05

Declared competing interests of the authors:
None.

Acknowledgements:
The ERG would like to thank Dr Majid Kazmi (Clinical Director, Oncology/Haematology, Guy's Hospital, London) and Dr Jaimal Kothari (Consultant Haematologist, Churchill Hospital, Oxford) for providing clinical advice throughout the project and Dr Kevin Boyd (Consultant Haematologist, The Royal Marsden Hospital, Surrey) for providing feedback on the clinical sections of the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Edwards SJ, Bacelar M , Barton S, Karner C, Masento N, Salih F. Dartumumab for treating relapsed and refractory multiple myeloma: A Single Technology Appraisal. BMJ-TAG, 2017.

Contributions of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report
Samantha Barton	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary and clinical results sections
Charlotta Karner	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary and clinical results sections
Natalie Masento	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary and clinical results sections
Mariana Bacelar	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Fatima Salih	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

TABLE OF CONTENTS

LIST OF BOXES

LIST OF TABLES

LIST OF FIGURES

TABLE OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AIC	Akaike information criterion
ALKY	Alkylating agents
ASCT	Autologous stem cell transplant
BIC	Bayesian information criterion
BSA	Body surface area
BSC	Best supportive care
CDC	Complement-dependent cytotoxicity
CDF	Cancer Drugs Fund
CE	Cost Effectiveness
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CR	Complete response
DOR	Duration of response
DRMM	Double relapsed and refractory multiple myeloma
DSU	Decision Support Unit
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMC	Electronic medicines compendium
eMIT	Electronic market information
EMR	Electronic medical record
EORTC	European Organization for Research and Treatment of Cancer
EPAR	European public assessment report
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FDA	US Food and Drug Administration
GCSF	Granulocyte colony-stimulating factor
GP	General practitioner
HiDex	High-dose dexamethasone
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IgA/D/G/M	Immunoglobulin A/D/G/M
IMF	International Myeloma Foundation
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IPD	Individual patient-level data
IRC	Independent review committee
IRR	Infusion-related reactions
ISS	International Staging System

ISSG	Information Specialists' Sub-Group
ITC	Indirect treatment comparison
IV	Intravenous
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LoDEX	Low-dose dexamethasone
LOT	Lines of treatment
LY	Life-year
MAIC	Matching-adjusted indirect comparison
mEBMT	Modified European Group for Blood and Marrow Transplant
MIMS	Monthly Index of Medical Specialities
MM	Multiple myeloma
MoA	Mechanism of action
MR	Minimal response
MRI	Magnetic resonance imaging
MRU	Medical resource utilisation
MTA	Multiple technology appraisal
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
N/R	Not reported
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analyses
PACE	Patient and Clinician Engagement
PD	Progressive disease
PFD	Progression-free disease
PFS	Progression-free survival
PH	Proportional hazard
PI	Proteasome inhibitor
PPS	Post-progression survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life-year
QoL	Quality of life
RBC	Red blood cell
RCT	Randomised controlled trial
rrMM	Relapsed and refractory multiple myeloma
RU	Resource use
RWE	Real world evidence
ScHARR	School of Health and Related Research

sCR	Stringent complete response
SCT	Stem cell transplant
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SmPC	Summary of product characteristics
STA	Single technology appraisal
TEAE	Treatment-emergent adverse events
TFI	Treatment-free interval
TSD	Technical support document
TTD	Time to treatment discontinuation
TTR	Time to response
VGPR	Very good partial response

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company of daratumumab (Darzalex®; Janssen) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of daratumumab monotherapy (hereafter referred to as daratumumab) in the treatment of people with relapsed and refractory multiple myeloma (rrMM) who have previously been treated with a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), and who have demonstrated disease progression on the last therapy.

Daratumumab has been granted a European marketing authorisation for treatment of people with rrMM and whose prior therapy included a PI and an IMiD and who have demonstrated disease progression on the last therapy.

The clinical evidence presented in the company's submission (CS) is derived from two studies MMY2002 and GEN501 Part 2. MMY2002 and GEN501 are a Phase II and Phase I/II study, respectively, that were carried out in parallel. Both studies were carried out in two stages, with the first stage in each study involving investigation of different doses of daratumumab. Subsequent to identification of the optimum dose of daratumumab, the final stage in each study involved following a single cohort to evaluate clinical effectiveness and safety of daratumumab at the licensed dose (16.0 mg/kg). Thus, the second stage of the study from which data are presented in support of the submission is observational in nature, not having a randomised component.

The final scope issued by NICE specified the population of interest to be people with rrMM who have previously been treated with a PI and an IMiD, and who have demonstrated disease progression on the last therapy. However, within the CS, the company positions daratumumab as a predominantly fourth-line treatment, which is narrower than the population set out in the final scope. Clinical advisors to the Evidence Review Group (ERG) support the company's proposed use of daratumumab in the treatment pathway for rrMM in UK clinical practice.

MMY2002 enrolled people with MM who had been previously treated with at least three lines of therapy that included a PI and an IMiD, or who were refractory to both a PI and an IMiD. By contrast, people were eligible for GEN501 Part 2 if they had MM requiring systemic therapy and had received two or more therapies, including IMiD, PI, chemotherapy or autologous stem-cell transplant (ASCT). The differences in inclusion criteria between MMY2002 and GEN501 Part 2 led to differences in baseline characteristics in some factors associated with prognosis. The ERG notes that people in MMY2002 and GEN501 Part 2 are younger than people with rrMM typically treated in UK clinical

practice, but that it is common for a population enrolled in a clinical trial to be younger than the representative population seen in clinical practice.

To consider the generalisability of the populations from which evidence is derived to UK clinical practice, the ERG considers it important to discuss therapies received prior to fourth-line treatment in the UK setting. When a person with rrMM reaches fourth-line treatment in the UK, they will have been exposed to lenalidomide in combination with dexamethasone (len+dex) and bortezomib. Nearly all people in both MMY2002 and GEN501 Part 2 had received lenalidomide and bortezomib as part of their previous disease management. However, other therapies given prior to daratumumab in MMY2002 and GEN501 included carfilzomib and pomalidomide, neither of which, at the time of writing, will have been used as a treatment for rrMM in England: carfilzomib is not an available treatment option and pomalidomide was recommended as an option in rrMM by NICE on 11 January 2017. A person who has not been exposed to a treatment is more likely to have a better outcome on receiving that treatment compared with a person who is re-treated with that intervention. In terms of number of and type of prior therapies received, the ERG's clinical experts advised that the population of GEN501 Part 2 is more closely aligned with the population who would most likely be eligible for daratumumab therapy in the UK. However, the company is positioning daratumumab as a treatment at the fourth line and greater, a setting that is better reflected by MMY2002 as most people enrolled have had three prior therapies. With the exception of number of lines of prior therapy in GEN501 part 2, the ERG's clinical experts fed back that neither study alone accurately represents the baseline characteristics of people in England most likely to receive daratumumab in clinical practice. In the context of daratumumab given at the fourth-line and higher in the UK, because of prior therapies received and differences in baseline characteristics across MMY2002 and GEN501 Part 2, the ERG considers the submitted evidence to partially represent people with rrMM in England who would most likely be eligible for treatment with daratumumab.

All clinically relevant outcomes were reported in the CS, with the exception of time to next treatment and health-related quality of life (HRQoL).

As data on clinical effectiveness of daratumumab are derived from the follow-up of a single group from each of MMY2002 and GEN501 Part 2, neither study has a comparator group that is relevant to this STA and there is no direct evidence of daratumumab in comparison with another intervention. In the final scope issued by NICE, the comparators of interest were identified as:

- panobinostat with bortezomib and dexamethasone (pano+bort+dex);
- len+dex

- pomalidomide with dexamethasone (pom+dex);
- bendamustine (not appraised by NICE but funded via the Cancer Drugs Fund; does not currently have a marketing authorisation in the UK for this indication).

Within the CS, the company presents the results of a matching-adjusted indirect comparison (MAIC) evaluating daratumumab versus pom+dex and versus pano+bort+dex. The company's rationale for not carrying out the MAIC versus len+dex was that len+dex is used earlier in the treatment pathway (i.e., third-line). In addition, re-treatment with lenalidomide is not an available treatment option in UK clinical practice. In the case of bendamustine, the company did not identify sufficient data of adequate quality to facilitate the MAIC analysis. However, throughout the CS, the company also comments that they do not consider bendamustine a valid comparator for daratumumab, given that daratumumab is likely to be used, if approved, prior to bendamustine. Bendamustine does not have a marketing authorisation in the UK for rrMM, and has, therefore, not undergone appraisal by NICE. Bendamustine is available through the Cancer Drugs Fund, and is therefore a NHS-funded treatment option. The ERG's clinical experts agree with the company's views on the likely sequence of treatments in rrMM, that is, len+dex will likely be used prior to daratumumab and bendamustine is considered the last available treatment option for rrMM. Accordingly, the ERG considers it appropriate to not consider the comparisons of daratumumab versus len+dex and versus bendamustine in the context of the decision problem.

1.2 Summary of clinical effectiveness evidence submitted by the company

As noted above, MMY2002 and GEN501 are a Phase II and Phase I/II study, respectively, that were carried out in parallel. Neither study had a site in the UK. Both studies were carried out in two stages, with the first stage in each study involving investigation of different doses of daratumumab. In MMY2002, people were initially randomised to daratumumab 8.0 mg/kg or 16.0 mg/kg. In GEN501, people were allocated sequentially to daratumumab, starting at 0.05 mg/kg dose, escalating to 16.0 mg/kg. Subsequent to identification of the optimum dose of 16.0mg/kg, the final stage in each study involved following a single cohort to evaluate clinical effectiveness and safety of daratumumab at the licensed dose (16.0 mg/kg). Thus, the second stage of GEN501 and both stages of MMY2002 from which data are presented in support of the submission are observational in nature, not having a randomised component. It is noted that guidance from the FDA reports that single-arm studies are not appropriate for capturing time-to-event data such as PFS and OS.

With a primary outcome of ORR, MMY2002 was designed to evaluate the clinical efficacy of daratumumab in people with rrMM previously treated with at least three therapies (including PIs and

IMiDs) or who were refractory to both a PI and an IMiD. By contrast, the primary goal of GEN501 was to assess safety and tolerability of daratumumab. The population enrolled in GEN501 Part 2 were those with MM whose disease was relapsed or relapsed and refractory to two prior lines of therapy and who did not have further established treatment options.

Comparison of baseline characteristics across MMY2002 and GEN501 Part 2 identified differences in characteristics associated with prognosis and outcome. Based on the median number of prior therapies (5 in MMY2002 vs 4 in GEN501 Part 2), and the proportion of people who were refractory to their last treatment (97.2% in MMY2002 and 76.2%), the ERG notes that people in MMY2002 are more heavily pre-treated and are more refractory to treatment than those in GEN501 Part 2. Furthermore, information on ISS stage and cytogenetics, characteristics that are also associated with prognosis, were not recorded for GEN501 Part 2.

Outcomes were captured at three time points in both MMY2002 and GEN501 Part 2. However, the same outcomes were not recorded at the same time points, with longer follow-up for ORR in GEN501 Part 2 compared with MMY2002.

Within the CS, the company presents results for MMY2002 and GEN501 separately, together with an integrated analysis of results from the studies. The ERG recognises that MMY2002 and GEN501 Part 2 represent the best available evidence on daratumumab but considers that the trials are associated with a high risk of bias that is inherent in observational studies. In addition, given the identified differences in baseline characteristics and lack of information on ISS stage and cytogenetics in GEN501 Part 2, the ERG considers it inappropriate to combine the data sets in an integrated analysis for estimation of non-comparative outcomes relating to daratumumab.

Given the differences between the studies, the ERG has chosen to focus reporting on MMY2002, as information on ISS and cytogenetics is available and the study was designed and planned to record ORR. The ERG recognises that with five median lines of prior therapy, the population is likely to be more heavily pre-treated than those who would be eligible for treatment with daratumumab in the UK and the results are likely to be biased against daratumumab in that setting.

At the time the ERG started this report, pom+dex, was undergoing review by NICE through the STA process (subsequently approved) for treatment of rrMM after lenalidomide, the ERG considers people without prior pomalidomide to be a subgroup of interest to the decision problem.

In MMY2002, daratumumab was associated with an ORR (people achieved at least a PR) of 29.2% (95% CI: 20.8% to 38.9%). The ERG notes that ORR is considered a good measure of anti-tumour activity but does not necessarily relate to disease stability or prognosis. The median time taken to

achieve the first response was 0.99 months, ranging from 0.9 to 5.6 months. Based on TTR, for people who respond to treatment with daratumumab, response is rapid, and shrinkage of tumours typically occurs within the first month of treatment. Median DOR in MMY2002 was 6.82 months (95% CI: 5.55 months to 11.07 months). Median PFS and OS were 3.7 months (95% CI: 2.8 months to 4.6 months) and 18.6 months (95% CI: 13.7 months to not reached), respectively, in MMY2002. In pomalidomide-naïve people, median PFS was 3.98 months (95% CI: 2.60 months to 7.39 months). Median OS could not be determined for those without prior exposure to pomalidomide. Results for pomalidomide-naïve people are *post hoc* analyses and should be interpreted with caution.

The ERG considered that the OS benefit reported for daratumumab in MMY2002 was substantially longer than would be expected based on the comparatively short PFS, given the typically poor prognosis of people at this stage of MM. The company proposes that the large difference between PFS and OS is not unexpected and is likely as a result of daratumumab's novel mode of action and immunomodulatory activity. However, a longer OS compared with PFS has been reported in other studies in people with rrMM, with one potential explanation proposed to be progression in disease being diagnosed biochemically, with clinical manifestation of relapse not occurring until months later.

Confounding of OS due to subsequent therapy given at disease progression is recognised in studies evaluating treatments in oncological conditions. In MMY2002, people who progressed received carfilzomib and re-treatment with lenalidomide or bortezomib, none of which are available treatment options in the UK. Carfilzomib, lenalidomide and bortezomib are likely to be associated with prolonged OS compared with other treatment options available in the UK setting for the population of interest.

The company reports that 71% of people (n=73) in MMY2002 went on to receive another intervention subsequent to treatment with daratumumab, which, as acknowledged by the company and its experts, is a large proportion and is likely to be smaller in clinical practice should daratumumab be approved (~55%). The ERG notes that the estimate of 55% of people going on to receive further therapy after daratumumab is similar to the proportion of people receiving subsequent treatment in MM-003 (44%). The company proposes that the high number of people receiving additional treatment after daratumumab is attributable to the "*...novel and unique MoA associated with daratumumab, alongside the favourable safety profile, that culminate in an improved health status of patients*". As the company outlines in their response to clarification, the more favourable adverse effect profile of daratumumab gives people, "*time to recover from the cumulative toxicity of previous treatments allowing a greater proportion of patients to receive subsequent therapy*." Additionally, the company proposes that the, "*novel MoA of daratumumab, which includes immune-mediated mechanisms, increases the likelihood of benefitting from subsequent therapy*". To evaluate the potential impact of confounding in OS due to therapies received after daratumumab, during clarification the ERG requested OS for MMY2002 and

GEN501 Part 2 based on those receiving no subsequent treatment, and those receiving any subsequent treatment. Median OS of those receiving [redacted].

In terms of safety, daratumumab was well tolerated and resulted in no patient death or treatment discontinuation due to drug toxicity. Three deaths occurred due to TEAEs, one case each of viral HIN1 infection, pneumonia and aspiration pneumonia. IRRs are a known AE of daratumumab, as reported in the SmPC. In the integrated analysis of MMY2002 and GEN501 Part 2, 48% of people experienced IRRs, with most IRRs (95.6%) occurring at the first infusion. Respiratory, thoracic and mediastinal disorder (nasal congestion, cough, allergic rhinitis, throat infection and dyspnoea) were the most common group of IRR, occurring in 36.5% of patients across all infusions. The number of IRRs reduced with each subsequent infusion. According to the company, IRRs were managed with pre- and post-infusion medications that included antihistamines, corticosteroids and paracetamol/ acetaminophen. All patients who experienced IRRs were able to continue daratumumab therapy at a full dose with these supportive treatments.

To address the lack of evidence from RCTs on comparative effectiveness of daratumumab, the company carried out a MAIC comparing daratumumab versus the identified relevant comparators of pom+dex and pano+bort+dex for PFS and OS. The company followed reported methods. The ERG's preferred dataset from the MAIC differs from that of the company. Based on guidance from the DSU, the ERG considers that the most adjusted dataset to be the most appropriate, which included adjustment for ISS and cytogenetics (therefore based on MMY2002 alone). For pomalidomide-naïve people, results for the MAIC are based on the dataset from the integrated analysis of MMY2002 and GEN501 Part 2.

For PFS, using the ERG's preferred dataset, results from the MAIC show no significant difference between daratumumab and pano+bort+dex (HR 0.85, 95% CI: 0.39 to 1.88) or pom+dex (HR 1.14, 95% CI: 0.64 to 2.03). The direction of the effect favours daratumumab compared with pano+bort+dex, but not when compared with pom+dex. In people without prior exposure to pomalidomide (based on integrated analysis), the MAIC found no statistically significant difference in PFS between daratumumab and pom+dex (HR 0.51, 95% CI: 0.24 to 1.06).

For OS, using the ERG's preferred dataset, the results generated by MAIC show no significant difference between daratumumab and pano+bort+dex (HR 0.61, 95% CI: 0.25 to 1.45) or pom+dex (HR 0.88, 95% CI 0.44 to 1.77). In the MAIC of the integrated dataset, in people without prior exposure to pomalidomide, daratumumab was associated with a statistically significant reduction in risk of mortality compared with pom+dex (HR 0.33, 95% CI: 0.17 to 0.66).

The ERG advises that the results of the MAIC are interpreted with caution. The most adjusted sets had small effective sample sizes, which indicates poor overlap between studies and that the estimates are likely to be unstable. In addition, there is considerable uncertainty around the results, as illustrated by the change in direction of effect within some MAIC and the wide 95% CIs.

1.3 Summary of cost effectiveness evidence submitted by the company

The company developed a *de novo* model in Microsoft Excel® to assess the cost-effectiveness of daratumumab in comparison with pom+dex and in comparison with pano+bort+dex in relapsed refractory multiple myeloma (rrMM) patients whose prior therapy included a proteasome inhibitor (PI) and an immunomodulatory (IMiD) agent and who have demonstrated disease progression on the last therapy. The company also assessed the cost-effectiveness of daratumumab when compared with bendamustine.

The company developed a cohort-based partitioned survival model which includes four health states: progression-free on treatment (PFT), progression-free off treatment (PFOT), progressed disease (PD), and death. The company reports that rrMM patients may withdraw from active treatment before disease progression therefore disaggregating the progression-free (PF) state into PFT and PFOT to allow treatment costs to be captured more accurately in the economic analysis. The cohort is allocated to the PFT state at the beginning of the economic analysis and is assumed to initiate treatment with daratumumab or with one of the three comparators. Patients occupying the PFT state are at risk of disease progression or death and can also discontinue treatment before disease progression. Patients in the PFOT state can move to the PD state or die. Patients occupying the PD state are also at risk of death and can receive further treatment lines in the model. After entering the PD state patients cannot enter remission. A life time horizon of 15 years is adopted in the model, and time is discretised into weekly cycles with a half-cycle correction not applied. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.

Treatment effectiveness within the model was implemented through a partitioned survival method, which uses the estimated OS and PFS data from the MMY2002/GEN501 integrated trial analysis to determine mortality and disease progression at each cycle of the economic model. Treatment effectiveness was also included in the model through the observed lower rates of adverse events (AEs) related with daratumumab. The clinical impact of subsequent treatments received after daratumumab was implicitly included in the economic model through the use of overall OS data from MMY2002 and GEN501, given that patients received further rrMM treatment after daratumumab.

In their base case analysis, the company used the integrated patient-level data from MMY2002 and GEN501 (described in Section 4 of the ERG report). In order to extrapolate OS, PFS and TTD data into the model time horizon the company fitted a variety of parametric curves to the integrated data. To derive the OS and PFS curves for pom+dex and pano+bort+dex the adjusted HRs derived from the matched adjusted indirect comparison (MAIC) were applied to the estimated unadjusted survival curves derived from MMY2002/GEN501 for daratumumab. For pom+dex, only mean and median TTD could be obtained from the literature, therefore the TTD curves for daratumumab were calibrated to match the observed mean and median from MM-003. The company could not find TTD data for pano+bort+dex or bendamustine therefore patients were assumed to be treated until progression, or when the maximum number of treatment cycles was reached for these two treatments.

The company's base case model assumes that the proportional hazards (PH) assumption holds for the comparison of daratumumab against pom+dex and pano+bort+dex, for OS and PFS data. The company's model allows the estimation of OS as well as PFS through an independent fit approach. The option to model curves independently uses the integrated MAIC-adjusted daratumumab data (for OS or PFS) and the unadjusted OS or PFS curves from MM-003 for pom+dex and from PANORAMA2 for pano+bort+dex. The company's model also includes an option to run the cost-effectiveness analysis using the MMY2002 and the GEN501 data separately. Nonetheless the combination of running individual trial data with independently fitted curves is not an option in the model. In summary, the options to run the model using different statistical approaches consist of:

1. Dependently fitted curves, with application of the MAIC HRs to the unadjusted daratumumab integrated curves to obtain the pom+dex and the pano+bort+dex OS and PFS curves;

2. Dependently fitted curves, with application of the MAIC HRs to the unadjusted daratumumab MMY2002 curves to obtain the pom+dex and the pano+bort+dex OS and PFS curves;

3. Dependently fitted curves, with application of the MAIC HRs to the unadjusted daratumumab GEN501 curves to obtain the pom+dex and the pano+bort+dex OS and PFS curves;

4. Independently fitted curves, using the integrated MAIC-adjusted daratumumab OS and PFS curves and the unadjusted fitted OS and PFS curves taken from MM-003 for pom+dex and from PANORAMA2 for pano+bort+dex.

The company concluded that the best fitting model for PFS data is the lognormal. To estimate the PFS curves for pom+dex and pano+bort+dex, the company applied the weighted HRs from the MAIC analysis when matching the top 11 patient baseline characteristics, while the PFS HR for pano+bort+dex was derived when matching the five top baseline characteristics across patients in the daratumumab

trials and PANORAMA2. The PFS HRs used in the company's base case are 1.24 (95% CI: 0.92 to 1.68) for pom+dex and 1.74 (95% CI: 1.24 to 2.26) for pano+bort+dex.

The company uses an exponential model to estimate OS curves for daratumumab. To estimate the OS curves for pom+dex and pano+bort+dex, the company applied the weighted HRs from the MAIC analysis matching the top 11 baseline characteristics while the OS HR for pano+bort+dex was derived when matching the five top baseline characteristics across patients in the daratumumab trials and PANORAMA2. The OS HRs used in the company's base case are 1.74 (95% CI: 1.24 to 2.46) for pom+dex and 1.19 (95% CI: 0.73 to 1.92) for pano+bort+dex.

The company assumes that patients' quality of life varies according to progression status and whether or not patients experience adverse reactions to the different treatments received. The health state utility values (HSUVs) used in the base case analysis are taken from a paper by Palumbo *et al.* which analyses EQ-5D data collected in the MM-003 trial. The EQ-5D data were valued using the UK general population time trade-off values, which resulted in a utility value of 0.61 for the pre-progression state and of 0.57 for the progressive disease state. The utility decrements attributed to AEs in the model are based on published estimates and the company's clinical experts' input.

The costs considered in the economic model consist of pharmacological costs (treatment acquisition, administration and concomitant treatment costs), disease management costs, AEs costs, subsequent therapy costs and end of life costs.

The company's primary base case results present an ICER of £55,766 per QALY gained for daratumumab compared with pom+dex and an ICER of £32,593 per QALY gained for daratumumab compared with pano+bort+dex. The ICER comparing daratumumab with bendamustine is £56,574 per QALY gained.

1.4 ERG commentary on the robustness of evidence submitted by the company

1.4.1 Strengths

Clinical

The CS contained a systematic review that addressed the decision problem outlined in the final scope issued by NICE. The company's search strategies were well designed.

Economic

The ERG is generally satisfied with the company's model structure and the patients' flow through the model. The partitioned survival approach employed by the company is appropriate. The company included a range of scenario analyses which attempted to explore some of the methodological and structural uncertainty in the analysis.

1.4.2 Weaknesses and areas of uncertainty

Clinical

Although the ERG is satisfied that the company's search strategy was comprehensive, the omission of a long-term follow-up study from the evidence base identified by the company generates some uncertainty that not all relevant evidence has been identified.

A key limitation of the submission is the lack of direct randomised evidence comparing daratumumab versus an active intervention of interest. Although two RCTs of daratumumab are ongoing, they are evaluating daratumumab in combination with other interventions, and so will not inform the decision problem that is the focus of this STA. Of the studies identified to inform the MAIC, one was a well-conducted RCT, but data from the trial are being used as an uncontrolled observational study and the second is an uncontrolled observational study.

Considering the populations from which evidence is derived, the ERG noted differences in the patient baseline characteristics between MMY2002 and GEN501 Part 2 including number of prior lines of therapy, the prior therapies received and the therapies to which people were refractory. Due to a lack of data presented in GEN501 Part 2 concerning disease stage and cytogenetic status, it is unclear how the population groups compare on these baseline demographics. Overall, the ERG considers that the available evidence on the clinical efficacy of daratumumab monotherapy for the treatment of rrMM is of limited quality due to the study design. However, the ERG also acknowledges that MMY2002 and GEN501 Part 2, at this time, represent the best available evidence on the clinical effectiveness of daratumumab monotherapy.

The ERG has concerns around the generalisability of the studies to the UK population most likely to be eligible for treatment with daratumumab. In MMY2002 and GEN501 Part 2, some of the therapies people had received prior to trial entry are not available treatment options within the UK (carfilzomib, and, until January 2017, pomalidomide). Moreover, some of the subsequent treatments given on disease progression are not available treatment options in this setting in UK clinical practice, which also affects

interpretation of OS estimates for daratumumab generated from MMY2002 and from the MAIC analyses. That said, the ERG reiterates that OS estimates should be interpreted with caution as those for daratumumab and pano+bort+dex are derived from single-arm studies, which is not considered an appropriate study design to measure time to event outcomes, such as PFS and OS.

Subsequent treatments given in MMY2002 were carfilzomib and re-treatment with lenalidomide or bortezomib, none of which are available treatment options in the UK. Carfilzomib, lenalidomide and bortezomib are likely to be associated with prolonged OS compared with other treatment options available in the UK setting for the population of interest. The ERG notes that there is considerable disparity between MMY2002/GEN501 Part 2 and MM-003, which informs the MAIC of daratumumab versus pom+dex, in subsequent treatments given, which should be considered when interpreting results from the MAIC for OS. In MM-003, the most commonly used subsequent therapies were dexamethasone, cyclophosphamide, bortezomib and bendamustine, which may have been used alone or in combination. Compared with MMY2002 and GEN501 Part 2, a considerably smaller proportion of people in MM-003 received carfilzomib, lenalidomide and bortezomib as a subsequent therapy. The ERG considers that the subsequent treatments given in MMY2002 are likely to be associated with increased OS compared with the most common treatments given on progression in MM-003.

Economic

Due to mistakes and/or discrepancies identified before and during the clarification process, the company provided two versions of the written submission of the economic evidence along with three electronic versions of the Microsoft Excel® based economic model.

The ERG has serious concerns with the robustness of the economic analysis undertaken by the company as it has encountered several errors and discrepancies in the different versions of the economic model, CS and data forward by the company to the ERG after the clarification stage. The specificities of this STA allied with the submission of multiple model versions and the limited time available for the ERG review, make it very likely that some mistakes were not detected. The key aspects of this STA are as follows:

- The absence of RCT evidence;
- The possible permutations for the data analysis (three datasets for daratumumab – MMY2002; GEN501 and integrated; two different trials for the two comparator; two subgroups of relevance related with subsequent therapies and pre-treatment received by patients; two possible modelling approaches – dependent or independent fit and finally the variation in the adjustment factors included in the MAIC).

The fact that ERG kept on finding mistakes in data handling and labelling increases the probability that some other similar mistakes were not identified. It is impossible to foresee the impact of such potentially unidentified mistakes. It is the ERG's opinion that the company's model and data analysis need further internal consistency checks and a thorough quality check before a robust ICER can be determined for daratumumab. The ERG summarises the key issues surrounding the cost-effectiveness of daratumumab below. These are related with:

- **Pre-treatment with pomalidomide**: Even though the ERG lacks confidence in the validity of the data sent through by the company at the clarification stage, the data suggest that there is no difference in PFS across pom-naïve and non-pom-naïve patients and that OS outcomes are better for pom-naïve patients than for the overall trial population. The ERG interprets this trend in the data as a possible consequence of the effect of daratumumab as a subsequent therapy. It can be hypothesised that given that pre-treatment with pomalidomide does not seem to influence PFS, the considerable difference in the OS curves across the pom-naïve and the overall trial population is due to the effect that pomalidomide would have as a subsequent treatment in the pom-naïve patients, compared to the effect that pomalidomide would have as a subsequent treatment in patients pre-treated with pomalidomide. Unfortunately the ERG cannot validate this hypothesis given the uncertainty around the data and the fact that company did not provide the OS KM curve for patients subsequently treated with pomalidomide, despite the ERG's request for such data;

- **Subsequent treatments received in MMY2002/GEN501**: The ERG is concerned with the highly confounded OS estimates in the company analysis. The ERG considers that the evidence put forward by the company is not robust enough to determine the cost-effectiveness of daratumumab monotherapy alone. To determine this, we would need to be able to disentangle further the estimate of OS for daratumumab alone vs daratumumab followed by other treatments. Similarly, if we are to consider the cost-effectiveness of daratumumab monotherapy followed by subsequent rrMM therapies, then the effectiveness of daratumumab would need adjusting for the impact of subsequent therapies currently not available in the UK. This is particularly important in this case given the lack of RCT data for daratumumab. While in theory this confounding effect might also apply to the comparator treatments, as pom+dex and pano+bort+dex patients could receive subsequent therapies in MM-003 and PANORAMA2, respectively, the ERG's investigation shows that the risk of OS confounding for pom+dex patients is likely to be considerably smaller than for daratumumab patients. This is related with the fact that 72% of patients in MMY2002/GEN501 received subsequent therapies, while the corresponding estimate for MM-003 is 44%, but more importantly, in MM-003 patients received carfilzomib, lenalidomide and bortezomib in much smaller numbers than in

MMY2002/GEN501 (2% vs 28% for carfilzomib; 5% vs 15% for lenalidomide and 18% vs 24% for bortezomib). Daratumumab patients also received pomalidomide (31%) while pom+dex patients did not receive any pomalidomide (or daratumumab) after the main treatment in MM-003. As discussed in the report, treatment with carfilzomib and retreatment with lenalidomide and bortezomib are not available in the UK and are likely to considerably increase overall survival as subsequent therapies for rrMM patients (Figure A).

[redacted]

Finally, there is an inconsistency in the company's proposed advantage of daratumumab. That is, it allows a higher proportion of patients to receive subsequent therapy. On one hand the company claims that the novel mode of action of daratumumab increases the likelihood of patients benefiting from subsequent therapy pointing to the fact that, "…*of the 148 patients treated with daratumumab 16mg/kg monotherapy in the MMY2002/GEN501 cohort, 72% went on to receive subsequent therapy compared with 39% of the 302 patients randomised to POM+DEX in MM-003*". On the other hand, the company also states that, "…*clinical opinion suggested that…this figure* [72%] *is high compared to what is seen in clinical practice*… [and that] *the proportion of patients who receive subsequent therapy after daratumumab is* [likely to be] *55%*". The company also assumed that the proportion for patients receiving subsequent therapy after pano+bort+dex is 55% in the model, making it equally likely for pano+bort+dex and daratumumab patients to receive subsequent therapy;

- **Statistical approach undertaken by the company to model survival outcomes:** The ERG has several concerns with the company's statistical approach to the economic analysis. The ERG considers that the curve fitting exercise undertaken by the company lacks transparency and consistency. This is related with the approach taken to model Gompertz curves and the lack of an appropriate assessment of the PH, PO and AFT assumptions consistently across modelled outcomes. The ERG disagrees with the company's assessment of PH for OS data and thus with the company's modelling approach. This has several implications considering the company's

use of exponential models to fit the daratumumab unadjusted OS curves and application of a HR to estimate the OS curves for comparator treatments. The ERG is also concerned with the validity of the curve fitting exercise undertaken by the company for OS data, as some of the OS extrapolated curves by the company differ considerably from the ones obtained by the ERG.

The company's original model included an option to run the cost-effectiveness analysis using independently fitted curves for OS. This could have overcome the PH issue, nonetheless, this would also imply using the 11-characteristics-adjusted daratumumab curves. Given the ERG's consideration that the company should be adjusting for the maximum number of characteristics possible across trials, the option to fit curves independently in the model is not ideal as it solves one problem but creates a potentially bigger one. The ERG's preferred statistical approach is therefore not currently allowed for in the company's model. The ERG's preferred approach would have been to use the independently fitted curves, however using the MAIC fully adjusted daratumumab curves for OS and PFS compared with unadjusted pom+dex and pano+bort+dex curves. The company has provided the ERG with these data (i.e. the fully MAIC-adjusted OS and PFS KM curves for daratumumab) at clarification. The ERG discusses the potential implications of these data however due to time constraints, and the remit of the ERG's review, does not use these KM data to fit and extrapolate curves for inclusion in the company's model. Analysis of the fully adjusted KM curves led to important conclusions:

- The number of characteristics included in the MAIC adjustment drastically changes the positioning of the daratumumab OS adjusted KM curves in relation to pom+dex (and to a less but also important extent) in relation to pano+bort+dex. In fact the fully adjusted, 28-characteristic-adjusted OS curve for daratumumab shows a lower survival benefit with daratumumab compared with pom+dex before month 10, and a modest benefit after that point in time (Figure C). This is a major departure from the 11-characteristic-adjusted OS curve, which crosses the pom+dex curve at month 4, to then show an impressive survival benefit compared with pom+dex (Figure C). This represents an even bigger departure from the dependent fit approach (company's base case) where the daratumumab OS curve is consistently above the pom+dex OS curve (Figure B). Conversely, the 5-characteristic-adjusted OS curve for daratumumab vs pano+bort+dex seems to underestimate the survival benefit for daratumumab when compared with the fully adjusted, 16-characteristic-adjusted OS curve.

  This has crucial implications for the OS estimated curves and therefore the cost-effectiveness of daratumumab when compared with pom+dex and pano+bort+dex. The company's base case approach overestimates the survival benefit of daratumumab

compared with pom+dex and is also likely to overestimate the survival benefit compared with pano+bort+dex. Analysis of Figure B, Figure C and Figure D show that the dependent fit approach is unlikely to be appropriate for the estimation of cost-effectiveness for daratumumab.

Figure B. Company's base case OS curves for daratumumab, pom+dex and pano+bort+dex

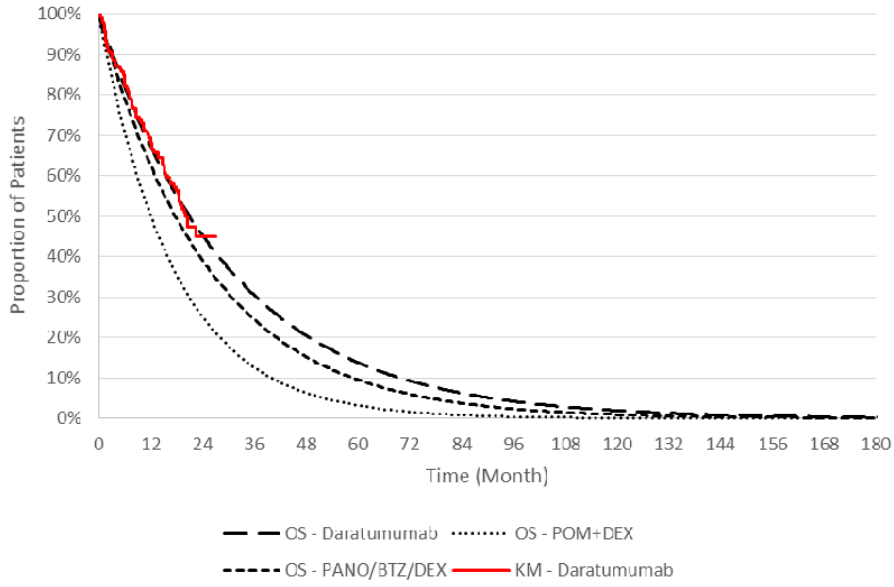


Figure C. Overall survival KM data for daratumumab (adjusted) vs pom+dex (unadjusted)

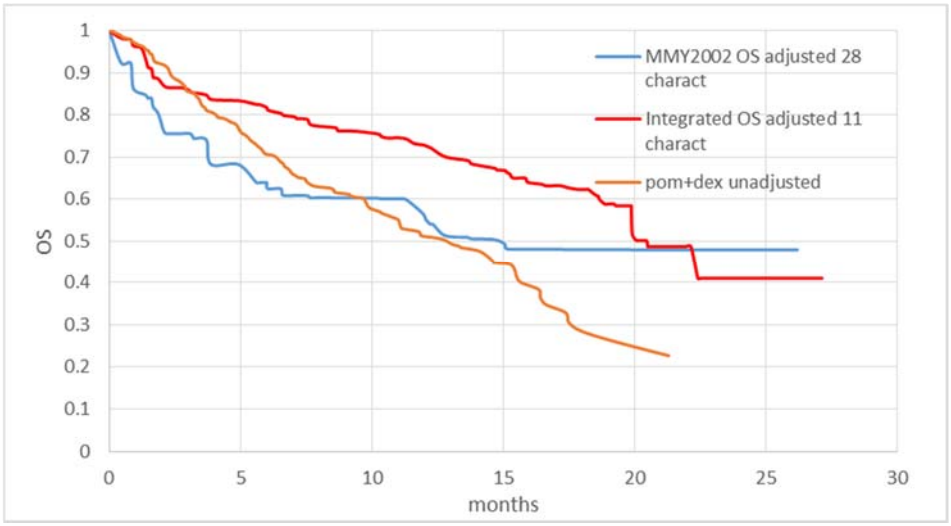
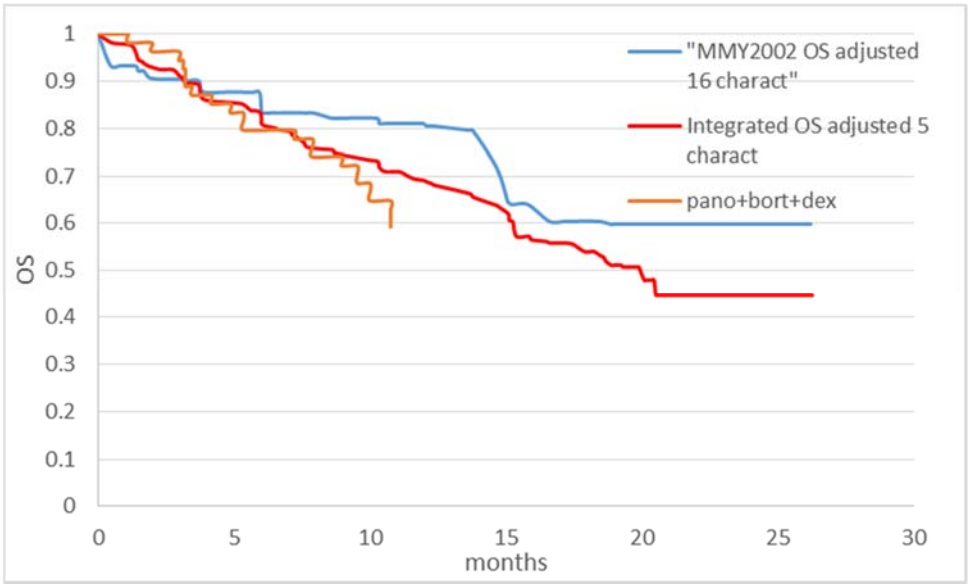


Figure D. Overall survival KM data for daratumumab (adjusted) vs pano+bort+dex (unadjusted)



- The number of characteristics included in the MAIC adjustment changes the positioning of the daratumumab PFS adjusted KM curves in relation to pom+dex and in relation to pano+bort+dex, although to a less extent than observed for OS data (Figure E, Figure F and Figure G). Regardless of this, given that PFS curves are a key diver of treatment costs, the slightest shift in the curves is likely to have an impact on the cost-effectiveness analysis' results;

Figure E. Company's base case PFS curves for daratumumab, pom+dex and pano+bort+dex

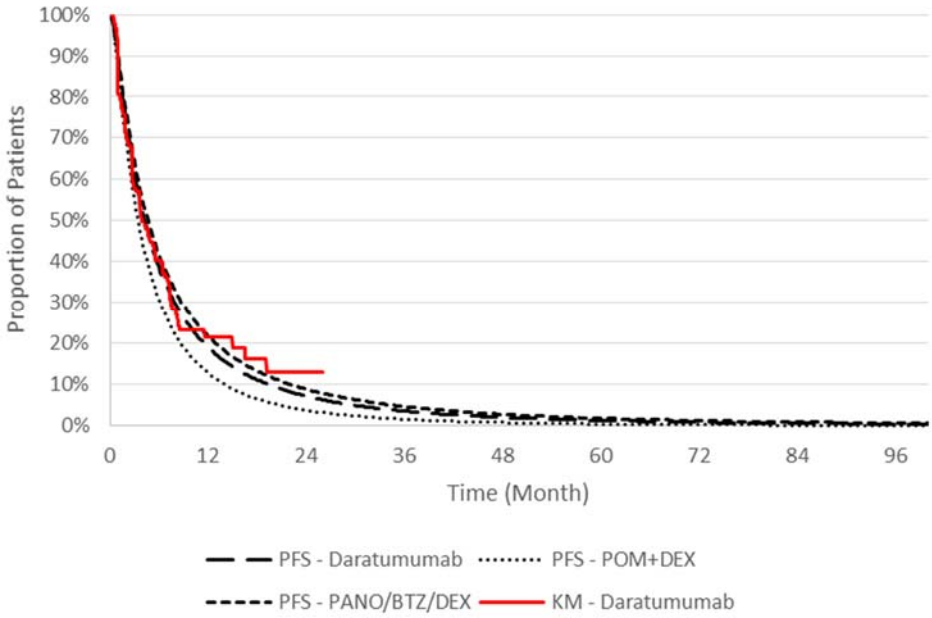


Figure F. Progression-free survival KM data for daratumumab (adjusted) vs pom+dex (unadjusted)

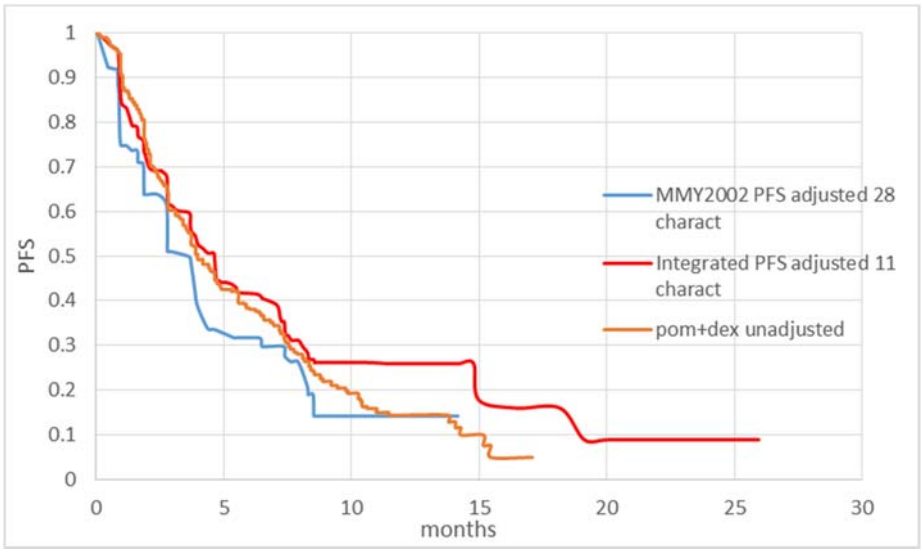
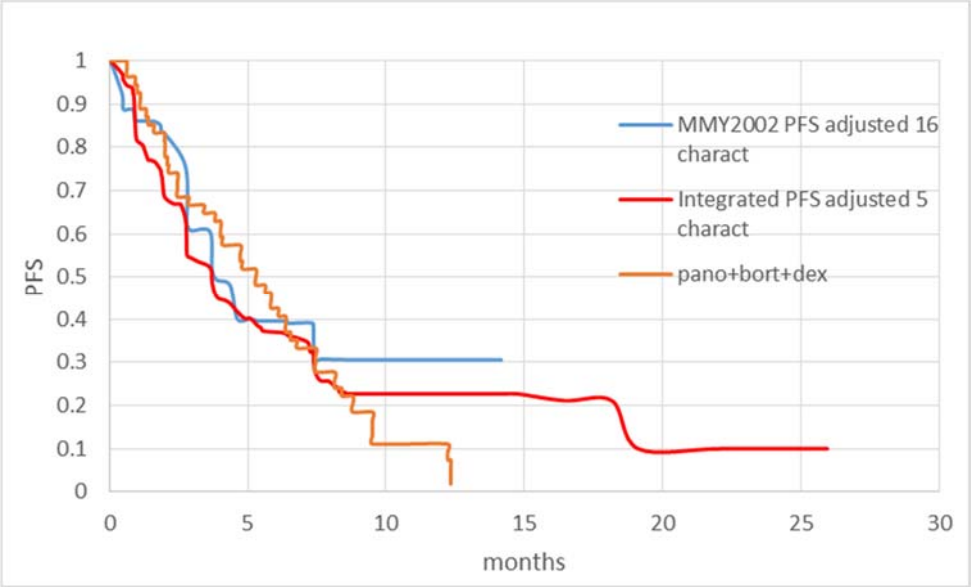


Figure G. Progression-free survival KM data for daratumumab (adjusted) vs pano+bort+dex (unadjusted)



Given that the ERG's preferred methodological approach is not available as a modelling option in the company's Excel model, the ERG undertook some exploratory analysis to assess the impact of using fully adjusted HRs in the company's base case approach. To note is that this approach carries the majority of the flaws in the company's base case analysis. It uses a dependent fit approach and fitted curves which may not be reliable. Nonetheless, it is a step in the right direction compared with the company's approach, as it uses the fully adjusted HRs.

The ERG's preferred, fully-adjusted OS HRs lead to a decrease in the HR for pom+dex (showing a smaller benefit in OS for daratumumab) but to a considerable increase in the pano+bort+dex HR. Equally noticeable, all the HRs using the ERG's preferred approach produce non-statically significant HRs against both comparators (which is not surprising considering the KM data shown in Figure C and Figure D). In their exploratory analysis, the ERG also changed the baseline curve used to model survival with daratumumab, using the Weibull instead of the exponential. This helps alleviate the strong assumption of a constant hazard specific to the exponential curve. The ERG approach (Figure I) is also a step improvement when compared with the company's approach to fitting curves dependently (Figure B) or independently (Figure H). The relative (and absolute) effectiveness of daratumumab has decreased for pom+dex however it is still seen throughout the entire model time horizon.

Figure H. Company's indepdendent fit approach to OS curves

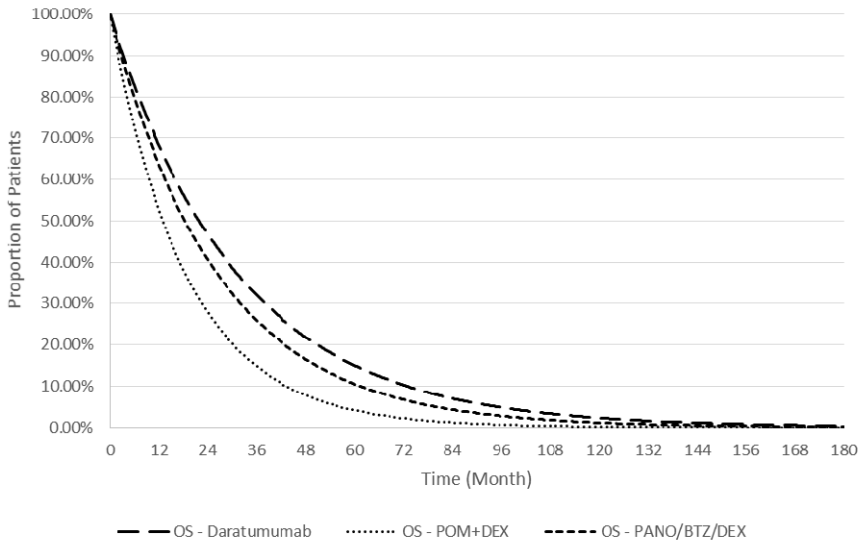
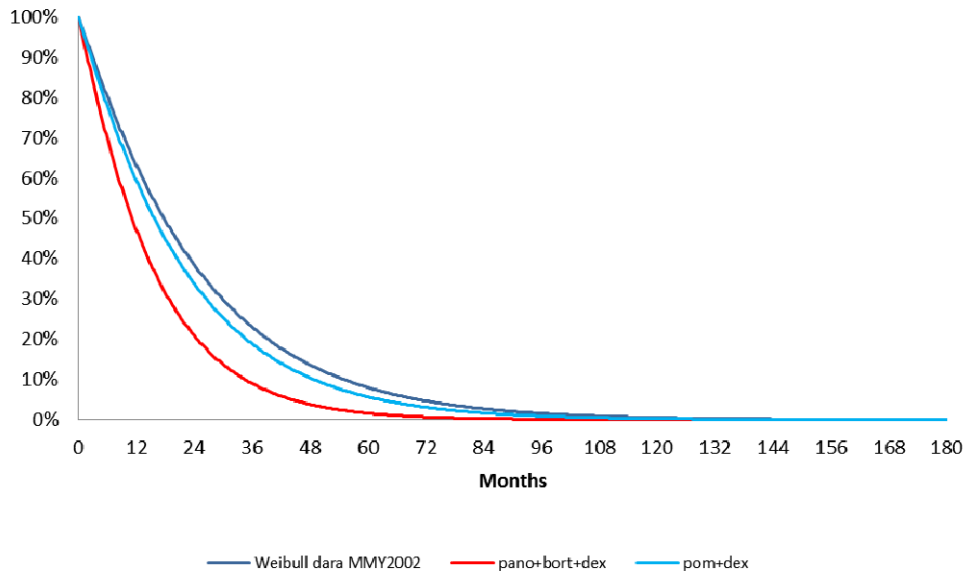


Figure I. ERG's indepdendent fit approach to OS curves



All estimates of relative treatment effect for PFS (company's base case, company's analysis using the MY2002 population and ERG exploratory analysis) show non-statistically significant HRs for daratumumab against pom+dex and pano+bort+dex. The ERG's preferred HRs lead to a decrease in the HR for pom+dex (reflecting a loss in the relative effectiveness of daratumumab) to the extent that pom+dex becomes more effective than daratumumab in delaying disease progression (Figure K). Conversely

the fully adjusted HRs lead to a considerable increase in the pano+bort+dex HR, showing a more effective daratumumab when compared with this treatment. This completely shifts the relative positioning of the curves when compared with the company's base case (Figure E) and the company's independent fit approach (Figure J). Also important is that the HRs used to model PFS in the model have a counterintuitive effect on the final ICERs, when PFS is used to model treatment costs. A beneficial change in the relative effectiveness of daratumumab's PFS increases the final ICER, while a detrimental change in the relative effectiveness of daratumumab's PFS decreases the final ICER, when compared with pom+dex. This is because the beneficial effect of pom+dex penalises this treatment in terms of treatment costs.

Figure J. Company's indepdendent fit approach to PFS curves

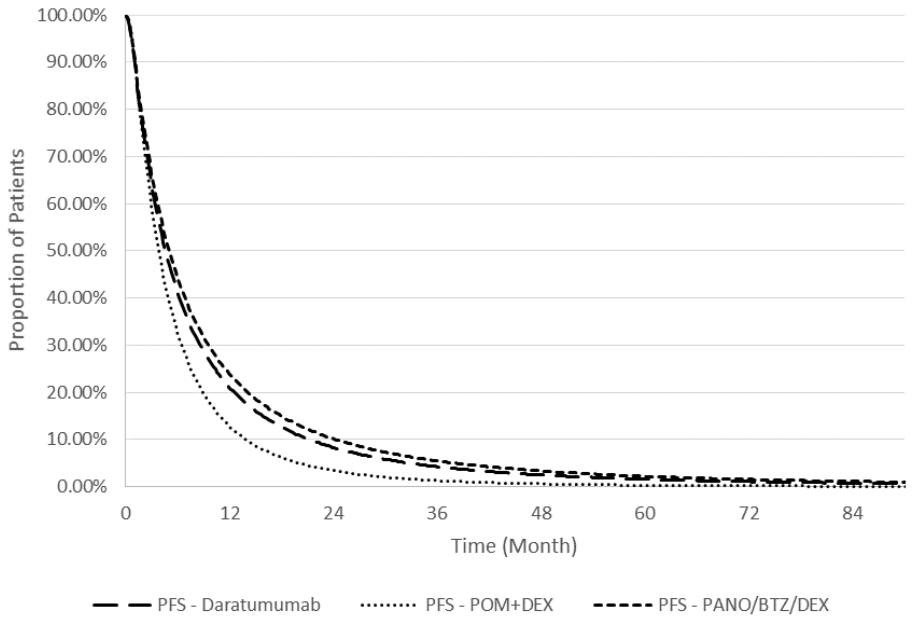
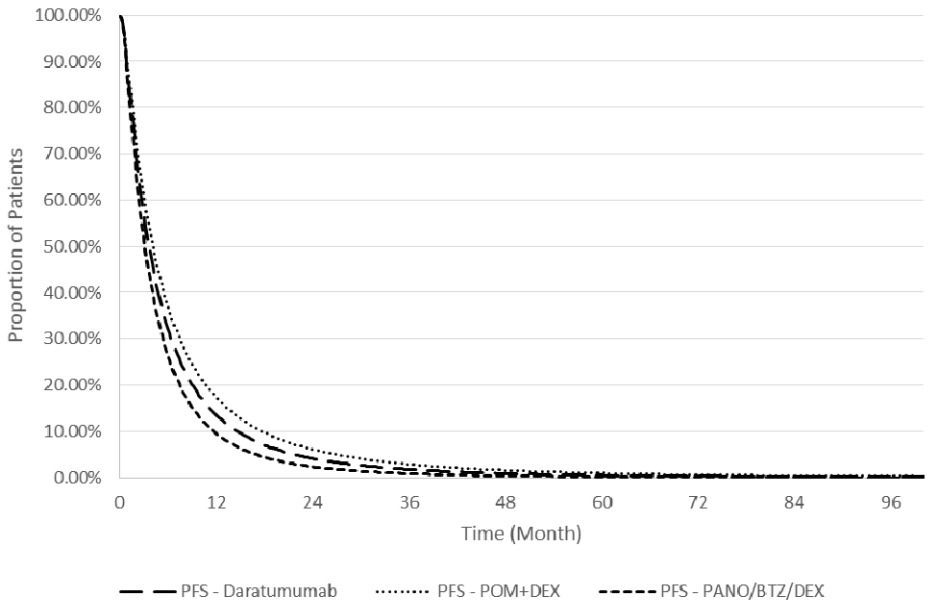


Figure K. ERG's indepdendent fit approach to PFS curves



- **Time to treatment discontinuation data**: The estimation of TTD curves in the company's analysis lacks transparency and clarity throughout the STA. Time to treatment discontinuation was not a pre-specified outcome in the MMY2002 and GEN501 trials but instead resulted from a *post-hoc* analysis of patient level data. Therefore the ERG has little to no information on this clinical outcome. Secondly, the estimation of adjusted TTD curves for daratumumab through the "calibration approach" is a black box in the company's analysis. No further details were provided by the company other than the fact that, "…*the TTD curves for daratumumab were calibrated to match the observed mean and median from MM-003*". Considering the uncertainty around the TTD data, the ERG considers that using these data in the economic analysis carries a potentially high risk. While the PFS curves and data are also not without problems, PFS curves were used as an exploratory approach to derive treatment costs, implying that patients receive treatment until progression;

- **Estimation of utility and subsequent treatment costs**: The ERG also has some concerns with the utility data used and with the application of disutility values to AEs. Similarly, the ERG found some issues in the company's estimation of subsequent treatment costs. These are described in the ERG report in detail but pale in significance when compared with the issues aforementioned.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

Economic

The ERG conducted exploratory analyses as an academic exercise to investigate the direction of the change in the final ICER when different approaches and data are used in the economic model. Nonetheless the ERG stresses its opinion that the company's model and data analysis need further internal consistency checks and a thorough quality check before a robust ICER can be determined for daratumumab. To this, it adds the need of further analysis to arrive at an unconfounded OS estimate for daratumumab monotherapy. Finally, the ERG considers that a new methodological approach is necessary for the modelling exercise, which is based on an independent fit approach, using fully adjusted daratumumab OS and PFS curves.

In their exploratory analysis, the ERG arrives at two possible sets of ICERs, both of which need careful interpretation. The first set of ICERs show a dominated daratumumab against pom+dex and pano+bort+dex. This is because the analysis uses HRs of 1 for both PFS and OS, leaving the economic analysis reduced to a cost-minimisation exercise. The use of HRs of 1 reflects the lack of statistical significance of HRs for OS and PFS in the ERG analyses. In this scenario, the total costs for daratumumab are £85,327, while the total costs for pom+dex are £73,260 and £68,798 for pano+bort+dex.

The alternative set of ICER, using the fully-adjusted, albeit non-statistically significant, HRs for OS and PFS produce a final ICER of £8,559 per QALY gained for daratumumab compared with pom+dex and £59,960 for the comparison of pano+bort+dex. However these results are extremely volatile. Firstly, these results depend on the synergy between PFS curves determining treatment costs and the fact that pom+dex shows a relative benefit to daratumumab for PFS outcomes, with a HR of 0.88 (95% CI: 0.49 to 1.56). The very wide range and the lack of statistical significance of the PFS HRs imprint a great amount of uncertainty in the analysis. Thus the ERG ran an additional exploratory analysis replacing the PFS HR for pom+dex with the value of 1.01 (reflecting a 1% gain in effectiveness for daratumumab against pom+dex). The final ICER went from £8,559 to £114,278 per QALY gained. This shows the fragility of the ICER for daratumumab against pom+dex, depending on the HR used for PFS (when treatment costs are determined by PFS curves). Secondly, these results are also highly dependent on the HRs for OS which are not only non-statistically significant, but show an incredible wide range of possible HRs with 95% confidence intervals going from 0.69 to 4.00. The OS HR for pom+dex is 1.14 (95% CI: 0.57 to 2.27) while the HR for pano+bort+dex is 1.64 (95% CI: 0.69 to 4.00). Therefore the ERG concludes that the "true" ICERs comparing daratumumab with pom+dex and with

pano+bort+dex can lie anywhere between dominant and dominated in the analysis undertaken by the company.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

Section 3 of the company's submission (CS) provides an overview of some of the key aspects of multiple myeloma (MM) and progression to relapsed and refractory MM (rrMM), including aetiology, and impact on the quality of life (QoL) of people with the condition and their carers. The final scope issued by the National Institute for Health and Care Excellence (NICE)[1] for this Single Technology Appraisal (STA) indicates the population of interest to the decision problem to be people with rrMM who have previously been treated with a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), and who have demonstrated disease progression on the last therapy.

Overall, the Evidence Review Group (ERG) considers the CS to present a reasonable overview of MM that is relevant to the decision problem. However, the ERG considers that some key elements of MM have been omitted from Section 3 of the CS, including information on prevalence and a discussion of factors affecting response to treatment and prognosis. Greater detail on some aspects of rrMM would aid in understanding the challenges faced in treating the population that is the focus of this STA, and the discussion of clinical effectiveness of daratumumab monotherapy (hereafter referred to daratumumab). Thus, the ERG provides supplementary information on the categorisation of relapsed MM versus rrMM, together with information on staging of disease, factors affecting response to treatment, and classification systems used to categorise severity of disease and measures of response to treatment.

All information presented in boxes in the ERG's report is taken directly from the CS, unless otherwise stated, and references have been renumbered.

Box 1. Overview of MM (adapted from CS, pgs 37 and 38)

MM is a rare haematological cancer characterised by clonal proliferation of malignant plasma cells in the bone marrow and production of excess monoclonal (M) protein (an abnormal immunoglobulin).[2] The median age of patients at diagnosis is 65-70 years, with people under 40 years of age rarely affected; MM is twice as common in black populations as it is in white and Asian populations, and more common in men than in women.[3-5] While the exact mechanism that triggers the malignant transformation of plasma cells is yet to be identified, the development of MM is preceded by a pre-malignant, asymptomatic state (monoclonal gammopathy of undetermined significance [MGUS]) that develops from a primary oncogenic event in the form of either a hyperdiploidy (having more than 46 chromosomes) or a chromosomal translocation (switching of genetic material between two different chromosomes).[6, 7]

MM itself is a genetically complex disease that develops from the continued accumulation of genetic abnormalities over time.[8] This results in subclones of plasma cells with considerable genetic heterogeneity that contribute to the progression of MM and the development of drug resistance.[8, 9] As a result of this heterogeneity, MM can take a variable clinical course,[3, 4] although, typically, the disease is characterised by multiple relapses with patients becoming refractory to treatment over time, with marked reduction in prognosis.[10-13]

In the relapsed and refractory setting, MM represents a serious and life-threatening disease. Patients whose disease follows an aggressive clinical course, despite receiving active therapy, have a particularly poor prognosis; survival estimates for patients with rrMM whose prior therapy included a PI and an IMiD does not exceed 12 months in real world evidence (RWE) studies.[14-19]

Abbreviations: CS, company submission; IMiD, immunomodulatory drug; MM, multiple myeloma; pgs, pages; PI, proteasome inhibitor.

In their description, the company reports that MM is preceded by the asymptomatic, benign condition monoclonal gammopathy of undetermined significance (MGUS). It is worth noting that it is accepted that all people with MM will have MGUS (possibly not identified) preceding their MM, but most people with MGUS do not progress to MM:[20] each year, about one per 100 people with MGUS will be diagnosed with MM.[21] Like MM, MGUS is more common in older people, men, and black people.[22] Those with first-degree family members (i.e., parent, sibling or child) who have a history of MM or MGUS are at an increased risk of developing MM.[5] Cancer Research UK lists other risk factors for MM as:[5]

- immunosuppression as a result of HIV (human immunodeficiency virus) or long-term immunosuppressant use after organ transplantation;
- previous exposure to high levels of radiation;
- obesity;
- some medical conditions (Gaucher disease and the autoimmune conditions of pernicious anaemia, alkylosing spondylitis, autoimmune haemolytic anaemia and systemic lupus erythematosis).

Of those with MGUS who go on to develop MM, some may have no symptoms or signs of the condition, which is referred to as smouldering MM. Typically, people with smouldering MM are not treated immediately, but are instead monitored closely for the development of symptoms. By contrast, those with symptomatic MM are treated immediately, with the goal of controlling the disease and prolonging survival rather than cure: at the time of writing, MM is considered to be incurable in most people. As described by the company, symptoms associated with MM are bone pain, fractures, anaemia, feeling thirsty and nauseous, and fatigue (additional detail is presented in Box 2).[23]

Box 2. Symptoms of MM (adapted from CS, pg. 38)

Patients with MM experience a variety of complications and disease-related symptoms, all of which affect normal living. The clinical and HRQL burden substantially increases as the disease progresses. The high number of plasma cell clones interferes with haematopoiesis in the bone marrow; this not only puts patients at increased risk of infection but can also result in the destruction of skeletal structures and associated neurological impairment.[2, 6, 24] In addition, the M protein produced by plasma cell clones can cause hyperviscosity and damage organs, specifically the kidney.[2, 6, 24] The acronym "CRAB" is often used to describe the following symptoms commonly associated with organ and bone damage caused by MM: hyperCalcaemia; Renal impairment; Anaemia; and Bone disease. CRAB symptoms require urgent treatment to minimise the development of additional complications and long-term organ damage.[2, 6, 10]
Abbreviations: CS, company submission; HRQL, health-related quality of life; MM, multiple myeloma; pg, page.

As the company outlines in the CS, the course of MM is characterised by a cycle of relapse and remission (Box 1). Additionally, people can become refractory to treatment. To supplement the reporting of the company, and to aid in understanding the population that is the focus of this STA, the ERG provides below criteria from the International Myeloma Working Group (IMWG) for the categorisation of relapsed MM versus rrMM:[25]

- Relapsed MM: disease that progresses and requires the initiation of salvage therapy, but does not meet the criteria for either primary refractory MM or rrMM;
- Primary refractory MM: disease that fails to achieve at least a minimal response (MR) to any treatment;
- rrMM: disease that progresses while the person is receiving salvage therapy or progresses within 60 days of last therapy in people who have previously achieved at least a MR to treatment.

Progressive disease is defined by the IMWG as at least a 25% increase in monoclonal-proteins (serum and urine), free light chain (FLC) levels (involved versus uninvolved), or bone marrow plasma cells, or a combination of these markers.[25, 26] Additionally, progressive disease can be established by a definitive development of new bone lesions or soft tissue plasmacytomas, or a clear increase in the size of pre-existing lesions or plasmacytomas. Presence of hypercalcaemia that cannot be attributed to another cause can also be an indicator of progressive disease.

As noted earlier in this section, the goal of treatment of rrMM is elongation of survival and maximising QoL rather than cure. The ERG's clinical experts advised that factors widely accepted as influencing

the magnitude of an individual's response to treatment, and hence prognosis, are the number of lines of previous therapy, baseline severity of disease, and, established more recently, the chromosomal abnormalities of a person's MM. Within the CS, the company provides limited information on the influence of baseline severity of MM on prognosis and, although it is stated that MM is a genetically complex disease, there is no reference to the association between specific chromosomal abnormalities and OS. Given the import of baseline characteristics on prognosis for those with MM, the ERG considers it useful to provide additional details of the systems used to classify severity of disease and the risk profile of genetic abnormalities. Additionally, the listed characteristics form part of the discussion around the clinical effectiveness of daratumumab in the population relevant to this STA.

As discussed by the company (Box 1), because there is no curative treatment for MM, the clinical course of MM is characterised by multiple relapses. Most people with MM will respond to first-line treatment and achieve disease stability for a period of time.[26, 27] Additionally, at least half of people with MM respond to second-line treatment.[26] However, after second-line treatment, response to treatment typically declines with each subsequent relapse until the person enters refractory end-stage disease. Thus, the greater the number of prior therapies (where a line of therapy is defined as completion of ≥1 cycle of treatment) a person has received, the less likely they are to respond to the current line of treatment.

Two other characteristics of MM that affect response to treatment and are inter-linked are the stage of the disease and its cytogenetic profile: in the context of MM, cytogenetics refers to analysis of bone marrow cells for abnormalities in the number and structure of chromosomes. The International Staging System (ISS) for MM, which has been adopted by the IMWG, specifies three categories of MM based on serum levels of beta$_2$-microglobulin and albumin, with the lower stage number indicating a better prognosis for those with MM. The definitions in the ISS were revised in 2015 to accommodate high-risk chromosomal abnormalities or elevated lactate dehydrogenase (LDH) levels (Table 1).[28] Serum level of LDH above the upper limit of normal indicates increased disease aggressiveness and is established as a predictor of poor prognosis for people with MM.[28, 29]

Table 1. Revised ISS definitions for stage of MM[28]

Stage	Revised ISS definition
I	beta$_2$-microglobulin <3.5 mg/L, albumin ≥3.5 g/dL,[a] no high-risk cytogenetics, and normal serum lactate dehydrogenase levels
II	Not stage I or III
III	beta$_2$-microglobulin ≥5.5 mg/L[b] and high-risk cytogenetics t(4;14); t(14;16) or del(17p),[c] or elevated serum lactate dehydrogenase levels

[a] Low serum albumin in MM is mainly caused by inflammatory cytokines that are secreted by the myeloma microenvironment.[28]
[b] High serum beta$_2$-microglobulin level reflects high tumour mass and reduced renal function.[28]
[c] High-risk cytogenetics are listed in of the ERG's report.
Abbreviations: ERG, Evidence Review Group; ISS, International Staging System; MM, multiple myeloma.

MM is characterised by several chromosomal abnormalities, some of which are consistently observed throughout the course of the disease, from MGUS to end-stage MM.[30] However, there are other genetic anomalies that vary during the course of MM, which makes analysis of the genetic profile challenging.[30] Cytogenetic abnormalities in MM influence all aspects of the disease, including development of malignancy, as well as response to therapy and prognosis. Chromosomal abnormalities associated specifically with outcome in MM are stratified into a standard, intermediate or high risk of poor outcome (summarised in Table 2).[30] To illustrate the influence of cytogenetics on outcome, it is noted that those with newly diagnosed MM and at standard risk of poor outcome have a median OS of 50.5 months, which is in marked contrast to the median OS of 24.5 months for high-risk MM.[28]

The impact of cytogenetics in the context of people experiencing multiple relapses (i.e., the population relevant to decision problem) is less well defined, and the prognostic importance in rrMM may be different from the setting of newly diagnosed MM. One study reports that some chromosomal abnormalities (e.g., secondary translocations and mutations of *RAS* or *FGFR3*, deletion in p18, or loss of expression or mutation in TP53) may influence tumour progression and resistance to treatment in rrMM.[8] Authors of reviews of treatment of rrMM noted that there is a lack of prospective studies evaluating the impact of cytogenetics on prognosis in this setting.[31, 32] Retrospective analyses of Phase II and III trials of single and combination treatments in rrMM provide conflicting data on the prognostic value of some cytogenetic abnormalities.[31, 32] Authors of one review commented that "current data on newer agents indicate that they may only partly overcome the deleterious impact of high-risk cytogenetics in the relapsed setting".[31]

Table 2. Risk stratification by cytogenetics for poor outcome in MM[30, 33, 34]

Risk stratification	Cytogenetic abnormalities
Standard risk[a]	Trisomies[b]
	t(11;14)
	t(6;14)
Intermediate risk[a]	t(4;14)
	Gain(1q21)
High risk[c]	Deletion of 17p
	t(14;16)
	t(14;20)
	Deletion of 1p

[a] Presence of del(17p) indicates high-risk MM regardless of other abnormalities; gain(1q21) (without other high risk abnormalities) is considered intermediate-risk.
[b] A trisomy is the occurrence of three instances of a particular chromosome, instead of the normal two.
[c] In the presence of concurrent trisomies, patients with high risk cytogenetics should be considered standard-risk.
Abbreviations: MM, multiple myeloma.

The final measure of severity of MM that the ERG wishes to highlight is performance status as established by the Eastern Cooperative Oncology Group (ECOG).[35] The ECOG scale assesses how a person's disease is progressing and the level to which their condition impedes their day-to-day

functioning (summarised in Table 3). The ECOG performance scale can be applied in all oncological conditions and is typically used to assess whether a person is physically well enough to receive chemotherapy, and whether dose adjustment is necessary. Performance status is a key indicator of how a patient will tolerate treatment, as well as OS. Those with a higher ECOG score are less likely to be able to tolerate chemotherapy and thus have a poorer prognosis.

Table 3. Summary of ECOG performance status[35]

Grade	ECOG performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead
Abbreviations: ECOG, Eastern Cooperative Oncology Group.	

As discussed above, stage of MM at diagnosis, performance status and number of lines of treatment all influence outcome of treatment. Cancer Research UK reports survival rates after diagnosis of MM in England and Wales to be:[5]

- more than 75 out of every 100 will survive for a year or more;
- almost 50 out of every 100 will survive for 5 years or more;
- almost 35 out of every 100 will survive 10 years or more.

As the company reports, life expectancy is markedly reduced for those whose MM progresses despite prior treatment with a PI and IMiD, and for those who are refractory to PI and IMiD (Box 3).

Box 3. Prognosis for rrMM (adapted from CS, pg. 42)

The life expectancy for patients with rrMM who have progressive disease despite prior treatment with a PI and an IMiD does not exceed 12 months, based on RWE.[14-19] For patients who are refractory to both a PI and an IMiD, life expectancy is further reduced to 8–9 months, and for patients who are refractory to three or four of the common PIs and IMiDs, life expectancy decreases to only 3–5 months.[18]
Abbreviations: CS, company submission; IMiD, immunomodulatory drug; pg, page; PI, proteasome inhibitor; rrMM, relapsed and refractory multiple myeloma; RWE, real world evidence.

People with MM experience a range of disease-related signs and symptoms, as well as having the psychological burden of a diagnosis of an incurable condition. Although prolongation of OS is the key goal of treatment, the impact of other factors, for example, treatment-related toxicity, on health-related (HR) QoL is also a consideration. The company provides an overview of the effect of MM on HRQoL,

and briefly mentions how the HRQoL of those with MM compares with that of people with other haematological cancers (Box 4). The company also considers the effect of MM on the HRQoL of carers, as well as the economic burden associated with the condition (Box 4).

Box 4. Overview of the effect of MM on HRQoL and the economic burden associated with MM (adapted from CS, pgs 38–40)

HRQoL for those with MM

...clinical burden results in a detrimental impact on HRQL and MM patients score significantly lower on the European Organization for Research and Treatment of Cancer 30-item Quality of Life Questionnaire (EORTC-QLQ-C30) in the physical, role, emotional, cognitive and social functional domains compared with the normative population ($p<0.0001$ for all domains).[36] Similarly, MM patients report significantly higher symptom scores for fatigue, nausea and vomiting, pain, dyspnoea, sleeping problems, appetite loss, constipation, diarrhoea, and financial problems, indicating worsened symptomology compared with the normative population.[36] There is also evidence that patients with myeloma report worse symptoms and problems than those with other haematological cancers, including lymphoma or leukaemia.[37]

As the disease progresses and the severity of MM symptoms increases, HRQL worsens with respect to global health status, quality of life, physical and social functioning and future perspective.[38] Treatment-emergent adverse events (TEAEs) can further reduce patient HRQL.

HRQoL for carers of those with MM

There is paucity of data on caregiver burden specifically related to MM,[39] but it is reasonable to assume that informal provision of supportive care also negatively impacts the HRQL of family and friends of patients with rrMM. As is observed in other types of cancer,[40] increasing caregiver burden can be expected with functional deterioration that can be associated with both disease progression and cumulative toxicity of multiple treatment lines for patients with rrMM.

Economic burden associated with MM

MM is also associated with a substantial economic burden that increases as the disease progresses and worsens.[39] Although direct care requirements are normally identified as key cost drivers in economic studies, management of treatment-related AEs also contribute to costs and resource use.[39] This further demonstrates the need for tolerable treatment options in clinical practice, particularly for patients at later stages of relapse who have already received multiple toxic agents.

Abbreviations: AEs, adverse events; CS, company submission; HRQoL, health-related quality of life; MM, multiple myeloma; pgs, pages; rrMM, relapsed and refractory MM.

2.1.1 Epidemiology

The company cites incidence data from Cancer Research UK, reporting that there were 4,703 new cases of MM in England in 2013. The ERG notes that, since the date specified by the company as date of last access to the site, Cancer Research UK has updated its statistics for MM to reflect incidence in 2014.[41] Data for 2014 indicate that there were 5,501 new cases of MM that year in the UK, comprising 4,652 and 269 new cases in England and Wales, respectively.[41] In 2014, MM was the 18th most common cancer in the UK, accounting for 2% of all new cases.[41]

In the UK, around 12,500 people remained alive up to 10 years after being diagnosed with MM (prevalence based on data from 2006):[41] prevalence at 1, 5 and 10 years is reported in Table 4. In 2012, the lifetime risk of developing myeloma was around 1 in 115 for men and around 1 in 155 for women in the UK.[41]

Table 4. Prevalence of MM in UK in 2006[41]

	Prevalence		
	1 year	**5 year**	**10 year**
Male	1,595	5,247	6,921
Female	1,294	4,175	5,544
Persons	2,889	9,422	12,465
Note: Data recorded up to 31 December 2006. Abbreviations: MM, multiple myeloma; UK, United Kingdom.			

2.2 Critique of company's overview of current service provision

The company presents a comprehensive review of global guidance on the treatment of MM and rrMM, including thorough and detailed reporting of various options available for the different lines of treatment. Here, the ERG focuses on guidance relevant to clinical practice in England and the wider UK.

As the company reports, NICE has published six Technology Appraisals (TAs) evaluating treatments for MM and rrMM,[42-47] the recommendations of which are summarised in Table 5: subsequent to the CS, NICE published updated guidance on pomalidomide plus dexamethasone (pom+dex) that supersedes one of the identified TAs (TA338; Table 5).[48] Additionally, there are also NICE pathways covering the management of MM[42] and rrMM.[49]

Table 5. Summary of exisiting Technology Appraisals in MM published by NICE (adapted from Table 4 in CS, pgs 44-50)

Line	Technology appraisal	Year	Title	Summary
Induction	TA311[44]	2014	Bortezomib for induction therapy in MM before high-dose	Bortezomib in combination with dexamethasone with or without thalidomide is recommended as an option for the

			chemotherapy and autologous stem cell transplantation	induction treatment of adults with previously untreated MM who are eligible for high-dose chemotherapy and stem cell transplantation
First line	TA228[46]	2011	Bortezomib and thalidomide for the first‑line treatment of MM	Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of MM in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate. Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of MM if high-dose chemotherapy with stem cell transplantation is considered inappropriate and the person is unable to tolerate or has contraindications to thalidomide
Second line	TA129[47]	2007	Bortezomib monotherapy for relapsed MM	Bortezomib monotherapy is recommended as an option for the treatment of progressive MM for people: • whose MM has relapsed for the first time after having received one previous therapy, and who have undergone, or are unsuitable for, bone marrow transplantation; • After not more than four cycles of treatment, a blood or urine test should be done to check how well the cancer has responded to bortezomib. Treatment should be continued only if there has been at least a partial response to the drug.[a]
Third line or later	TA171[45]	2009, updated in 2014	Lenalidomide for the treatment of MM in people who have received at least one prior therapy	Lenalidomide in combination with dexamethasone is recommended as an option for the treatment of people with MM who have received at least two prior therapies. The manufacturer of lenalidomide has agreed to cover the cost of the drug for people who stay on treatment for more than 26 cycles (normally a period of 2 years)
	TA338[43]	2015	Pomalidomide for rrMM previously treated with lenalidomide and bortezomib	Pomalidomide in combination with dexamethasone is not recommended for treating rrMM in adults who have had at least two prior therapies, including lenalidomide and bortezomib, and whose disease has progressed on the last therapy **Note: Guidance superseded by TA427[48]**
	TA427[48]	2017	Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib	On 11 January 2017, NICE recommended pomalidomide in combination with low-dose dexamethasone as an option for treating multiple myeloma in adults at third or subsequent relapse; that is, after 3 previous treatments including both lenalidomide and bortezomib, only when the company provides pomalidomide with the discount agreed in the patient access scheme

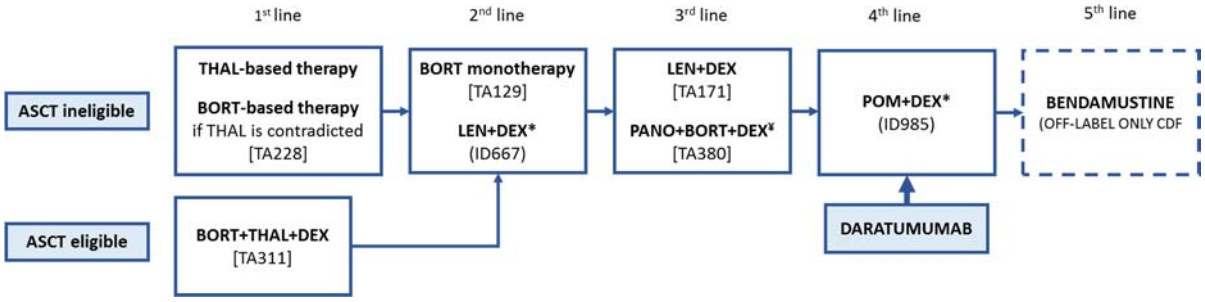
	TA380[42]	2016	Panobinostat for treating MM after at least two previous treatments	Panobinostat in combination with bortezomib and dexamethasone is recommended for adults with rrMM who have received at least two prior therapies, including bortezomib and an IMiD

[a] Subject to the manufacturer covering the cost of the drug for people who, after a maximum of four cycles of treatment, have less than a partial response. Partial response defined as reduction in serum M protein of 50% or more or, where serum M protein is not measurable, an appropriate alternative biochemical measure of response.
Abbreviations: AWMSG, All Wales Medicines Strategy Group; IMiD, immunomodulatory drug; MM, multiple myeloma; NICE, National Institute for Health and Care Excellence; pgs, pages; rrMM, relapsed and refractory MM; TA, technology appraisal.

2.2.1 Management of relapsed and refractory multiple myeloma

In the UK, the treatment algorithm for newly diagnosed symptomatic MM and subsequent relapses of MM has been established based on the NICE TAs summarised in Table 5. The company provides their representation of the treatment pathway for MM, which is presented here (Figure 1). Although the focus of this STA is rrMM, because some of the treatments used at first and second line typically influence subsequent intervention choices, the ERG considers it useful to outline the pathway in full, from management of newly diagnosed MM through to rrMM.

Figure 1. Treatment pathway for MM in the UK and proposed placement of daratumumab (reproduced from CS, pg. 42)



Abbreviations: ASCT, autologous stem-cell transplant; BORT, bortezomib; BORT+THAL+DEX, bortezomib plus thalidomide plus dexamethasone; CDF, Cancer Drugs Fund; LEN+DEX, lenalidomide plus dexamethasone; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; pg, page; POM+DEX, pomalidomide plus dexamethasone.

Initial management of people with newly diagnosed symptomatic MM involves an assessment of a person's eligibility for high-dose chemotherapy with subsequent autologous stem cell transplantation (ASCT). NICE advises considering using a person's age, performance status and co-morbidities as indicators of their ability to tolerate the intensive treatment required prior to ASCT.[42] For transplant-eligible people, as the company reports, NICE recommends induction treatment with bortezomib in combination with dexamethasone, with or without thalidomide, prior to ASCT (see Table 5).[44] For those not eligible for ASCT, recommended first-line therapy is thalidomide in combination with an alkylating agent and a corticosteroid.[46] Bortezomib can be substituted for thalidomide for transplant-ineligible patients who are unable to tolerate or who are contraindicated to thalidomide.[46]

At first relapse of MM in those having undergone ASCT, NICE recommends offering a second ASCT to those who complete induction therapy for a second time without disease progression and had a

response duration of more than 24 months after their first transplant.[49] Those unsuitable for a second ASCT are given bortezomib monotherapy for four cycles, after which response is evaluated and the decision taken to continue treatment based on the caveats listed in Table 5.[49]

The ERG notes that the company's depiction of the treatment pathway (Figure

1) suggests that the combination of lenalidomide plus dexamethasone (len+dex) can be used as a second-line treatment, that is, for first relapse of MM. The ERG considers it important to emphasise that, as the company states in the CS, this is not currently the case: "lenalidomide plus dexamethasone (LEN+DEX) is currently recommended for patients who have received at least two prior regimens [TA171] and is being assessed for treating MM after one prior treatment with bortezomib (ID667)". At the time of drafting of the ERG's report, NICE had not published recommendations on the use of len+dex after bortezomib.

At second relapse, that is third-line treatment, two treatment options are available to clinicians in the England:

- len+dex;[45]
- panobinostat in combination with bortezomib plus dexamethasone (pano+bort+dex).[42]

The company comments that they have been advised by clinicians that, due to toxicity concerns around panobinostat, pano+bort+dex is unlikely to be used in place of len+dex in the third-line setting, a view that is supported by the ERG's clinical advisers. Thus, pano+bort+dex is likely to be reserved for people for whom len+dex is unsuitable, or who have progressed while on len+dex, and as such could be used as a third or fourth-line treatment.

Based on NICE guidance, pano+bort+dex is recommended for adults with rrMM who have specifically received at least two prior therapies, including bortezomib and an IMiD. In England, there can be stipulations around the therapies previously received before a person is eligible for a treatment, which typically involve IMiDs and PIs, either alone or in combination. For clarity, the ERG thinks it useful to give a brief overview of the drug(s) that form the classes of IMiDs and PIs. PIs act by inhibiting enzyme complexes (proteasomes) in cells from breaking down proteins important for controlling cell division, and the only PI approved for use in UK clinical practice by NICE is bortezomib. IMiDs reviewed for the treatment of rrMM in England are thalidomide and its analogues, that is, lenalidomide and pomalidomide. IMiDs have anti-angiogenic, anti-inflammatory and anti-proliferative effects. At this time, all three IMiDs (thalidomide, lenalidomide and pomalidomide) have been recommended by NICE as treatment options for MM and rrMM.

In 2015, as part of the STA process, NICE reviewed the combination of pom+dex for treatment of rrMM in adults who had received at least two prior therapies, including lenalidomide and bortezomib, and whose disease has progressed on the last therapy.[43] At that time, NICE did not recommend use of pom+dex in the specified population.[43] However, on 11 January 2017, NICE approved pom+dex as an option for treating MM in adults at third or subsequent relapse, and, specifically, after previous treatments including both lenalidomide and bortezomib.[48] In this setting, pom+dex is positioned as a fourth-line treatment, and, as noted by the company and the ERG's clinical experts, it is anticipated that pom+dex, if approved, is likely to be the predominant fourth-line treatment for rrMM in UK clinical practice.

In the CS (pg. 41), the company indicates that, based on available data from trials, they anticipate daratumumab to be positioned as an alternative treatment for people with rrMM who have received three or more prior therapies, that is, fourth line and greater. In another section of the CS (pgs 16 and 20), the company states that, based on available data from trials, they envisage daratumumab being used specifically at the fourth line of treatment. The proposed positions are both narrower than the population specified in the positive opinion for daratumumab issued by the European Medicines Agency (EMA), which specified the licensed population to be "...patients with rrMM, whose prior therapy included a PI and an IMiD and who demonstrated disease progression on the last therapy".[50] The ERG's clinical experts support, to an extent, the positioning of daratumumab as a fourth-line treatment, feeding back that their preference would be to use daratumumab after len+dex but before pano+bort+dex. Should len+dex be recommended by NICE as a second-line therapy, then daratumumab would likely be used at third line, with pano+bort+dex used from fourth line. With the approval of pom+dex as a treatment option at the fourth-line setting, clinicians may choose to use this combination regimen prior to daratumumab.

Clinical advice is that there is an unmet clinical need for treatments at fourth and higher relapses of rrMM, and greater flexibility in choice of treatment at this stage of rrMM is needed. At this level of relapse of rrMM, there is no optimum treatment and people are typically given the treatment that their clinician thinks they can best tolerate, based on, for example, performance status and bone marrow function. Daratumumab is administered intravenously, whereas pomalidomide and dexamethasone are both oral treatments. Thus, in some instances, pom+dex might be preferred. Alternatively, daratumumab has a more favourable adverse effect profile, being considerably less toxic than pom+dex (discussed in greater detail in Section 4.3.3). Thus, for a person no longer able to tolerate toxic therapy, daratumumab may be favoured over pom+dex.

The company positions bendamustine as the last treatment option for rrMM (Figure 1). As stated by the company, "bendamustine is currently available through the Cancer Drugs Fund (CDF) and is used off-

label for rrMM, where all other treatments are contraindicated or inappropriate". Feedback from the ERG's clinical experts on the use of bendamustine is in agreement with the company's comment that "RWE also indicates there is significant geographical variation in the use of bendamustine and, in line with CDF terms, it is indeed reserved for patients with no other treatment option".

The company also highlighted guidance from The British Committee for Standards in Haematology (BCSH) on the diagnosis and management of MM.[10] The BCSH reports that there is extensive evidence supporting the use of thalidomide-, bortezomib- and lenalidomide-based regimens at first and subsequent relapse.[10] To maximise response rate, the BCSH advises that thalidomide, bortezomib or lenalidomide regimens be delivered in combination with dexamethasone, with or without chemotherapy. The guidance from BCSH does not outline a set sequence of treatments for each relapse, instead advising that treatment is individualised for people with rrMM and decisions around treatment consider various factors (time of relapse, age, prior therapy, bone marrow function, comorbidities, and patient preference).

Overall, the ERG considers the company's overview of current service provision to be an accurate, relevant representation of clinical practice in England for the treatment of rrMM. After consultation with clinical experts, the ERG considers the proposed position of daratumumab in the treatment pathway of rrMM as subsequent to len+dex to be appropriate, with daratumumab most likely to be used at fourth or fifth line.

2.2.2 Resources required to administer daratumumab

In terms of resources required to administer daratumumab within the National Health Service (NHS), the company proposes that additional infrastructure will not be required to implement treatment with daratumumab. The Summary of Product Characteristics (SmPC) for daratumumab stipulates that daratumumab be administered by a healthcare professional in an environment where resuscitation facilities are available.[51] The company proposes that established haematology units likely to be administering treatment will have such facilities in place. The ERG's clinical experts concur with the company on this point.

The company recognises that daratumumab is associated with additional resource requirement relating to administration cost, as a consequence of daratumumab being provided as a concentrate solution for intravenous (IV) infusion rather than as an oral treatment, as in the case of pom+dex and panobinostat. Additionally, as the company acknowledges, the infusion time required for daratumumab, particularly for the first infusion, is much longer than other IV formulations (i.e., median time of 7–8 hours for daratumumab [CS, table 11, pg. 72] versus 3–5 seconds with bortezomib[51]). The ERG's clinical experts and reviewer stressed that the additional costs of administering daratumumab are likely to be

considerable, with one expert commenting that giving daratumumab will place substantial additional pressure on haematology day units, which are typically already running at full capacity: in the opinion of one of the ERG's clinical experts, extra nurses and haematology unit spaces would likely be required to accommodate administration of daratumumab. The ERG's clinical experts fed back that, in their experience, the first infusion of daratumumab can take as long 12 hours, and can lead to hospital admission and extensive additional resource and costs. The ERG's clinical experts concur with the company that the length of infusion and risk of IRR markedly decrease with subsequent infusions, and therefore second and subsequent infusions are likely to be administered as part of an outpatient appointment.

As the company acknowledges, one of the key adverse effects associated with daratumumab administration is an infusion-related reaction (IRR). Regular monitoring for IRR is key, as early identification and intervention for IRR are important for the safe use of daratumumab. In some cases, the severity of the IRR may require treatment necessitating an overnight stay in hospital. To minimise risk of IRR, as outlined in the SmPC, pre- and post-infusion medications should be administered to all patients.[51]

2.2.3 Estimated number of people eligible for treatment with daratumumab

The company estimates that 705 people annually will be eligible for treatment with daratumumab. The company's estimate is based on data from 2013, and with administration of daratumumab limited to fourth-line setting. As noted earlier, incidence statistics for MM were updated subsequent to the CS being drafted. For completeness, the ERG considers the company's estimate to require revising in terms of relevance to the NHS. Based on advice from clinical experts (discussed in greater detail in Section 3.1), dependent on the approval of pom+dex, the ERG considers it appropriate for the company to focus on use of daratumumab as a fourth-line treatment in the NHS.

The incidence of MM in 2014 for England was 4,652.[41] Applying the estimate that 15% of people with rrMM receive four or more lines of therapy in clinical practice,[52] the ERG estimates that 698 people in 2014 were eligible for treatment with daratumumab. Cancer Research UK reports that incidence of MM over the past 10 years has increased by 14%.[41] Thus, the ERG proposes that 698 is a conservative estimate of number of people who will be eligible per year for treatment with daratumumab. The ERG's clinical experts fed back that the estimate of 15% of people with rrMM would receive four or more lines of therapy reflects the situation in UK clinical practice. It should be noted that the ERG's clinical experts indicated that it would be difficult to obtain an accurate estimate of the number of patients potentially eligible for treatment with daratumumab, and that the company's original estimate, and the ERG's revised estimate, seem reasonable.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company provided a summary of the final decision problem issued by the National Institute for Health and Care Excellence (NICE; company's submission [CS], pg. 22),[1] together with a brief description of the rationale for any deviation from the decision problem (Table 6).

Table 6. Summary of decision problem as outlined in the CS

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with relapsed and refractory multiple myeloma that has previously been treated with a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.	People with relapsed and refractory multiple myeloma that has previously been treated with a proteasome inhibitor and an immunomodulatory agent, and who have demonstrated disease progression on the last therapy. The typical position of daratumumab monotherapy is anticipated to be as an alternative treatment for people who have received three or more prior therapies.	The anticipated positioning is based on the available trial data for daratumumab monotherapy.
Intervention	Daratumumab	Daratumumab monotherapy	–
Comparator(s)	• Panobinostat with bortezomib and dexamethasone • Lenalidomide with dexamethasone • Pomalidomide with dexamethasone (subject to ongoing NICE appraisal) • Bendamustine (not appraised by NICE but funded via the Cancer Drugs Fund; does not currently have a marketing authorisation in the UK for this indication)	• Panobinostat with bortezomib and dexamethasone • Pomalidomide with dexamethasone (subject to ongoing NICE appraisal) • Bendamustine (not appraised by NICE but funded via the Cancer Drugs Fund; does not currently have a marketing authorisation in the UK for this indication)	Due to the anticipated positioning for daratumumab monotherapy, and the preclusion of fair comparison due to lenalidomide pre-treatment in the daratumumab trial patients len+dex is not considered
Outcomes	The outcome measures to be considered include: • Progression-free survival; • Overall survival; • Response rates; • Time to next treatment;	The outcome measures to be considered include: • Progression-free survival; • Overall survival; • Response rates; • Time to next treatment;	–

	• Adverse effects of treatment • Health-related quality of life.	• Adverse effects of treatment; • Health-related quality of life; • Time to treatment discontinuation.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.	A cost-effectiveness analysis expressed in terms of incremental cost per quality-adjusted life year is presented. A lifetime time horizon of 15 years is used in the base-case analysis. Costs are considered from a NHS and Personal Social Services perspective. List prices are used within the submission document as requested by NICE (with PAS analyses presented in Appendix 16).	–
Subgroups to be considered	N/A	N/A	–
Special considerations, including issues related to equity or equality	N/A	N/A	–
Abbreviations: CS, company submission; len+dex, lenalidomide + dexamethasone; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme.			

3.1 Population

Data submitted in support of the clinical effectiveness of daratumumab are derived from two observational studies, MMY2002[53, 54] and GEN501.[55, 56] Both studies were multicentre studies, but no site, in either study, was based in the UK.

MMY2002 is an open label, Phase II, two-part study designed to evaluate the clinical effectiveness and safety of daratumumab in people with rrMM previously treated with at least three therapies (including PIs and IMiDs) or who were refractory to both a PI and an IMiD (design of MMY2002 described in greater detail in Section 4.2).[53, 54] Data from MMY2002 are supported by results from GEN501, which is a Phase I/II, two-part dose-escalating study focusing on safety of daratumumab (design of GEN501

described in greater detail in Section 4.2):[55, 56] evidence in support of the submission is presented specifically from Part 2 of GEN501. GEN501 included people with MM whose disease was relapsed or relapsed and refractory to two prior lines of therapy and who did not have further established treatment options. Inclusion criteria for GEN501 do not specify prior treatment with PI and IMiD, which is of relevance to the decision problem that is the focus of this STA (Table 6). However, baseline characteristics for GEN501 Part 2 indicate that everyone enrolled in the group from which relevant data are taken had received prior PI therapy and most people (95%) had received prior IMiD therapy.[55]

Both MMY2002 and GEN501 Part 2 evaluated and reported results for daratumumab at doses of 8 mg/kg body weight and 16 mg/kg body weight (hereafter referred to as 16 mg/kg). The conditional marketing authorisation issued by the European Medicines Agency (EMA) approves use of daratumumab at a dose of 16 mg/kg,[50] therefore, unless specified otherwise, information on patient characteristics and data presented on clinical effectiveness and safety pertains to daratumumab 16 mg/kg.

As noted in a preceding paragraph, inclusion criteria differed slightly between the two studies, and, as a result, people in MMY2002 were more heavily pre-treated than those participating in GEN501 Part 2 (inclusion criteria provided in Section 4.2). Compared with people in GEN501 Part 2, people in MMY2002 had, on average, received more lines of prior therapy, and a larger proportion of people was refractory to the last line of therapy (Table 7).[55] Of note, people in GEN501 Part 2 had a longer mean time since initial diagnosis of MM compared with those participating in MMY2002 (Table 7). Given that people in MMY2002 have been diagnosed later than those in GEN501 Part 2 but received, on average, more lines of treatment, they could be considered a more treatment-refractory population. Alternatively, difference between studies in median time since diagnosis may be attributable to variation in clinical practice in management of rrMM across the countries hosting trial sites for the two studies: MMY2002 was carried out at 20 sites across Canada (6), Spain (4) and the USA (16), whereas GEN501 Part 2was carried out at 6 sites across Denmark (2), Sweden (2), Netherlands (1) and the USA (1).

It is unknown how the study populations compare in terms of the prognostic characteristics of cytogenetics and ISS as this information was not collected during the conduct of GEN501. For MMY2002, equal proportions of people were categorised as ISS I and ISS II (37.7% of people in each category), and, based on the cytogenetic abnormalities reported in the Clinical Study Report (CSR), 25 people (out of 95 people for whom data were available) had a high-risk cytogenetic profile.[28, 53] Other baseline characteristics were similar between the studies, including age, and proportion of people with ECOG score of 1 or 2 (Table 7).[53, 55] The ERG notes that people in MMY2002 and GEN501 Part 2 are younger than people with rrMM typically treated in UK clinical practice. The ERG notes that it is

common for a population enrolled in a clinical trial to be younger than the representative population seen in clinical practice.

Table 7. Summary of baseline characteristics discussed in Section 3.1 of ERG report

Baseline characteristic	MMY2002 N=106	GEN501 N=42
Mean number of prior lines of therapy (SD)	5.6 (2.35)	4.9 (2.61)
Number of people refractory to the last line of therapy (%)	103 (97.2%)	32 (76.2%)
Mean time since initial diagnosis of MM (SD)	6.06 (4.06) years	84.64 (53.49) months
Age (SD), years	62.9 (10.00)	63.8 (8.27)
Number of people with ECOG score 1 (%)	69 (65.1%)	28 (66.7%)
Number of people with ECOG score 2 (%)	8 (7.5%)	2 (4.8%)
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ERG, Evidence Review Group; MM, multiple myeloma; SD, standard deviation.		

In UK clinical practice, before receiving daratumumab, people with rrMM will have been exposed to len+dex and bortezomib. Nearly all people in both MMY2002 and GEN501 Part 2 had received lenalidomide and bortezomib as part of their previous disease management (≥95% for each treatment; Table 9). Other therapies given prior to daratumumab in MMY2002 and GEN501 included carfilzomib and pomalidomide, neither of which, at the time of writing, will have been used as a treatment for rrMM in England: carfilzomib is not an available treatment option and pomalidomide was recommended as an option by NICE on 11 January 2017.[48] Carfilzomib was given prior to daratumumab in 50% of people in MMY2002 and 19% of people in GEN501 Part 2. Correspondingly, 63% and 36% of people in MMY2002 and GEN501 Part 2, respectively, received pomalidomide prior to daratumumab. In terms of number of and type of prior therapies received, the ERG's clinical experts advised that the population of GEN501 Part 2 is more closely aligned with the population who would most likely be eligible for daratumumab therapy in the UK.

The final scope for the decision problem defines the population relevant to this STA to be people with rrMM that has previously been treated with a PI and an IMiD and who have demonstrated disease progression on the last therapy (Table 6): the population specified in the final scope mirrors the population for which the EMA approved marketing authorisation of daratumumab, that is, "...patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy".[50] Given the specified population criteria, both MMY2002 and GEN501 Part 2 are relevant to the decision problem. However, the company is positioning daratumumab as a treatment at the fourth

line and greater, a setting that is better reflected by MMY2002 as most people enrolled have had three prior therapies.

With the exception of number of lines of prior therapy in GEN501 part 2, the ERG's clinical experts fed back that neither study alone accurately represents the baseline characteristics of people in England most likely to receive daratumumab in clinical practice. In the CS, the company presents clinical effectiveness data for an integrated analysis of results from MMY2002 and GEN501 Part 2. Although the ERG and the ERG's clinical experts appreciate that the company has taken a pragmatic approach to increase the sample number available for analysis, given the absence of baseline data on cytogenetics and ISS for GEN501 Part 2 and the other differences between the studies, the ERG and its experts have some reservations around the appropriateness of a simple pooling of data from the two studies (discussed in greater detail in Section 4.3).

In summary, the ERG considers the data presented within the submission to represent the population of interest to the decision problem as set out in the final scope issued by NICE.[1] However, as discussed above, the ERG considers that the population in the UK who would be eligible for daratumumab is narrower than the scope, being limited to people in the fourth-line and higher setting. In the context of daratumumab given at the fourth-line and higher in the UK, again, for the reasons outlined above, the ERG considers the submitted evidence to partially represent people with rrMM in England who would most likely be eligible for treatment with daratumumab. Any bias, and its likely direction, introduced into the interpretation of the clinical effectiveness results by differences between the populations in the studies from which data are derived, and the population that is the focus of this STA, is discussed in greater detail in relevant sections in Section 4.

3.2 Intervention

The CS provides an overview on the regulatory status and mode of action of daratumumab, which, as per the final scope issued by NICE, is the intervention of interest to the decision problem. In September 2015, the company applied to the EMA for a marketing authorisation for daratumumab.[50] After reviewing the submission through the accelerated application procedure, in April 2016 the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on allowing the company to market daratumumab in the European Union, with the approval of marketing authorisation following in May 2016.[50] In addition, due to the classification of MM as a rare disease, daratumumab had previously been granted orphan drug status (in 2013). The positive opinion issued by the CHMP is subject to review, and, in the case of daratumumab, continued approval is dependent on findings from two ongoing Phase III trials that evaluate daratumumab in combination with lenalidomide and dexamethasone (len+dex) in one trial (MMY3003; ClinicalTrials.gov identifier NCT02076009) and with bortezomib plus low dose dexamethasone (bort+dex) in the second trial (MMY3004; ClinicalTrials.gov identifier NCT02136134). The ERG notes that the ongoing Phase III studies are not relevant to the decision problem that is the focus of this STA, which is evaluating the clinical and cost effectiveness of daratumumab when given as a monotherapy.

As noted by the company, in November 2015, the US Food and Drug Administration (FDA) approved the use of daratumumab (monotherapy) for the treatment of rrMM, indicating the population suitable for treatment with daratumumab to be those "...with multiple myeloma (MM) who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and immunomodulatory agent".[57] The FDA approval aligns with the company's positioning of daratumumab as an alternative treatment at fourth-line and higher (Table 6), which is a narrowing of the population specified in the final scope (see Section 3.1). As discussed in Section 2.2, the ERG's clinical experts have indicated that, given treatment options for rrMM available at this time, they consider the company's restriction of daratumumab to an option at fourth line and greater to be appropriate.

Daratumumab is a human monoclonal antibody that is known to target CD38, a transmembrane glycoprotein that is expressed on the surface of many immune cells, including plasma cells and myeloma cells. The exact mode of action of daratumumab has yet to be elucidated, but it is thought that daratumumab triggers apoptosis (cell death) of tumour cells through several mechanisms, as described in the CS and presented in Box 5. The CS also provides a figure illustrating the proposed modes of action of daratumumab (Figure 2). A key tenet of the company's application to NICE is the proposed unprecedented benefit afforded by daratumumab, which the company attributes to "...the novel and unique multifactorial MoA [mechanism of action] of daratumumab which appears to change the natural

course of disease, such that the disease is effectively reset". Additionally, the company proposes that the novel mode of action of daratumumab increases the likelihood of patients benefiting from subsequent therapy.

Box 5. Mode of action of daratumumab (adapted from CS, pgs 29 and 30)

Daratumumab is a first-in-class, fully human $IgG1_K$ mAb with a serum half-life of 21 days.[58] Daratumumab binds to CD38, a transmembrane glycoprotein that is highly and ubiquitously expressed on the surface of many immune cells, including plasma cells and myeloma cells.[59, 60] CD38 has several functions in cell adhesion, signal transduction and calcium signalling, such that CD38-positive cell populations are associated with decreased immune function and disease progression in multiple myeloma (MM).[58, 61] CD38 is a distinct and novel target from those of other approved agents for MM due to its universal expression in plasma and myeloma cells. This universal expression not only allows daratumumab to induce myeloma cell death through the multifactorial mechanisms described below, but also means daratumumab is effective, irrespective of clonal heterogeneity, which is crucial in the relapsed and refractory setting where clonal heterogeneity is commonly observed.

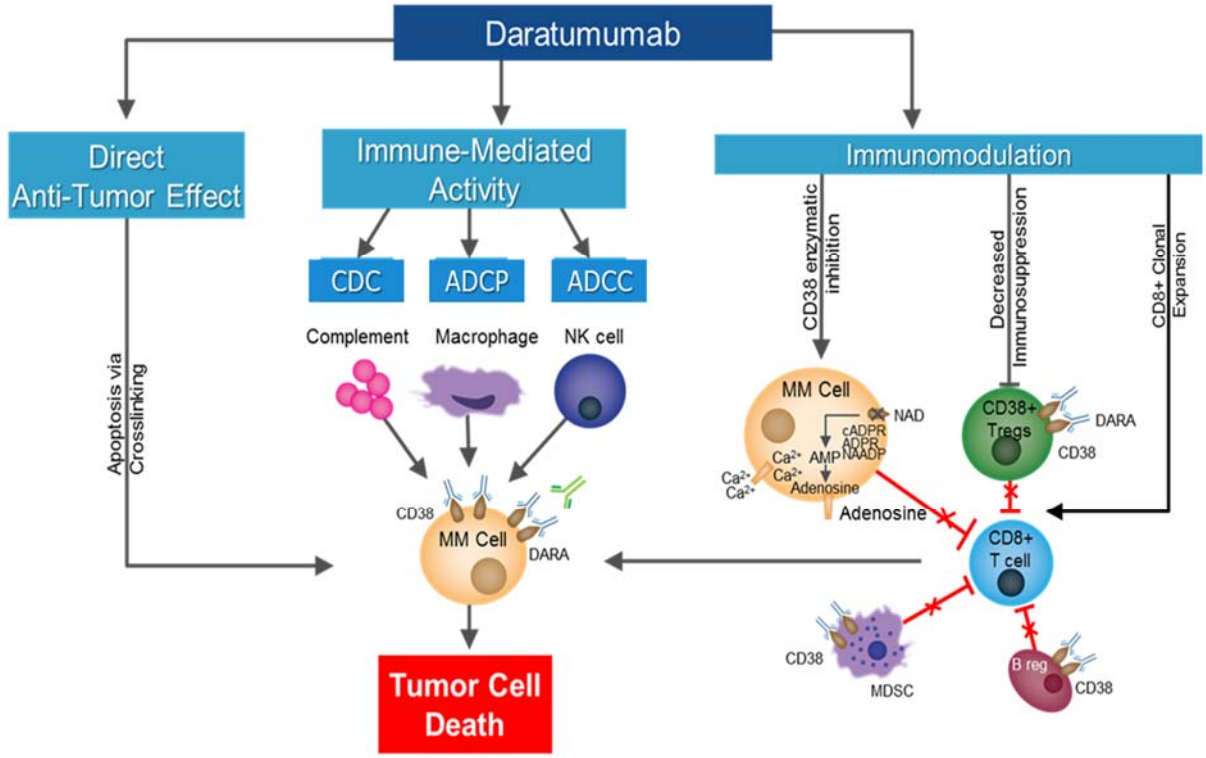
As depicted in Figure 2, daratumumab binding to CD38 induces a number of parallel processes that contribute to myeloma cell death. These processes include immune-mediated mechanisms of action (complement-dependent cytotoxicity [CDC], antibody-dependent cell-mediated cytotoxicity [ADCC] and antibody-dependent cellular phagocytosis [ADCP]), as well as induction of myeloma cell apoptosis (via Fc receptor-mediated crosslinking) and various immunomodulatory mechanisms.[61-65] The extent of the immunomodulatory effects of daratumumab is still under investigation, but, to date, its immunomodulatory mechanisms described include:

- Reduction of CD38-positive immunosuppressive cell populations including T regulatory cells, myeloid derived suppressor cells and B regulatory cells;[63]
- Modulation of the enzymatic activity of CD38 that may lead to a reduction in immunosuppressive adenosine levels;[63]
- Induction of helper and cytotoxic T-cell expansion and production of interferon-gamma in response to viral peptides;[63]
- Increased T-cell receptor (CD38) clonality.[63]

These immunomodulatory mechanisms serve to decrease immunosuppression and increase adaptive immune responses that may contribute to deeper clinical responses and enhanced survival.

Abbreviations: CS, company submission; pgs, pages.

Figure 2. Mechanism of action of daratumumab (reproduced from CS [Figure 2, pg. 30])



Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; CS, company submission; MM, multiple myeloma; NK, natural killer; pg, page.

The Summary of Product Characteristics (SmPC)[51] and marketing authorisation issued by the EMA[50] indicate that daratumumab be used at a dose of 16 mg/kg, initially given weekly (weeks 1-8), followed by bi-weekly (weeks 9-24), and lastly every fours weeks until disease progression (week 25 onwards).[51] The listed infusion rates for administration of daratumumab indicate that the first infusion of daratumumab be given in a dilution volume of 1000 ml, compared with 500 mL for all subsequent infusions. As noted in Section 2.2.2, it is recognised that the first infusion of daratumumab takes considerably longer than subsequent infusions. Data are presented in the CS to support the clinical effectiveness of daratumumab at a dose of 16 mg/kg. The ERG considers the use of daratumumab in the key trials presented in the CS to align with both the final scope issued by NICE, in terms of the specified intervention of interest, and the marketing authorisation for the drug.

3.3 Comparators

MMY2002 and GEN501, the key studies from which clinical effectiveness data are derived, are both two-part studies with data presented from a single group in support of the submission. Neither study has a comparator group that is relevant to this STA. Within the CS, the company presents the results of an integrated analysis of daratumumab from the two studies for various clinical effectiveness outcomes (Section 4.3), together with a matching-adjusted indirect comparison (MAIC) evaluating daratumumab versus pom+dex and versus pano+bort+dex.

As can be seen from Table 6, two additional comparators were specified by NICE in the final scope:

- len+dex;
- bendamustine.

The company's rationale for not carrying out the MAIC versus len+dex is that "In current practice, len+dex is used earlier in the treatment pathway (i.e. third-line). Trial data for daratumumab monotherapy are derived from a heavily pre-treated patient group, of whom 98% had received prior lenalidomide and 84% were refractory to lenalidomide".

In the case of bendamustine, the company did not identify sufficient data of adequate quality to facilitate the MAIC analysis. However, throughout the CS, the company also comments that they do not consider bendamustine a valid comparator for daratumumab, given that daratumumab is likely to be used, if approved, prior to bendamustine. As highlighted in Table 6, bendamustine does not have a marketing authorisation in the UK for rrMM, and has, therefore, not undergone appraisal by NICE: NICE does review unlicensed medications when they are a valid comparator but does not make recommendations on their use. Bendamustine is available through the Cancer Drugs Fund, and is therefore a NHS-funded treatment option. The ERG's clinical experts fed back that, in the context of the decision problem, it is unlikely that bendamustine would be used in preference to daratumumab.

The ERG's clinical experts agree with the company's views on the likely sequence of treatments in rrMM, that is, len+dex will likely be used prior to daratumumab and bendamustine is considered the last available treatment option for rrMM. Accordingly, the ERG considers it appropriate to not consider the comparisons of daratumumab versus len+dex and versus bendamustine in the context of the decision problem.

3.4 Outcomes

The company presents evidence on clinical effectiveness of daratumumab for most of the outcomes listed in the final scope issued by NICE.[1] Data were presented on:

- Progression-free survival (PFS);
- Overall survival (OS);
- Response rates (specifically overall response rate [ORR] and more granular measures of response, for example, complete response [CR], and partial response [PR];
- Adverse effects of treatment.

Other outcomes specified in the final scope for which evidence is not presented in the CS are:

- Time to next treatment;
- HRQoL.

Additional outcomes for which clinical effectiveness data are reported in the CS, but which are not specified in the final scope are:

- Time to response (TTR);
- Duration of response (DoR).

The company reports that they have also captured and reported data on time to discontinuation (TTD; Table 6). The ERG could not locate a definition of or results for TTD within the CS, nor in the CSRs for MMY2002 and GEN501.[53, 55] TTD is implemented in the economic model and was found by the ERG to have a considerable impact on cost effectiveness analyses. Thus, as part of the clarification process, the ERG asked the company to provide their definition of TTD. The company clarified that "TTD is time to treatment discontinuation and not time to progression". The company also stated that "data were taken from *post hoc* analyses of the patient level data (difference between start and stop date of DARA-treatment)". The ERG is unclear how the definition of TTD differs from that of duration of treatment provided in the CSR: the CSR for MMY2002 states for duration of treatment that "the Treatment Phase started from Cycle 1 Day 1 and continued until disease progression, unacceptable toxicity, study treatment discontinuation, or withdrawal of consent for treatment".[53] Although data for time to next treatment are not reported, data on TTR, DoR, and PFS are available.

The pre-specified primary outcome reported in MMY2002 is ORR (defined as PR or better). Within the CSR for MMY2002, secondary clinical outcomes captured are listed as DoR, TTR, time to disease progression (TTP), PFS, OS, and safety and tolerability of daratumumab.[53] It is stated within the CSR for MMY2002 that evaluations of ORR, and the other outcomes, were based on criteria recommended by the International Myeloma Working Group (IMWG):[66] IMWG consensus recommendations for evaluating response are provided in Appendix 10.4 (Table 36; reproduced from the CSR for MMY2002).

In contrast to MMY2002, GEN501 was designed to establish the safety profile of daratumumab rather than clinical effectiveness.[55] As described in greater detail in Section 4.2, GEN501 was conducted in two parts: Part 1 and Part 2. The CSR for GEN501 reports that clinical effectiveness variables were secondary outcomes, and some were captured through both Part 1 and Part 2, and some variables were collected in only Part 2. Measures of clinical effectiveness included in Part 1 and 2 were:[55]

- ORR;
- TTR;
- Serum/Urine M-Protein or FLC reduction;
- Change in bone marrow % plasma cells.

Additional efficacy variables captured in only Part 2 were:

- DoR;
- TTP;
- PFS;
- OS.

Given that data presented from MMY2002 and GEN501 Part 2 are taken from a single group and are thus not relative effect estimates, the ERG considers it worth mentioning direction from the FDA on the validity and robustness of data from single-arms studies in oncological conditions. Of particular relevance, the FDA comments that single-arm studies enrolling people with refractory tumours, and for whom there is no available therapy, provide an accurate assessment of ORR.[67] However, given the variability in the natural history of many cancers, single-arm studies, such as MMY2002 and GEN501, do not sufficiently characterise time to event endpoints, such as OS.[67] ORR is considered a direct measure of the antitumor activity of a drug but not as a measure of the stability of disease, and clinical

benefit in tumour response does not necessarily lead to benefit in OS. OS is considered to be the most reliable endpoint in randomised controlled trials evaluating interventions in oncological conditions, and is generally the preferred endpoint. However, it is also recognised that long follow-up periods and potential confounding from post-progression therapies can hinder the collection and analysis of survival data. The potential confounding around post-progression therapies and the impact on OS in MMY2002 and GEN501 Part 2 is discussed in more detail in Section 4.3.

Based on advice from clinical experts, the ERG considers that the outcomes presented in the submission are clinically relevant to the decision problem and, with the exception of time to next treatment and HRQoL, include those specified in the final scope for this STA.

3.5 Timeframe

The CS presents results on the clinical effectiveness of daratumumab from both MMY2002 and GEN501 Part 2 separately, and as an integrated analysis of the results of the two studies. The CS reports data for a primary analysis (data cut off of January 2015), an interim analysis of OS (6 months after the last patient received their first dose) and a later analysis at 18 months after the last patient received their first dose of daratumumab (data cut off of December 2015). The primary analysis was carried out at a median duration of follow-up of 9.3 months (range of 0.5 to 14.4 months) in MMY2002 and 10.2 months (range of 1.2 to 16.0 months) in GEN501 Part 2. Various outcomes were reported for both studies for this analysis, including safety, ORR, DoR, PFS and OS. For the third analysis, results for DoR and OS were reported for MMY2002 and ORR, DoR, PFS and OS were presented for GEN501 Part 2. Median follow-ups at this time point were reported to be 20.7 months (range of 0.5 to 26.3 months) and 20.5 months (range of 1.2 to 27.1 months) for MMY2002 and GEN501, respectively.

The ERG considers the duration of follow-up in both MMY2002 and GEN501 to be sufficient to assess clinical effectiveness and safety of treatment with daratumumab at the time points reported.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

4.1.1 Searches

The company carried out a systematic search of the literature to identify studies evaluating the clinical effectiveness of daratumumab and its relevant comparators for treating patients with relapsed and refractory multiple myeloma (rrMM) who had received at least two prior therapies. The company's systematic review was carried out from a global perspective (rather than focused on the UK setting relevant to the decision problem) and therefore the scope of comparators included in the search strategy was wider than is relevant to the final scope issued by the National Institute for Health and Care Excellence (NICE) for this Single Technology Appraisal (STA).[1]

Electronic databases (MEDLINE, Embase, The Cochrane Library: Cochrane Central Register of Controlled Trials, the Cochrane database of systematic reviews, and database of abstracts of reviews of effectiveness [DARE]) were initially searched in January 2016. All databases were searched from inception without date restrictions. The search was not restricted by language. Randomised control trials (RCTs), systematic reviews (SR) and non-randomised studies, such as prospective and retrospective observational studies, were included. In addition to the database searches, proceedings from recent key conferences (2014 and 2015) were searched by hand for relevant research. Relevant conferences identified by the company were: The American Society of Hematology; The European Hematology Association (EHA); The American Society of Clinical Oncology (ASCO); The European Society for Medical Oncology; and The British Journal of Haematology. An update search was conducted in July 2016, in which electronic databases were searched from January 2016 to July 2016 to identify any new evidence published after the initial search. Only conference proceedings from the EHA 2016 and the ASCO 2016 were hand-searched for the update search.

The search strategy devised by the company included terms relating to the disease area, rrMM and interventions of interest. The company identified comparator therapies to include in the search strategy by assessing clinical guidelines, Health Technology Assessment (HTA) recommendations, National Cancer Drug Fund list v6.0 (UK), on-going Phase II clinical studies via clinicaltrial.gov registry and real-world evidence (RWE) studies. The list of identified comparators was refined based on interventions used in routine clinical practice or anticipated to be used in clinical practice by the time of daratumumab licensing. Search terms were identified by examining prior systematic searches used in Cochrane reviews[68-70] and previous submissions to NICE.[47, 71, 72] The search was limited by study design (RCTs, SRs and observational studies) using search terms adapted from the Scottish Intercollegiate Guideline Network (SIGN).[73]

The Evidence Review Group (ERG) notes that the company makes no reference in the company submission (CS) to searching clinical trial registries (clinicaltrials.gov, clinicaltrialsregister.eu) for evidence of clinical effectiveness of interventions, only referring to trial registries for the purpose of identifying relevant comparators. Clinical trial registries are an important resource to identify on-going clinical trials, and, therefore, if such registries have not been searched to identify studies of clinical effectiveness, potentially relevant evidence could have been overlooked.

The company also carried out a systematic search of the literature for evidence on adverse effects (AEs) for daratumumab and its comparators. Two searches were carried out, the initial search in January 2016 and an update search in July 2016. The electronic databases MEDLINE and Embase were searched using AE search terms adapted from a search filter developed by British Medical Journal (BMJ) *Clinical Evidence*. The eligibility criteria and methods of reference selection were the same as those used for the clinical efficacy literature search. A total of nine primary source studies were identified in the AE evidence search. Of these nine, five related to interventions of interest (pomalidomide plus dexamethasone [pom+dex] and bendamustine). However, the company provides reference details for only four studies,[74-77] with no reason given for omitting the details of the fifth study. No further information was provided by the company relating to the five AE studies. Additionally, it is unclear whether the AE evidence was used in the CS.

The ERG identified an article detailing a longer follow-up period for a key study (MM-003) relevant to the decision problem that was not listed in the references identified by the company.[78] The data on longer term follow-up was published in October 2015. The ERG acknowledges that the time lag between publication and indexing in electronic databases could have led to the citation not being retrieved by the search carried out in January 2016. However, in the ERG's opinion, it is likely that the publication would have been retrieved in the July 2016 update search. MM-003 is a study investigating pom+dex and is a key component of the evidence base for this decision problem. The ERG argues this article should have been identified and included in the evidence presented by the company.

The ERG considers the search strategies designed by the company for clinical effectiveness and AE to be comprehensive and appropriate. However, based on the company not having included relevant evidence relating to pom+dex, a key comparator of interest, the ERG cannot definitively conclude the company's search and appraisal process has identified all relevant evidence.

4.1.2 Inclusion criteria

The eligibility criteria for the review of clinical effectiveness of daratumumab compared with relevant comparators is summarised in Table 8.

Table 8. Eligibility criteria for the search strategy (adapted from CS, pg. 55, Table 6)

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	• Adult patients with rrMM • Received ≥2 prior regimens	• Non rrMM population • Paediatric patients • Treatment naïve population • Patients who have received <2 prior therapies
Comparators	• Any active therapy • Best supportive care • Placebo • No treatment	-
Outcomes	• Clinical response (including response rates, time to response, duration of response) • HRQL • Overall survival • Progression free survival • Safety/tolerability • Time to progression • Time to next treatment	-
Study design	• RCTs • Non-RCTs • Prospective observational studies • Retrospective observational studies • Safety studies	• Case studies/series • Case reports • *In vitro* studies • Animal studies • Letter • Commentary • Editorial
Subgroups of interest	• Received ≥3 prior regimens including a PI and an IMiD • Received ≥2 prior regimens including a PI and an IMiD • Double relapsed and/or refractory to a PI and an IMiD	-
Language restrictions	• None • Papers not available in English assessed on English abstract	-

Abbreviations: CS, company submission; HRQL, health-related quality of life; IMiD, immunomodulatory agent; pg, page; PI, proteasome inhibitor; RCT, randomised controlled trial; rrMM, relapsed refractory multiple myeloma.

The ERG notes that the details outlined by the company in the eligibility criteria are broader than the NICE final scope, with the inclusion of all comparators in the disease area rather than specifying those relevant to the decision problem. The company highlights in the CS that the review was conducted from a global perspective and therefore would be broader than the specifications in the NICE scope.

The eligible population outlined by the company is also broader than the NICE scope for this STA, with the inclusion of patients that have received ≥2 prior regimens, but with no specification of the type of previous treatments. The ERG acknowledges that the company does outline a more refined population in the subgroups of interest, with details given on the number and type of prior therapy received by those with rrMM. One of the subgroups of interest listed by the company is the population specified in

the final scope issued by NICE, that is, people who have received ≥2 prior regimens including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD). The subgroup of people with rrMM who have received ≥3 prior regimens, including treatment with a PI and an IMiD, is the population that the company puts forward to be the most appropriate to the decision problem based on the proposed position of daratumumab as a fourth-line treatment for rrMM.

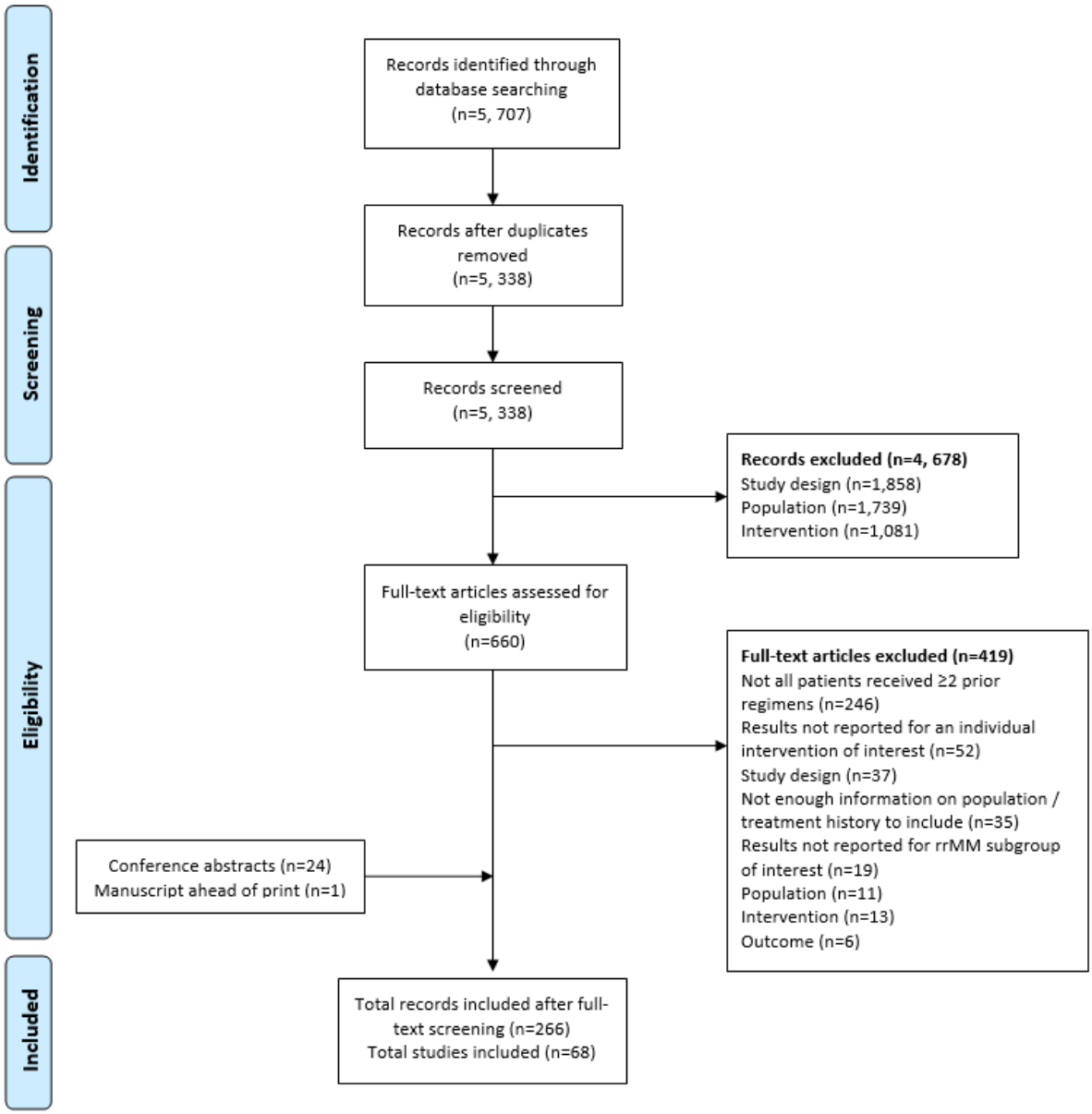
The ERG considers the inclusion criteria for the evidence review to be appropriate for identifying all studies relevant to the NICE final scope. In addition, the ERG considers the company's approach to assess all studies, irrespective of language of publication, to be good practice. The ERG acknowledges that the eligibility criteria presented by the company are broader than the specifications outlined in the NICE scope. However, the company's specified subgroups of interest address the decision problem set out by NICE and also the company's proposed positioning of daratumumab in the treatment pathway.

4.1.3 Critique of screening process

The company outlines the methods implemented to screen the studies retrieved by the systematic search of the literature. Following methods in line with those recommended by the Centre for Reviews and Dissemination,[79] initial record selection from titles and abstracts was undertaken by two independent reviewers and, in the case of disagreement, the record was independently assessed by a third reviewer.

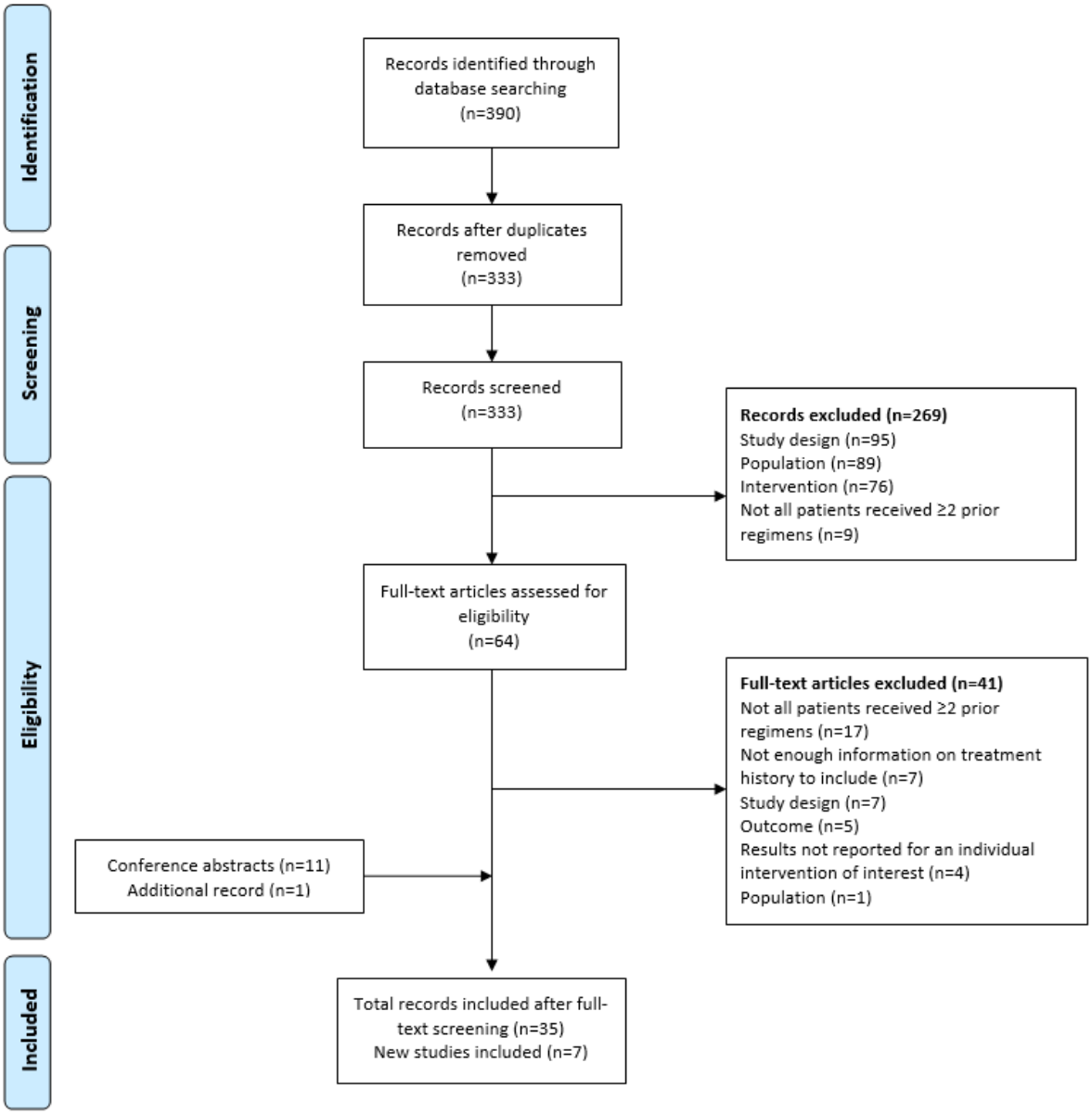
The initial search in January 2016 retrieved 5,338 records, of which 4,678 were excluded at the title and abstract stage. The full publications of the remaining 660 records were assessed. Appraisal of the full text led to the exclusion of an additional 419 records, with reasons for exclusion including mixed population, no outcomes of interest reported, or study design. Thus, 241 references met the inclusion criteria of the company's review. An additional 24 conference abstracts and one manuscript ahead of print were manually identified and included by the company, resulting in a final total of 266 relevant references that described 68 individual studies. A flow diagram of the screening process is presented in Figure 3.

Figure 3. PRISMA flow diagram for the search and appraisal of evidence on clincial effectivness, January 2016 (adapted from CS, pg. 58, Figure 5)



The update search from January to July 2016 retrieved 333 records, of which 269 were excluded based on assessment of title and abstract. A total of 64 records were assessed at full text stage, and, of these, 41 were excluded due to mixed population, study design and no outcome of interest. In addition to the 23 records identified from searching electronic databases, 11 conference abstracts and one other record were retrieved through manual searches. The 35 new records retrieved by the update search included references relating to seven studies additional to the 68 studies identified in the initial search. A summary of the update search process is provided in Figure 4.

Figure 4. PRISMA flow diagram for the search and appraisal of evidence on clincial effectivness, January 2016 to July 2016 (adapted CS, pg. 60, Figure 6)



The search carried out by the company from the global perspective retrieved references reporting on 75 different studies. However, when considering the comparators of interest to the decision problem as outlined in the NICE scope, the number of relevant studies is narrowed to 29, which investigated daratumumab (2 studies), pom+dex (17 studies), panobinostat in combination with bortezomib and dexamethasone (pano+bort+dex; 2 studies) and bendamustine (10 studies). A summary of the studies is provided in Appendix 10.1. Regarding evidence relating to daratumumab, no evidence from RCTs was identified. However, two studies, MMY2002[54] and GEN501,[56] were identified among the 29 included studies.

The company narrowed down the list of relevant studies based on study quality and comparability of patient characteristics. The company prioritised studies that best addressed the population as outlined in the decision problem. Two studies were found evaluating pano+bort+dex, that is, PANORMA 1 [80] and PANORMA 2 (also discussed in Section 4.3.1.1).[(81)] Although PANORAMA 1 is an RCT, the company's preferred study for comparison of daratumumab with pano+bort+dex is the Phase II singe-arm study PANORMA 2 as the baseline characteristics of the population are more similar to those of the populations in MMY2002 and GEN501 Part 2.

For the other comparators, one study (MM-003)[82] out of the 17 identified for pom+dex was found to be of high quality and was therefore included. No studies identified for bendamustine were included in the indirect treatment comparison (ITC), due to their poor quality and limited availability of data. Details of the included studies are listed in the CS Appendix 7 (pg. 63; summary provided in Appendix 10.1).

Due to the lack of suitable identified studies to inform the efficacy of bendamustine, the company expanded their search to include real world evidence (RWE) and also commissioned retrospective chart reviews. The company identified eight RWE studies. However, due to a lack of survival data, the company concluded that these studies were not suitable to be included in the ITC. It should also be noted that, as discussed in Section 3.3, bendamustine is not considered to be a comparator of interest to the decision problem.

The company commissioned two retrospective chart reviews, one with the International Myeloma Foundation (IMF) and one with the Haematological Malignancy Research Network (HMRN), which may contribute evidence on bendamustine for an ITC. Although the IMF retrospective review found only a small number of people who had been treated with bendamustine, this was the best available evidence and the data were included in the ITC analyses. The HMRN chart review, a UK-specific population-based cohort, also identified only a small number of people treated with bendamustine. In the case of the HMRN chart review, individual patient data (IPD) were not available and therefore the results from the review could not be included in the ITC analyses. The company provides the methodology and a quality assessment for the IMF review (CS Appendix 8, pg. 84, Table 17).

The ERG focuses on evidence concerning daratumumab in Sections 4.1.4 and 4.2. Further details concerning the identified comparator studies and indirect comparisons are discussed in Section 4.4.

In summary, due to the omission of a long-term follow-up publication of a key study, the ERG cannot definitively conclude that the company's search and appraisal process identified all relevant evidence on the clinical efficacy of daratumumab and relevant comparators. The ERG highlights the lack of high-quality evidence for several interventions, with only 1 RCT available and no comparative observational

studies to establish clinical efficacy of daratumumab compared with relevant comparators. In addition, estimates of clinical effectiveness of daratumumab are based on data from single arms from MMY2002 and GEN501 Part 2, as will be discussed in Section 4.1.4 and 4.2.

4.1.4 Quality assessment

The company provided assessments of the quality for the two studies MMY2002 and GEN501 using criteria that was adapted from an RCT assessment tool to assess non-RCT studies. The ERG notes that the company does not specify the source of the implemented quality assessment checklist. Domains included in the assessment were: selection bias; population eligibility; whether the study is reflective of UK practice; methods to account for missing participants; outcomes measured; type of analyses; and internal and external validity of results. Each of the domains was assessed as being at a 'low', 'medium' or 'high' risk of bias, with additional qualitative justifications provided. Summaries of the company's assessments, together with those of the ERG, for MMY2002 and GEN501 Part 2 are provided in Appendix 10.2. Details of quality assessments of studies investigating the efficacy of relevant comparators are covered in Section 4.4.

The company assessed both trials as being of low risk of bias, with the exception of patients in both studies being more heavily pre-treated than would be expected in UK clinical practice. In addition, based on the marketing authorisation issued by the European Medicines Agency (EMA), the populations enrolled in MMY2002 and GEN501 Part 2 only partially represent the licensed population.

The ERG's quality assessments of MMY2002 and GEN501 Part 2 differ from those of the company in some domains. The ERG's opinion is that, as long-term single-arm studies, both MMY2002 and GEN501 Part 2 are at a high risk of bias due to the inherent bias associated with their study design, which relates to the internal validity of the studies. In addition, in the context of how closely the studies reflect UK clinical practice, as discussed in Section 3.1, the ERG notes that some treatments received before enrolment are not (carfilzomib), or were not until January 2017 (pomalidomide), available treatment options in UK clinical practice, which weakens the external validity of the studies for the decision problem that is the focus of this STA (discussed in more detail in Section 4.2.3). The difference in prior treatments compared with the population in the UK that would likely be eligible for treatment with daratumumab is due to the disparate treatment options available in the countries in which the studies were carried out (as noted earlier, there was no study site in the UK).

Both studies initially assessed daratumumab at different doses and/or dosing schedules. In MMY2002, people were randomised to different doses (8 mg/kg vs 16 mg/kg of daratumumab). By contrast, in GEN501, people were sequentially allocated to different dosing schedules, with no randomisation (study is at a high risk of selection bias). As previously discussed in Section 3.1, both populations were

heavily pre-treated (further discussion in Section 4.2.3) with a median of four and five prior therapies for GEN501 Part 2 and MMY2002, respectively. The ERG agrees with the company that, based on the suggested positioning of daratumumab as a fourth-line therapy, most people in the two studies, and particularly MMY2002, are at a later line of therapy than would be expected in UK clinical practice.

Overall, the ERG considers MMY2002 and GEN501 to be of low quality due to the non-comparative design in the second stage of the studies. In addition, the ERG considers the studies are not generalisable to the UK rrMM population and UK clinical practice in terms of number and type of prior treatment.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

MMY2002 is a Phase II trial designed to evaluate the clinical effectiveness of daratumumab, whereas GEN501 (a Phase I/II trial) was designed to assess the safety and tolerability of daratumumab. Both studies comprised two phases, the first of which involved assessment of different doses of daratumumab. The primary outcome in MMY2002 was overall response rate (ORR), whereas the main focus of GEN501 was safety. Secondary outcomes in both studies included progression-free survival (PFS), overall survival (OS), duration of response (DoR), time to response (TTR), as well as safety for MMY2002 and ORR for GEN501. The studies had similar protocols and were run in parallel.

4.2.1 MMY2002

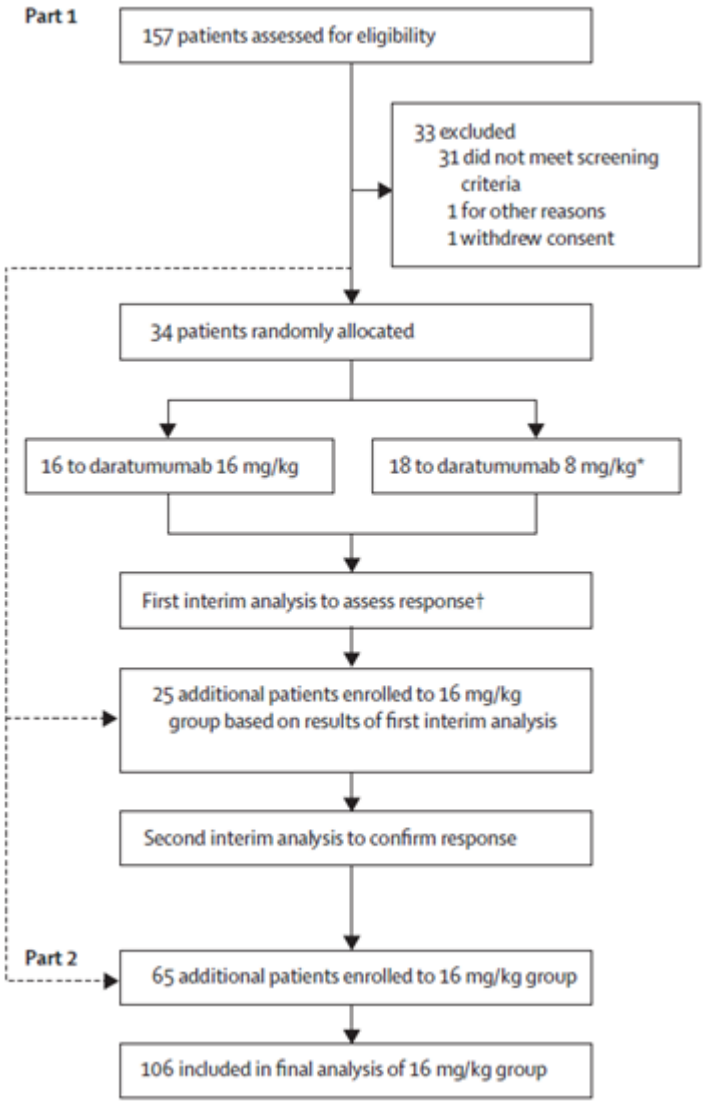
MMY2002 was a randomised, multicentre, open label study designed to assess efficacy and safety daratumumab in people with MM who had been previously treated with at least three lines of therapy that included a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who were refractory to both a PI and an IMiD.

The MMY2002 study was initiated in September 2013 and the final data cut-off point was December 2015. People were eligible for the study if they were 18 years or older, had been diagnosed with MM and had evidence of disease progression within 60 days of last dose of most recent treatment regimen. People must have responded to at least one prior treatment and received at least three previous lines of treatment including a PI and an IMiD, or be refractory to both a PI and an IMiD. To be eligible, people must have had an Eastern Cooperative Oncology Group (ECOG) score of two or lower (described in Table 3). The study was carried out across 26 sites in the USA, Canada and Spain.

The study consisted of two sequential parts, as shown in Figure 5. Part 1 was a dose comparison study in which 40 people were randomly allocated in a 1:1 ratio to either 8 mg/kg (N=20) or 16 mg/kg (N=20) of daratumumab (Stage 1). After the first interim analysis, the lower dose of 8 mg/kg was discontinued due to an unmet ORR and people had the opportunity to cross over to daratumumab 16 mg/kg. The

company highlights that three people moved to the 16 mg/kg dose but were not included in efficacy analyses. People that responded to and tolerated daratumumab 16 mg/kg at the first interim analysis continued treatment (N=16). In Stage 2 of Part 1, after the initial interim analysis, a further 25 people were enrolled and received daratumumab 16 mg/kg. Part 2 of the study was an expansion of Part 1 to further evaluate the selected daratumumab dose of 16 mg/kg, for which a further 65 patients were enrolled into the study. Thus, the total study population of MMY2002 consisted of 106 patients that received daratumumab 16 mg/kg dose across both Part 1 and Part 2 of the study in a predominantly non-randomised manner. Over the duration of the study, 90 people (85%) discontinued treatment with daratumumab. The most common reason for discontinuation was disease progression (82 people [77%]). Five people (5%) discontinued daratumumab because of AEs not related to treatment, and three people (3%) withdrew due to symptoms related to disease progression.

Figure 5. Patient flow diagram of MMY2002 study (reproduced from the company's clarification response, pg. 71, Figure 1)



The primary endpoint for MMY2002 was ORR as assessed by an independent review committee (IRC). Secondary endpoints included DoR, PFS, TTR and OS. Safety assessments were also carried out based on monitored AEs. All patients that received at least one dose of daratumumab 16 mg/kg were included in efficacy and safety analyses. Outcomes were assessed at three time points. At the primary analysis data cut-off in January 2015, outcomes assessed were ORR, DoR, PFS, OS, TTR, and safety. At this time point, the median follow up was 9.3 months (range of 0.5-14.4 months). OS was also evaluated at an interim analysis in June 2015, which was 6 months after the last patient received their first dose of daratumumab. Median follow-up at the interim analysis was 14.7 months (range of 0.5-20.0 months). At the final data cut-off point (December 2015), DoR and OS were assessed: final data cut off occurred 18 months after the last patient received their first dose of daratumumab. Median follow-up was 20.7 months (range of 0.5-26.3 months) at this time point.

4.2.2 GEN501

GEN501 was a multicentre, open-label study with the primary aim of evaluating the safety of daratumumab in people with rrMM. Patients were enrolled from March 2008 and the latest data-cut off was December 2015. Patients were eligible for enrolment if they were 18 years or older, had myeloma requiring systemic therapy and had received two or more therapies, including IMiD, PI, chemotherapy or autologous stem-cell transplant (ASCT). As discussed in Section 3.1, the NICE scope outlines that the relevant patient population for the decision problem is people with rrMM who have previously received a PI and an IMiD and who have demonstrated disease progression on the last therapy. To be eligible for GEN501, people do not have to have received both a PI and an IMiD, which does not fully reflect the population specified in the decision problem. All patients enrolled in the study had previously had a PI, but not people had previously been treated with an IMiD (95%). Patients also had to have a life expectancy of at least 3 months, an ECOG performance status score of $\leq$2 and measurable level of M protein or free light chains (FLCs) according to the International Myeloma Working Group (IMWG) guidelines. The study was carried out across 10 sites in the USA, Denmark, Sweden, and the Netherlands.

Like MMY2002, GEN501 was a two-part study. Part 1 (N=32) was a dose-escalation study with people sequentially assigned to one of 10 dose groups (0.005, 0.05, 0.1, 0.5, 1, 2, 4, 8, 16, 24 mg/kg). A 1+3 design was used for the lower dose groups (0.005 and 0.05 mg/kg); one patient received the starting dose (0.005 mg/kg) and, if the person did not experience dose-limiting toxicities (DLT), the dose was escalated and three new patients started treatment at the escalated dose. By contrast, a 3+3 design was used for the remaining eight dose groups (0.1, 0.5, 1, 2, 4, 8, 16 and 24 mg/kg), in which three patients received treatment (0.1 mg/kg) and a further three received the escalated dose providing the people receiving the lower dose did not experience a DLT. In Part 2, 72 patients were enrolled to five cohorts

assessing daratumumab 8 mg/kg (3 cohorts) and 16 mg/kg (2 cohorts) in different treatment schedules. The two cohorts in GEN501 Part 2 (N=42) receiving daratumumab 16 mg/kg, which is the licensed dose, form the population of interest to the decision problem.

In GEN501 Part 2, in both dosing schedules for daratumumab 16 mg/kg, the first dose of daratumumab was a 1000 ml infusion over a period of 6 hours, with subsequent infusions for both schedules given as a 500 ml infusion over a period of 3.25 to 4 hours. The key difference between the two schedules was the process used to manufacture daratumumab, with no substantial variation between the two dosing schedules. All participants in GEN501 Part 2 received monthly infusions until disease progression occurred or AEs became unmanageable. At the time of the primary analysis (January 2015), 14 people (19%) across all five cohorts in GEN501 Part 2 were still receiving treatment, all of whom were on daratumumab 16 mg/kg. All 30 people who received daratumumab 8 mg/kg discontinued treatment as a result of disease progression. The 28 people who received daratumumab 16 mg/kg and discontinued treatment did so because of disease progression or AEs.

The primary endpoint of GEN501 was safety, relating to the frequency and severity of AEs, which were monitored at each treatment visit. An IRC evaluated serious AEs, non-serious AEs at Grade 3 or higher, and AEs that led to patients withdrawing from the study. The secondary endpoints of GEN501 included ORR according to the IMWG response criteria for myeloma, TTP, DoR, PFS, and OS. It is noted that evaluations of disease status were done through a computerised algorithm, with regular review of unblinded data by an Independent Data Monitoring Committee (IDMC), which provided recommendations on the continuation, modification, or termination of GEN501. During clarification the company reported that the "computerised algorithm for assessing efficacy data was developed based on MMY2002 data, and the same algorithm was utilized for efficacy assessment in study GEN501. The validity of this algorithm assessment was evaluated against the IRC assessment in study MMY2002". The company went on to comment that "A detailed summary of the reliability of the computerized algorithm is presented in MMY2002 CSR Section 5.2, which concludes that the agreement between the IRC assessment and computerized algorithm assessment was almost perfect". The ERG confirms that the kappa coefficient for the agreement between determinations made by the IRC and the computer algorithm was 0.98 (95% CI: 0.94 to 1.00):[53] a kappa coefficient of ≥0.8 is considered excellent agreement.[53]

Assessment of outcomes took place at three time-points (median follow-up reported for daratumumab 16 mg/kg groups):

- January 2015: primary analysis for all outcomes (safety, ORR, DoR, PFS and OS) with a median follow-up 10.2 months (range 1.2-16.0 months);

- June 2015: interim analysis for OS with a median follow-up of 15.2 months (range of 1.2-21.4 months);

- December 2015: final data cut-off (ORR, DoR, PFS and OS) with a median follow-up of 20.5 months (range of 1.2-27 months).

The ERG notes that the primary outcome measure of safety was assessed at the earlier cut-off of January 2015.

4.2.3 Baseline characteristics

Baseline characteristics of people in MMY2002 and GEN501 Part 2 are summarised in Table 9. Although, in both studies patients received various doses of daratumumab, as noted in Section 3.1, here the ERG focuses on the licensed dose of daratumumab of 16 mg/kg.

People in MMY2002 and GEN501 Part 2 had a similar median age of around 64 years and the proportions of patients with ECOG performance status 0, 1 or 2 were also similar. However, the proportion of men was larger in GEN501 Part 2 (64%) compared with MMY2002 (49%), and time since initial diagnosis was longer in GEN501 Part 2 than in MMY2002 (5.8 years versus 4.8 years, respectively). However, counterintuitively the median number of lines of prior treatments was lower in GEN501 Part 2 than in MMY2002 (4 versus 5, respectively). As discussed in Section 3.1, the ERG proposes one potential reason for this observation is that people in MMY2002 had shorter periods of response to prior treatments before enrolment in the study, and thus could be more refractory to treatment than those enrolled in GEN501 Part 2. It is noted that a larger proportion of people in MMY2002 (97%) was refractory to the last line of treatment compared with GEN501 Part 2 (76%; Table 9), which would be expected based on the inclusion criteria for MMY2002 that people could be double-refractory to PI and IMiD. In addition, there were differences between the studies in refractoriness to individual treatments (Table 9). For example, 48% of patients in MMY2002 were refractory to carfilzomib compared with 17% of people in GEN501 Part 2 (Table 9). Alternatively, the difference in median time since diagnosis may be attributable to variation in clinical practice in management of rrMM across the countries hosting trial sites for the two studies.

The ERG's clinical experts highlight that with each subsequent line of therapy patients are likely to have a poorer prognosis. In addition, with each line of therapy, the patient is also exposed to more toxic treatments. As noted in Section 3.1, some of the prior treatments people had received at enrolment are not, or were not until recently, available treatment options in UK clinical practice, that is, carfilzomib and pomalidomide. Pomalidomide is known to be associated with severe AEs. Therefore, patients that were pom+dex-naïve at baseline are likely to have a better performance status and tolerate additional

lines of therapy better than patients exposed to pomalidomide. In MMY2002, 63% of the population received pomalidomide, compared with 36% in GEN501 Part 2. The proportion of people who received carfilzomib as a prior therapy also differs between the studies, with 50% of people in MMY2002 receiving carfilzomib compared with 19% in GEN501 Part 2. The ERG notes that the variation between studies in exposure to carfilzomib and pomalidomide is likely associated with availability of each treatment before recruitment to the studies.

Table 9. Baseline characteristics of patients in MMY2002 and GEN501 Part 2 (adapted from CS, pg. 73, Table 12)

	MMY2002	**GEN501 Part 2**
	Dara 16 mg/kg (N=106)	**Dara 16 mg/kg (N=42)**
Age, median (range)	63.5 (31-84)	64.0 (44-76)
Male, n (%)	52 (49)	27 (64)
ECOG score, n (%)		
0	29 (27)	12 (29)
1	69 (65)	28 (67)
2	8 (8)	2 (5)
ISS staging, n (%)		Not assessed
I	26 (25)	
II	40 (38)	
III	40 (38)	
Extramedullary plasmacytomas, n (%)		
0	92 (87)	38 (90)
≥1	14 (13)	4 (10)
Cytogenetic profile, n (%)	N=95	Not assessed
t(4;14)	9 (9.5)	
del17p	16 (16.8)	
del13q	30 (31.6)	
amp1q21	23 (24.2)	
other	43 (45.3)	
Time since initial diagnosis, median years (range)	4.8 (1.1-23.8)	5.8 (0.8-23.7)
Number of lines of prior therapy, median (range)	5 (2-14)	4 (2-12)
>3 prior lines of therapy, n (%)	87 (82)	26 (62)
Prior PI, n (%):	106 (100)	42 (100)
Bortezomib	105 (99)	42 (100)
Carfilzomib	53 (50)	8 (19)
Prior IMiD, n (%)	106 (100)	40 (95)
Lenalidomide	105 (99)	40 (95)
Pomalidomide	67 (63)	15 (36)
Thalidomide	47 (44)	19 (45)
Refractory to last line of therapy, n (%)	103 (97)	32 (76)

Refractory to PI/IMiD, n (%)	101 (95)	27 (64)
PI only	3 (3)	3 (7)
IMiD only	1 (1)	4 (10)
Refractory to PI + IMiD + alkylating agent, n (%)	79 (75)	21 (50)
Refractory to, n (%):		
Bortezomib	95 (90)	30 (71)
Carfilzomib	51 (48)	7 (17)
Lenalidomide	93 (88)	31 (74)
Pomalidomide	67 (63)	15 (36)
Thalidomide	29 (27)	12 (29)
Alkylating agent	82 (77)	25 (60)
Abbreviations: CS, company submission; Dara, daratumumab; ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory agent; ISS, International Staging System; PI, proteasome inhibitor		

As outlined in Section 2.1 of the ERG report, there are key characteristics that can have an influential role in how patients respond to treatment, including ISS stage and cytogenetics. In GEN501 Part 2, data on the cytogenetic profile and ISS staging were not recorded, which makes it difficult to draw conclusions on the comparability of baseline characteristics of people in MMY2002 and GEN501 Part 2, as well as whether the study population in GEN501 Part 2 is representative of the rrMM population in the UK.

For the data that are available, as touched on in Section 3.1, the baseline characteristics of neither MMY2002 nor GEN501 Part 2 fully represent the population in UK clinical practice who would likely be eligible for treatment with daratumumab. In both trials, some patients has received prior carfilzomib, a treatment undergoing a NICE technology assessment but not currently approved. In addition, a substantial proportion of patients had also previously been given pomalidomide, which was recently (January 2017) approved as a fourth-line treatment in the UK. Given the proposed position of daratumumab by the company as a fourth-line therapy, pomalidomide would be a direct comparator and would not be given to rrMM patients prior to daratumumab. Importantly, in the context of the decision problem, no person in the UK who would likely be eligible for treatment with daratumumab will have received pomalidomide as a prior treatment at the time of writing. Fewer patients in GEN501 Part 2 had been treated with carfilzomib or pomalidomide compared with MMY2002. Therefore, in terms of type of prior therapy received, GEN501 Part 2 is more representative of UK clinical practice. At the clarification stage, the company provided a more detailed breakdown of number of prior lines of therapy at enrolment, which is summarised in Table 10. These data show that a larger proportion of patients that received less than 3 prior treatments in GEN501 Part 2 (21.43%) compared with MMY2002 (1.89%). Therefore, despite both study populations being heavily pre-treated, the ERG considers the MMY2002 study population to be more aligned with the proposed positioning of daratumumab, in terms of number of prior treatments.

Table 10. The number of patients at baseline by the previous number of therapies (reproduced from company response at clarification, pg. 73, Table 23)

Number of lines of prior therapy	MMY2002, Dara 16mg/kg (N=106)		GEN501 Part 2 Dara 16mg/kg (N=42)	
	n	%	n	%
2	2	1.89	9	21.43
3	17	16.04	7	16.67
4	23	21.70	7	16.67
5	19	17.92	5	11.90
6	14	13.21	3	7.14
7	11	10.38	3	7.14
8	7	6.60	3	7.14
9	6	5.66	3	7.14
10	3	2.83	1	2.38
11	2	1.89	0	0.00
12	0	0.00	1	2.38
13	1	0.94	0	0.00
14	1	0.94	0	0.00

Overall both study populations are substantially different from the UK MM population who is expected to be eligible for treatment with daratumumab, in terms of number of lines and type of prior therapies. In addition, based on the highlighted differences between the trials, and given the absence of baseline data on cytogenetics and ISS for GEN501 Part 2, the ERG and its experts have some reservations around the appropriateness of the naïve pooling of data from the two studies as described in the CS (discussed in greater detail in Section 4.3).

4.2.4 Description and critique of statistical approach used

The company provide a summary of the statistical analyses plan for both MMY2002 and GEN501 Part 2; a summary is provided in Table 11.

4.2.4.1 MMY2002

The primary endpoint in MMY2002 was ORR. Response rates for each treatment group were tabulated and presented with two-sided 95% confidence intervals (CI). An IRC assessed the primary endpoint of the study at the primary data cut-off point in January 2015. Secondary endpoints included time-to-event outcomes, such as OS and PFS, which were analysed using Kaplan-Meier (KM) methods with the median value and corresponding CI provided. All patients who received at least one dose of daratumumab were used for efficacy and safety analyses. Pre-specified subgroup analyses were carried out for ORR, including patients that were refractory to prior therapies including PI, IMiD or both.

For Part 1 of MMY2002 (the randomised dose comparison), it was calculated that 40 patients needed to be enrolled to each of the treatment groups to detect an ORR of at least 15%. The sample size

calculation was based on an estimated 10% drop-out rate, a one-sided α of 2.5%, and a power of 85%. The CSR for MMY2002 indicates that, if it was determined at the end of Part 1 that a treatment group was to be further evaluated in Part 2, then up to an additional 60 subjects were to be enrolled.[53]

Patients who were lost to follow-up, withdrew from the study, died due to causes other than disease progression or who completed the study without progression and were still alive at data-cut off were censored at the last disease assessment date. For measures including TTP and DoR patients who started subsequent therapy for MM were censored at last disease assessment prior to the start of subsequent therapy. For measure of TTR, patients without response were censored either at disease progression or if they did not progress at the last disease assessment before subsequent therapy. For OS, if a patient was still alive or information on vital status was unknown the patient's data were censored at the last known date of life.

4.2.4.2 GEN501

The GEN501 study had no formal statistical hypotheses or power calculations to determine sample size. Part 1 of the study was planned to include a maximum of 62 patients and Part 2 a maximum of 80 patients, resulting in a total population of 112 for both study parts.

The primary endpoint was safety, which was assessed by an IDMC. Secondary endpoints included OS and PFS, which were calculated using KM methods with median values and 95% CI provided. For ORR, the number of patients in each response category was tabulated and two-sided 95% CIs were provided for treatment groups. These secondary outcomes were assessed by a computer algorithm created based on MMY2002 data and validated by the MMY2002 IRC. A series of subgroup analyses were carried out for ORR assessing different groups, including the number of lines of prior therapy patients had received (≤3 lines and >3 lines of therapy), prior therapies to which patients were refractory, and age (18-64 years, 65-74 years and ≥75 years).

Patients without response were censored at progressive disease or, if progression didn't occur, at the last disease assessment before the start of subsequent therapy. Patients who were lost to follow up, withdrew from study due to disease progression or died due to causes other than disease progression were censored at last disease assessment date. For time-to-event measures (TTP, PFS and DoR) patients who started subsequent therapy for MM were censored at the last disease assessment before starting subsequent treatment. For OS, patients alive at data cut-off or whose vital status was unknown were censored at last date of contact.

The company outline that different data cut-off points were used for ORR and PFS assessment in the integrated analysis of MMY2002 and GEN501 Part 2. In MMY2002, efficacy was assessed at the primary data cut-off point in January 2015, whereas in GEN501 Part 2 efficacy was assessed at the last

data cut-off point in December 2015. At the clarification stage, the company provided justification for the mix of data cut-off points used in the integrated analysis; in MMY2002 independent review only occurred at the primary assessment in January 2015 whereas for GEN501 Part 2 a computerised algorithm was utilised and assessed efficacy data at all data cut-off points including the last point in December 2015.

Overall, the ERG considers the statistical approaches in MMY2002 and GEN501 to be appropriate for the study design, with the caveat that GEN501 had no a priori hypotheses or power calculations.

Table 11. Summary of statistical analyses in the MMY2002 and GEN501 studies (Adapted from CS Appendix 4, pg. 55)

Study ID	MMY2002	GEN501
Hypothesis objective	The null hypothesis was that the ORR was at most 15%, and the alternative hypothesis was that the ORR was at least 40%.	Formal statistical hypotheses were not formulated or tested.
Statistical analysis	For the primary endpoint of ORR, the number and percentage of subjects in the following response categories were tabulated by treatment group: sCR, CR, stringent CR + CR, VGPR, PR, ORR, MR, ORR + MR, SD, PD, and NE. For each of the above categories, two-sided 95% exact CI were presented by treatment group. Time-to-event endpoints were analysed with the use of the KM method. Median values and corresponding 95% CIs were provided. Descriptive statistics were also provided to summarise first response and time to best response.	For the primary efficacy endpoint of ORR, the number and percentage of subjects in the following response categories were tabulated by treatment group: sCR, CR, stringent CR + CR, VGPR, PR, ORR, MR, ORR + MR, SD, PD, and NE. For each of the above categories, two-sided 95% exact CI were presented by treatment group. Time-to-event endpoints were analysed with the use of the KM method. Median values and corresponding 95% CIs were provided. Descriptive statistics were also provided to summarise first response and time to best response. Pharmacokinetic variables were estimated by means of a non-compartmental analysis.
Sample size, power calculation	Within each randomised treatment group, a 2-stage design was employed. With a one-sided α of 2.5%, and a power of 85%, the total sample size within each randomised treatment group in Part 1 was 36 response-evaluable subjects. Assuming a non-evaluable rate of 10%, up to 40 subjects were to be enrolled within each randomised treatment group. The Stage 1 analysis was to be performed when approximately 15 subjects were enrolled in each treatment group and had sufficient data (i.e. up to 8 weeks of treatment) to be evaluable for response. Future enrolment into each treatment group was to be terminated if it was determined during the first stage that the treatment group was considered as ineffective or not well-tolerated. If a treatment group proceeded to the second stage with a total of 36 evaluable subjects with 2 stages combined, the null hypothesis was to be rejected if 11 or more responses were observed.	No power calculations were performed. For Part 1, a maximum of 62 subjects was planned (1+3+3 at the 2 lowest dose levels, and 3+3 at each of the remaining 8 dose levels). One subject at the 2 lowest dose levels, with the possibility to expand to 7 subjects and 3 subjects per dose level at the remaining dose levels with the possibility to expand to 6 subjects, was considered sufficient to establish the safety basis for escalation to the next dose level. For Part 2, up to 80 subjects could be enrolled, for a maximum of 112 subjects enrolled across both parts. With the descriptive statistics methodology for the primary endpoint in mind, the impact of different sample sizes on the descriptive statistics is presented by the probability of making at least 1 observation of an event with rare incidence.
Data management,	For TTP and DoR patients who started subsequent therapy for multiple myeloma were	For both time to first response and time to best response, patients without response

Study ID	MMY2002	GEN501
patient withdrawals	censored at the last disease assessment prior to the start of subsequent therapies or the date of cross-over, whichever was earlier. Patients who were lost to follow-up, withdrew consent, withdrew from study without disease progression, or died due to causes other than disease progression were to be censored at the last disease assessment date. For PFS, patients who started subsequent therapy for multiple myeloma were censored at the last disease assessment prior to the start of subsequent therapies or the date of cross-over, whichever was earlier. Patients who withdrew from study without disease progression were to be censored at the last disease assessment date. Patients who completed the study, had not progressed, and were still alive at the cut-off date of the analysis or were lost to follow-up were to be censored at the last disease assessment. For TTR, patients without response were to be censored either at disease progression, or in the absence of disease progression, at the last disease assessment before the start of subsequent therapy. For OS, if the patient was alive, or the vital status unknown, the patient's data were to be censored at the date the patient was last know alive.	were censored either at progressive disease or, in the absence of progressive disease, at the last disease assessment before the start of subsequent therapy. Patients with no post-baseline disease assessment were censored on Day 1. For TTP, PFS, DoR patients who started subsequent therapy for multiple myeloma were censored at the last disease assessment prior to the start of subsequent therapies (inclusive). Patients who were lost to follow-up, withdrew consent, withdrew from study without disease progression, or died due to causes other than disease progression were censored at the last disease assessment date. For OS, data for patients who were alive at the date of the last contact or had an unknown status were censored at the date of the last contact. Subjects who had withdrawn were censored at the date of withdrawal.
Abbreviations: CI, confidence interval; CR, complete response; DoR, duration of response; IRC, independent review committee; KM, Kaplan–Meier; MR, minimal response; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; SD, stable disease; TTP, time to progression; VGPR, very good partial response.		

4.2.5 Summary statement

Evidence on clinical effectiveness of daratumumab in rrMM was derived from two observational studies, MMY2002 and GEN501. MMY2002 and GEN501 are a Phase II and Phase I/II study, respectively, that were carried out in parallel. Neither study had a site in the UK. Both studies were carried out in two stages, with the first stage in each study involving investigation of different doses of daratumumab. In MMY2002, people were initially randomised to daratumumab 8.0 mg/kg or 16.0 mg/kg. In GEN501, people were allocated sequentially to daratumumab, starting at 0.05 mg/kg dose, escalating to 16.0 mg/kg. Subsequent to identification of the optimum dose of 16.0 mg/kg, the final stage in each study involved following a single cohort to evaluate clinical effectiveness and safety of daratumumab at the licensed dose (16.0 mg/kg). Thus, the second stage of GEN501 and both stages of MMY2002 from which data are presented in support of the submission is observational in nature, not having a randomised component. It is noted that guidance from the FDA reports that single-arm studies are not appropriate for capturing time-to-event data such as PFS and OS.

With a primary outcome of ORR, MMY2002 was designed to evaluate the clinical efficacy of daratumumab in people with rrMM previously treated with at least three therapies (including PIs and

IMiDs) or who were refractory to both a PI and an IMiD. By contrast, the primary goal of GEN501 was to assess safety and tolerability of daratumumab. The population enrolled in GEN501 Part 2 were those with MM whose disease was relapsed or relapsed and refractory to two prior lines of therapy and who did not have further established treatment options.

The outcomes assessed in the studies and presented in the CS are clinically relevant. Outcomes were captured at three time points in both MMY2002 and GEN501 Part 2. However, the same outcomes were not recorded at the same time points, with longer follow-up for ORR in GEN501 Part 2 compared with MMY2002.

Comparison of baseline characteristics across MMY2002 and GEN501 Part 2 identified differences in characteristics associated with prognosis and outcome. Based on the median number of prior therapies (five in MMY2002 vs four in GEN501 Part 2), and the proportion of people who were refractory to their last treatment (97.2% in MMY2002 and 76.2%), the ERG notes that people in MMY2002 are more heavily pre-treated and are more refractory to treatment than those in GEN501 Part 2. In addition, information on ISS stage and cytogenetics, characteristics that are also associated with prognosis, were not recorded for GEN501 Part 2.

The ERG has concerns around the generalisability of the studies to the UK population most likely to be eligible for treatment with daratumumab. In MMY2002 and GEN501 Part 2, some of the therapies people had received prior to trial entry are not available treatment options within the UK (carfilzomib, and, until January 2017, pomalidomide). Moreover, some of the subsequent treatments given on disease progression are not available treatment options in this setting in UK clinical practice.

Within the CS, the company presents results for an integrated analysis of MMY2002 and GEN501 Part 2. Given the differences between the studies in baseline characteristics, the ERG considers it inappropriate to combine the data of the two studies. Furthermore, the ERG considers the methods used by the company to pool the data to be inappropriate (discussed further in Section 4.2). However, the ERG acknowledges the company has taken a pragmatic approach to combining the studies to increase the sample size and power of the analysis.

4.3 Clinical results

Before discussing the clinical effectiveness results, the ERG wishes to address a comment made by the company in their response to clarification questions. The company stated “During the clarification stage, Janssen requested further information on the rationale and priority of the additional analyses requested. As this was not forthcoming, Janssen have addressed priority questions in the order presented below. In addition to this, Janssen requested clarification on some questions for which it was unclear what was required. As no clarification was received, Janssen have interpreted these questions as best as

we are able and apologise if the data presented is not what was required". The ERG wishes to inform readers of the report that the ERG responded to the queries raised and NICE confirmed that the document had been forwarded to the company.

4.3.1 Results for outcomes evaluating clinical effectiveness

Evidence submitted to NICE in support of daratumumab is derived from two observational studies, MMY2002 and GEN501, and is non-comparative in nature. As described in Section 4.2, MMY2002 was designed to evaluate efficacy of daratumumab and had a primary outcome of ORR. In contrast to MMY2002, the focus of GEN501 was the safety and tolerability of daratumumab.

Within the CS, the company reports data for various clinical outcomes for MMY2002 and GEN501 Part 2, and for an integrated analysis of the two studies. As part of the clarification process, the ERG requested additional detail on the methods used to generate results for the integrated analysis, and how the integrated analysis differs from "crude pooling" of results (referred to in the footnote of Table 46 of the CS). The company indicated that "For all outcomes except safety, which is reassessed in all patients from the integrated analysis set, the integrated analysis pools the latest data available from individual trials; across datasets, the median follow-up for the 31 December 2015 data cut-off was 20.7 months (range: 0.5, 27. 1)". Based on the company's response, the ERG considers that the integrated analysis is a simple pooling of data rather than a meta-analysis of single-arm studies.

It should be noted that simple pooling of data from different studies naïvely assumes that the baseline risk is the same for all studies, as if all patients came from one large study. However, patients within a study are likely to be similar (e.g., from the same population group, and likely to be treated by the same healthcare professionals) and thus the responses for patients in the same study will be correlated. Within study correlation can be accounted for by meta-analysing the aggregate study results or stratifying the individual patient data (IPD). A meta-analysis of weighted proportions using a random-effects model to synthesise data from single-arm studies may be appropriate, if, as in pair-wise meta-analysis, the demographics of the study populations and inclusion/exclusion criteria of the studies are sufficiently similar.[83].

Given the differences in population baseline characteristics and the inclusion criteria between the MMY2002 and GEN501 Part 2 (outlined in Section 4.2.3), the lack of detail about ISS and cytogenetic characteristics in GEN501, and the disparity in length of follow-up for some outcomes, the ERG has reservations about the appropriateness of a combining of results of the studies through meta-analysis or simple pooling. As noted by the ERG's clinical experts, neither MMY2002 or GEN501 Part 2 fully represents the population likely to be eligible for treatment with daratumumab in the UK. Based on the availability of baseline data on ISS and cytogenetics, the ERG considers results from MMY2002 to be

of more relevance to the decision problem that is the focus of this STA. The ERG recognises that, considering the interventions people received in MMY2002 prior to daratumumab, the results of the full trial population are likely to underestimate the effectiveness of daratumumab in the UK setting.

For completeness, in the sections that follow, clinical efficacy results for GEN501 Part 2 and the integrated analysis are presented alongside those for MMY2002.

At the time of drafting clarification response pom+dex was not an available treatment option for rrMM. In an attempt to present results for a population that better reflects those most likely to receive daratumumab in the UK, based on advice from the ERG's clinical experts and as acknowledged by a report referenced by the company,[84] the ERG requested additional analyses at clarification for MMY2002 excluding people pre-treated with pomalidomide (results discussed in subsequent sections).

4.3.1.1 Response to treatment

In both MMY2002 and GEN501, ORR was defined as the proportion of people achieving a partial response (PR) or better based on IMWG criteria (presented in Appendices 5). In MMY2002, 31 people (29.2%, 95% CI: 20.8% to 38.9%) achieved at least a PR (Table 12). The median time taken to achieve the first response was 0.99 months, ranging from 0.9 to 5.6 months (Table 12). Based on TTR, for people who respond to treatment with daratumumab, response is rapid, and shrinkage of tumours typically occurs within the first month of treatment. Median DOR in MMY2002 was 6.82 months (95% CI: 5.55 months to 11.07 months; Table 12).

As discussed in Section 3.4, the ERG considers that clinical effectiveness of daratumumab in pomalidomide-naïve people would be of particular relevance to the decision problem. As part of the clarification process, the ERG requested data on clinical outcomes for the subgroup of people enrolled in MMY2002 who had not been treated with pomalidomide at study entry. Data provided by the company for ORR and associated outcomes for the requested subgroup are listed in Table 12. The ERG considers that the company has inadvertently provided incorrect data for ORR for pomalidomide-naïve people: the results presented in the clarification response for ORR match exactly the numbers reported for ORR for the full population of MMY2002. According to the CSR for MMY2002, 67 people had received prior pomalidomide at baseline, which would leave 39 people who are pomalidomide-naïve.[53] Numbers provided for DOR during clarification suggest that 11 people who had not received pomalidomide achieved a response of PR or better, which equates to 28.2% (95% CI 14.1% to 42.3%; calculated by ERG). However, the ERG does not consider this a robust estimate as the proportion of people achieving a PR or better in this subgroup has not been confirmed by the company. The TTR for pomalidomide-naïve people could not be estimated. However, median DOR was reported to be 15.90 months for people not receiving pomalidomide prior to daratumumab. The ERG advises caution when

interpreting the results of this *post hoc* subgroup analysis: the estimate of median DOR is based on a small population (only 11 responders) and the 95% CI is not defined (upper limit could not be calculated), indicating considerable uncertainty around the estimate.

The ERG considers it important to reiterate (as discussed in Section 3.4) that ORR is a measure of anti-tumour activity and does not necessarily relate to disease stability or prognosis.

Table 12. Summary of ORR, TTR and DOR for MMY2002 and GEN501 Part 2 (IRC assessed; various data cut-offs) (adapted from CS, Tables 13–15 [pgs 77–79] and Table 24 [pg. 94])

	MMY2002		**GEN501 Part 2 (N=42)**	**Integrated analysis of MMY2002 and GEN501 Part 2 (N=148)**
	All-treated population (N=106)	**People not previously treated with pomalidomide (N=39)[a]**		
ORR, n (%) (95% CI for %)	31 (29.2) (20.8% to 38.9%)	31 (29)	15 (35.7) (21.6% to 52.0%)	46 (31.1) (23.7% to 39.2%)
Data cut off	9 January 2015	9 January 2015	31 December 2015	Various
Clinical benefit rate, n (%)[b]	36 (34.0)	36 (34)	19 (45.2)	55 (37.2)
BOR, n (%)				
sCR	3 (2.8)	3 (3)	0	3 (2.0)
CR	0	0	4 (9.5)	4 (2.7)
VGPR	10 (9.4)	10 (9)	3 (7.1)	13 (8.8)
PR	18 (17.0)	18 (17)	8 (19.0)	26 (17.6)
MR	5 (4.7)	5 (5)	4 (9.5)	9 (6.1)
SD	46 (43.4)	46 (43)	22 (52.4)	68 (45.9)
PD	18 (17.0)	18 (17)	0	18 (12.2)
NE	6 (5.7)	6 (6)	1 (2.4)	7 (4.7)
Time to response[c]	**N=31**	**N=11**	**N=15**	**N=46**
Data cut off	9 January 2015	9 January 2015	9 January 2015	9 January 2015
Time to first response, median months (range)	0.99 (0.9 to 5.6)	NE (95% CI 2.73 to NE)	0.92 (0.5 to 3.2)	1.0 (0.5 to 5.6)
Time to best response, median months (range)	1.87 (0.9 to 7.4)	N/R	1.84 (0.5 to 9.0)	N/R
Time to VGPR or better, median months (range)	1.84 (0.9 to 7.4)	N/R	0.49 (0.5 to 0.5)	N/R
Duration of response[d]	**N=31**	**N=11**	**N=15**	**N=46**
Data cut off	31 December 2015	31 December 2015	31 December 2015	31 December 2015
Median DOR, months (95% CI)	6.82 (5.55 to 11.07)	15.90 (3.71 to NE)	18.66 (5.55, not reached)	8.02 (6.47 to 14.65)

3 month progression-free rate, % (95% CI)	86.7 (68.3 to 94.8)	N/R	86.2 (55.0 to 96.4)	86.5 (72.3 to 93.7)
6 month progression-free rate, % (95% CI)	63.3 (43.6 to 77.8)	N/R	79.0 (47.9 to 92.7)	68.3 (52.4 to 79.8)
12 month progression-free rate, % (95% CI)	26.7 (12.6 to 43.0)	N/R	71.8 (41.1 to 88.4)	40.6 (26.1 to 54.6)
18 month progression-free rate, % (95% CI)	20.0 (8.1 to 35.6)	N/R	54.7 (25.0 to 76.9)	30.6 (17.5 to 44.6)
24 month progression-free rate, % (95% CI)	13.3 (3.2 to 30.6)	N/R	43.8 (15.7 to 69.1)	22.0 (9.6 to 37.7)

[a] All data, barring clinical benefit rate (calculated by ERG) in the column are taken directly from the company's response to clarification.

[b] Clinical benefit rate = ORR plus MR.

[c] TTR was defined as the time from the date of first dose of daratumumab to the date of initial documentation of a response (PR or better).

[d] DOR was calculated from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease, as defined in the IMWG criteria.

Abbreviations: CI, confidence interval; CR, complete response; CS, company submission; DOR, duration of response; ERG, Evidence Review Group; IRC, independent review committee; MR, minimal response; NE, not estimable; N/R, not reported; ORR, overall response rate; PD, progressive disease; pgs, pages; PR, partial response; sCR, stringent complete response; SD, stable disease; TTR, time to response; VGPR, very good partial response.

The company carried out a MAIC comparing daratumumab against pano+bort+dex and versus pom+dex, the results of which are discussed in Section 4.3.1.4.

The company asserts that daratumumab offers an unprecedented benefit in clinical efficacy, and particularly OS. As there are no direct head-to-head comparative data of daratumumab and its relevant comparators, for context in this section, the ERG considers it useful to present the ORR for the pano+bort+dex and pom+dex groups as reported in the full publications of the trials (Table 13). The ERG emphasises that no conclusions on comparative clinical effectiveness can be drawn from estimates from single arms from different studies. The studies from which the data are taken are discussed in greater detail in Section 4.3.1.4, with only key considerations for interpreting the effect estimate mentioned here.

The combination of pano+bort+dex was evaluated in one Phase II single-arm study (PANORAMA 2[81]) and one RCT comparing pano+bort+dex versus placebo plus bortezomib plus dexamethasone (PANORAMA 1[80]). PANORAMA 1 enrolled people with rrMM who had received between one and three previous treatments.[80] By contrast, to be eligible for enrolment in PANORAMA 2, people had to have received a minimum of two prior lines of therapy.[81] Baseline characteristics indicate that people enrolled in PANORAMA 1 and PANORAMA 2 were, on average, less heavily pre-treated than those in MMY2002. The ERG agrees with the company that the baseline characteristics of the population in PANORAMA 2, compared with those of PANORAMA 1, are more closely matched to the population that is the focus of the decision problem. In PANORAMA 2, pano+bort+dex was associated with an

ORR of 34.2% (95% CI: 22.0% to 47.1%; 95% CI calculated by ERG): ORR based on 19 people out of 55 enrolled achieving a response of PR or better.

The clinical effectiveness of pom+dex was assessed in a RCT (MM-003) comparing pom+dex (low dose) versus dexamethasone alone (high dose).[82] Eligible people were those with rrMM who were refractory to their last treatment and who had failed at least two previous consecutive treatments of bortezomib and lenalidomide, either alone or in combination: people with prior exposure to pomalidomide were not eligible for inclusion. Given the inclusion criteria, it would be anticipated that the population of MM-003 would also be less heavily pre-treated than that of MMY2002. Details on median or mean number of prior lines of treatment are not presented in the full publication of MM-003.[82] However, a NICE "guidance in development" document available online in January 2017 reporting the STA for pom+dex in the treatment of rrMM gives more details on baseline characteristics of MM-003.[85] The document outlines that the median number of prior therapies in the pom+dex group was 5 (range of 2 to 14). Thus, people in MM-003 have been as heavily pre-treated as those in MMY2002, and are pomalidomide-naïve. In the pom+dex group, 31.4% of people achieved a PR or better (95% CI: 26.2% to 36.7%; 95% CI calculated by ERG): ORR based on 95 people out of 302 randomised to pom+dex achieving a response of PR or better.[82]

Table 13. Summary of ORR for daratumumab, pano+bort+dex and pom+dex

Intervention	ORR (%)	95% CI[a]
Daratumumab	29.2	20.8 to 38.9
Pano+bort+dex[b]	34.2	22.0 to 47.1
Pom+dex[c]	31.4	26.2 to 36.7

[a] 95% CI calculated by ERG.
[b] ORR in PANORAMA 2 defined as per modified European Group for Blood and Marrow Transplantation criteria.
[c] ORR in MM-003 defined as achieving at least a PR: CR, sCR, VGPR and PR assigned by an investigator in accordance with IMWG criteria.
Abbreviations: CI, confidence interval; CR, complete response; ERG, Evidence Review Group; ORR, overall response rate; Pano+bort+dex, panobinostat plus bortezomib plus dexamethasone; Pom+dex, pomalidomide plus dexamethasone; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

4.3.1.2 Progression-free survival

The CSRs for MMY2002 and GEN501 outline that, in both studies, PFS was defined as "the time between the date of first dose of daratumumab and either disease progression or death, whichever occurred first. Relapse from CR was not considered as disease progression".

Median PFS of people in MMY2002 was reported to be 3.7 months (95% CI: 2.8 months to 4.6 months; Table 14), based on 75 events:[53] KM plots for PFS are provided in Figure 3. The CSR of MMY2002 reports that, at the time of the primary analysis of PFS, 71% of people had progressed or died based on assessment by the IRC.[53] During clarification, the company reported that median PFS of pomalidomide-naïve people (N=39) in MMY2002 was 3.98 months (95% CI: 2.60 months to 7.39 months): results of the *post hoc* subgroup analysis should be interpreted with caution.

The ERG notes that the median PFS for people evaluated in GEN501 Part 2 was 6.2 months, which is considerably longer than median PFS for MMY2002. In addition, there is only 0.4 months overlap of the reported 95% CIs for median PFS. There is also considerable disparity between the studies in the proportions of people who have not progressed at the follow-up points reported (Table 14). The variation in PFS supports the ERG's position that pooling of the data for an integrated analysis is not appropriate, and also indicates the presence of differences between the two populations in known and unidentified baseline prognostic factors.

The full publication of PANORAMA 2 reported the median PFS for pano+bort+dex to be 5.4 months (95% CI not reported).[81] Additional detail on PFS was acquired from the company's (Novartis) submission on panobinostat to the German Federal Joint Committee.[86] In the report, median PFS of pano+bort+dex was listed as 164 days, with an accompanying 95% CI of 107.0 days to 204.0 days. In MM-003, median PFS in the pom+dex group was 4.0 months (95% CI: 3.6 months to 4.7 months).[82]

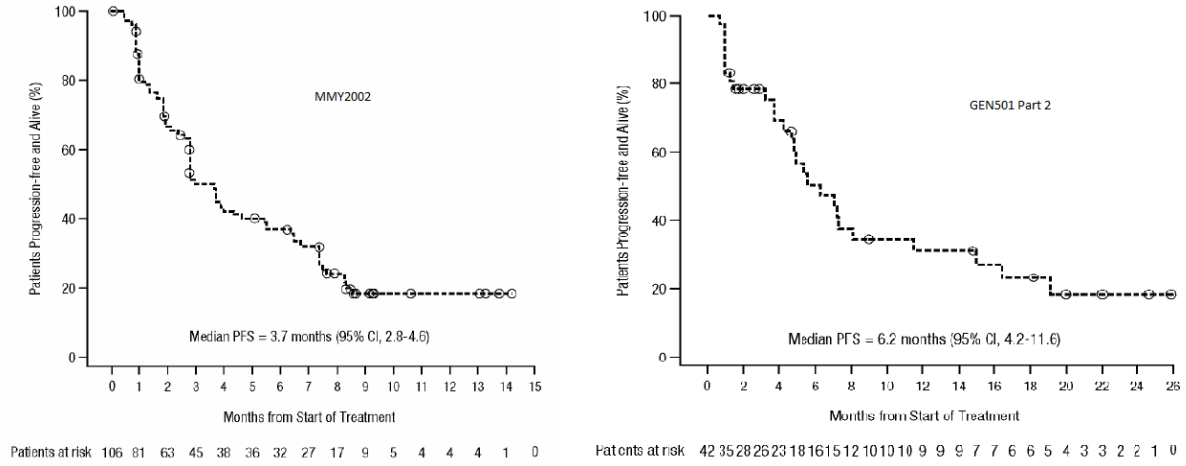
Table 14. Summary of PFS for MMY2002 and GEN501 Part 2, and integrated analysis (IRC assessed, adapted from CS, Tables 17 [pg. 84] and 26 [pg. 100])

	MMY2002 (N=106)	**GEN501 Part 2 (N=42)**	**Integrated analysis of MMY2002 and GEN501 Part 2 (N=148)**
Median PFS, months (95% CI)	3.7 (2.8 to 4.6)	6.2 (4.2 to 11.6)	4.0 (2.8 to 5.6)
Data cut off	9 January 2015	31 December 2015	Various
Number of events, n (%)	75 (70.8)	27 (64.3)	102 (68.9)
PFS rate at:			
3 months, % (95% CI for %)	50.2 (39.8 to 59.6)	78.3 (62.4 to 88.1)	57.8 (49.0 to 65.7)
6 months, % (95% CI for %)	36.7 (27.0 to 46.4)	50.5 (32.9 to 65.6)	40.5 (32.0 to 48.9)
12 months, % (95% CI for %)	18.3 (10.7 to 27.5)	31.2 (16.4 to 47.2)	21.6 (14.4 to 29.8)

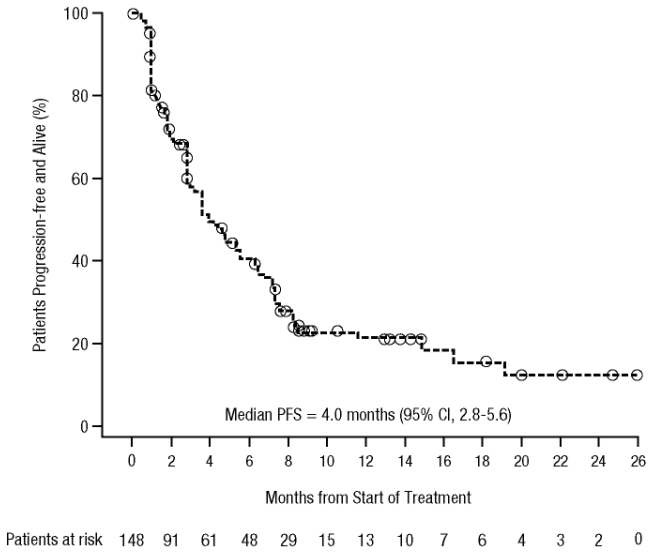
Abbreviations: CI, confidence interval; CS, company submission; IRC, independent review committee; PFS, progression-free survival; pg, page.

Figure 6. KM plot for PFS for MMY2002 and GEN501 Part 2, and integrated analysis (IRC assessed)

Panel A KM plots for MMY2002 and GEN501 Part 2 (reproduced from CS, Figure 12, pg. 85)



Panel B KM plot for integrated analysis of MMY2002 and GEN501 Part 2 (reproduced from CS, Figure 19, pg. 101)



Abbreviations: CI, confidence interval; CS, company submission; IRC, independent review committee; KM, Kaplan–Meier; PFS, progression-free survival; pg, page.

4.3.1.3 Overall survival

The CSRs for MMY2002 and GEN501 outline that, in both studies, OS was defined as "the time from the date of first dose of daratumumab to the date of the subject's death from any cause. If the subject was alive or the vital status was unknown, then the subject's data was to be censored at the date the subject was last known to be alive".

Median OS of people in MMY2002 was reported to be 18.6 months (95% CI: 13.7 months to not reached; Table 15), based on 57 events and a median follow-up of 20.7 months: Kaplan-Meier (KM) plots for OS are provided in Figure 4. During clarification, the company reported that median OS of

pomalidomide-naïve people (N=39) in MMY2002 could not be estimated. The lower 95% CI was given as 15.08 months, with the upper limit not evaluable: results of the *post hoc* subgroup analysis should be interpreted with caution.

Median OS for pano+bort+dex as reported in the company's (Novartis) submission on panobinostat to the German Federal Joint Committee was 534 days (95% CI: 329.0 days to 767.0 days), which approximates to median OS of 17.6 months.[86] In the full publication of MM-003 identified by the company, median OS in the pom+dex group was 12.7 months (95% CI: 10.4 months to 15.5 months).[82] However, a subsequent publication of MM-003 evaluating impact of prior treatment and depth of response on survival reports an updated analysis of OS (captured 6 months later).[87] Updated median OS for pom+dex was reported as 13.1 months (95% CI not reported).[87] The subsequent report was published in October 2015, and, therefore, the ERG considers that the company's search of the literature to update identified results, which was carried out in July 2016, should have retrieved the later study.

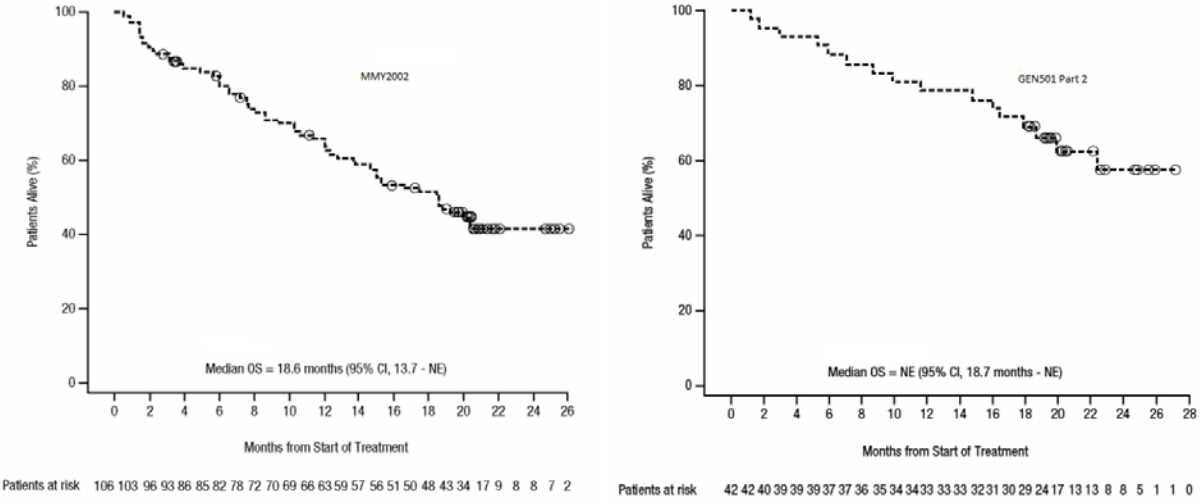
The company proposes that daratumumab monotherapy affords an unprecedented survival benefit. The ERG considers it important to reiterate that a single-arm study, such as MMY2002 and PANORAMA 2, is not considered an appropriate design to capture time-to-event outcomes like PFS and OS. In addition, the ERG has presented the results for pom+dex from a single group, rather than as a relative effect estimate from the RCT. Thus, the ERG considers that the median OSs reported for all interventions should be interpreted with caution. The ERG also notes that conclusions around comparative effectiveness of interventions should not be made from results from single-arm studies. Due to the lack of head-to-head data, the company carried out an MAIC to compare daratumumab with pano+bort+dex and with pom+dex, which is discussed in greater detail in Section 4.3.1.4.

Table 15. Summary of OS for MMY2002 and GEN501 Part 2 (adapted from CS, Tables 16 [pgs 81–82] and 25 [pg. 97])

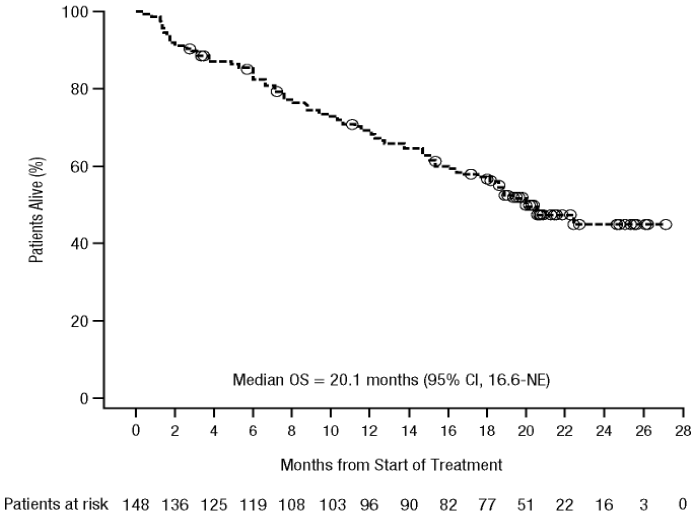
	MMY2002 (N=106)	**GEN501 Part 2 (N=42)**	**Integrated analysis of MMY2002 and GEN501 Part 2 (N=148)**
Median OS, months (95% CI)	18.6 (13.7, not reached)	Not reached (18.7, not reached)	20.1 (16.6, not reached)
Data cut off	31 December 2015	31 December 2015	31 December 2015
Number of events, n (%)	57 (53.8)	16 (38.1)	73 (49.3)
OS rate at:			
6 months, % (95% CI for %)	81.8 (73.0 to 88.0)	88.1 (73.7 to 94.9)	83.6 (76.5 to 88.7)
12 months, % (95% CI for %)	64.7 (54.5 to 73.1)	78.6 (62.9 to 88.2)	68.7 (60.5 to 75.6)
18 months, % (95% CI for %)	51.3 (41.1 to 60.6)	69.0 (52.7 to 80.7)	56.5 (47.9 to 64.2)
24 months, % (95% CI for %)	41.3 (31.0 to 51.2)	57.4 (38.7 to 72.3)	45.0 (35.5 to 54.1)
Abbreviations: CI, confidence interval; CS, company submission; OS, overall survival; pg, page.			

Figure 7. KM plot for OS for MMY2002 and GEN501 Part 2

Panel A KM plots for MMY2002 and GEN501 Part 2 (reproduced from CS, Figure 11, pg. 83)



Panel B KM plot for integrated analysis of MMY2002 and GEN501 Part 2 (reproduced from CS, Figure 17, pg. 98)



Abbreviations: CI, confidence interval; CS, company submission; KM, Kaplan–Meier; NE, not evaluable; OS, overall survival; pg, page.

The ERG considered that the OS benefit reported for daratumumab in MMY2002 was substantially longer than would be expected based on the comparatively short PFS, given the typically poor prognosis of people at this stage of MM and that treatment with daratumumab ended with disease relapse or progression. The company proposes that the large difference between PFS and OS is not unexpected and is likely as a result of daratumumab's immunomodulatory activity. However, a longer OS compared with PFS has been reported in other studies in people with rrMM, with one potential explanation proposed to be progression in disease being diagnosed biochemically, with clinical manifestation of relapse not occurring until months later.[82] The difference between PFS and OS for MMY2002 (14.9 months) is not that much greater than that of PANORAMA 2 (12.2 months). As noted earlier, the ERG emphasises that naïve comparisons of effectiveness should not be made between results from single groups. The ERG reports the difference in PFS and OS for the MMY2002 and PANORAMA 2 to illustrate that the difference between outcomes is over a year in both studies. Again, the ERG considers it important to emphasise that time-to-event data from MMY2002 and PANORAMA 2 should be interpreted with caution.

Confounding of OS due to subsequent therapy given at disease progression is recognised in studies evaluating treatments in oncological conditions. In an RCT, randomisation would minimise confounding between groups for unknown factors, and the same treatments would be available to people in each group. In the case of MMY2002 and its comparators, there is considerable disparity in the types of subsequent treatments received at progression. The issue of confounding in the estimates of comparative effectiveness is discussed in more detail in Section 4.3.1.4. In the context of MMY2002, it is important to note that the subsequent treatments of carfilzomib and re-treatment with lenalidomide

or bortezomib are not available treatment options in the UK. Carfilzomib, lenalidomide and bortezomib are likely to be associated with prolonged OS compared with other treatment options available in the UK setting for the population of interest.

Considering the proportion of people who go on to receive another therapy, for MMY2002, the company reports that 71% of people (n=73) in MMY2002 received another intervention subsequent to treatment with daratumumab, which, as acknowledged by the company, is considerably higher than the corresponding patient group in MM-003 (39% of 202 people). The company proposes that the high number of people receiving additional treatment after daratumumab is attributable to the "...novel and unique MoA associated with daratumumab, alongside the favourable safety profile, that culminate in an improved health status of patients". As the company outlines in their response to clarification, the more favourable adverse effect profile of daratumumab gives people "time to recover from the cumulative toxicity of previous treatments allowing a greater proportion of patients to receive subsequent therapy." Additionally, the company proposes that the "novel MoA of daratumumab, which includes immune-mediated mechanisms, increases the likelihood of benefitting from subsequent therapy".

The ERG considers it important to contextualise the reported numbers of people receiving subsequent treatment in MMY2002 and MM-003. At a median follow-up of 9.3 months, 55% (n=58) of people in MMY2002 had received subsequent treatment.[53] The proportion reported by the company in the CS (71%) is based on more mature data at a median follow-up of 20.7 months. It should be noted that the company's experts' believe that it is unlikely that 71% of people will receive treatment after daratumumab in clinical practice, which is reflected in the costing of subsequent treatment in the economic model (costed at 55% of people receive subsequent treatment with no adjustment to efficacy).

Considering MM-003, median follow-up for the reported 39% of people receiving subsequent treatment in MM-003 was 10.0 months.[82] In a subsequent publication, at a median follow-up of 15.4 months, 44.4% (n=134) of people had gone on to receive subsequent treatment.[87] The clinical experts acting for the company (Celgene) in the STA for pom+dex asserted that the proportion of people receiving subsequent treatment is likely to be larger in clinical practice.[85] Taking all comments together, the ERG considers that there is likely to be little difference in the number of people going on to receive treatment after daratumumab compared with after pom+dex.

To evaluate the potential impact of confounding in OS due to therapies received after daratumumab, during clarification the ERG requested OS for MMY2002 and GEN501 Part 2 based on those receiving no subsequent treatment, and those receiving any subsequent treatment. The company kindly provided the data, which are presented in Table 16. Median OS of those receiving

[redacted].

The ERG also requested OS for the integrated analysis by subsequent treatment received, focusing on bortezomib, carfilzomib, lenalidomide, and pomalidomide (Table 16). As highlighted by the company in their response to clarification, the ERG acknowledges that the analyses are *post hoc* and, as such, should be interpreted with caution. Considering the issue of heterogeneity within the groups noted by the company, the ERG considers that the largest bias within the analysis is the inclusion of people from GEN501 Part 2, for the reasons outlined in Section 3.1. The ERG recognises that the results provided are based on people receiving the specified treatment at any line of therapy subsequent to daratumumab (e.g., immediately after daratumumab or at later line), and the treatment could be given alone or in combination with other interventions, and agrees with the company that it is likely there are differences across the groups in these aspects of treatment. Finally, as the company notes, there is some level of selection bias in that people receiving subsequent treatment are of a higher performance status as they have been judged able to tolerate the treatment and are likely to have a better prognosis. The ERG considers that the company's reasoning around selection bias is counterintuitive to the company's proposal that daratumumab increases the probability of a person being able to tolerate treatment after daratumumab.

The ERG observes that there [redacted] across median OS per individual subsequent treatment (Table 16). The implications of [redacted] are discussed in greater detail in the analysis of cost effectiveness of daratumumab (Section 5.5.7.2). The results of the ongoing Phase III studies of daratumumab in combination with len+dex (MMY3003) and with bort+dex (MMY3004) will help to elucidate whether the proposed benefit afforded by daratumumab is exclusive to its use as a monotherapy, particularly when people receiving the combination treatments in the Phase III studies will not have had an equivalent rest period from more toxic chemotherapies.

Table 16. Summary of OS for MMY2002 and GEN501 Part 2 based on no or any treatment after daratumumab

Subsequent treatment received	Number of people	Median OS (95% CI)
MMY2002		
None	[redacted]	[redacted]
Any	[redacted]	[redacted]
GEN501 Part 2		
None	[redacted]	[redacted]
Any	[redacted]	[redacted]
Integrated analysis of MMY2002 and GEN501 Part 2		

Bortezomib	[redacted]	[redacted]
Carfilzomib	[redacted]	[redacted]
Lenalidomide	[redacted]	[redacted]
Pomalidomide	[redacted]	[redacted]
Abbreviations: CI, confidence interval; NE, not evaluable; OS, overall survival.		

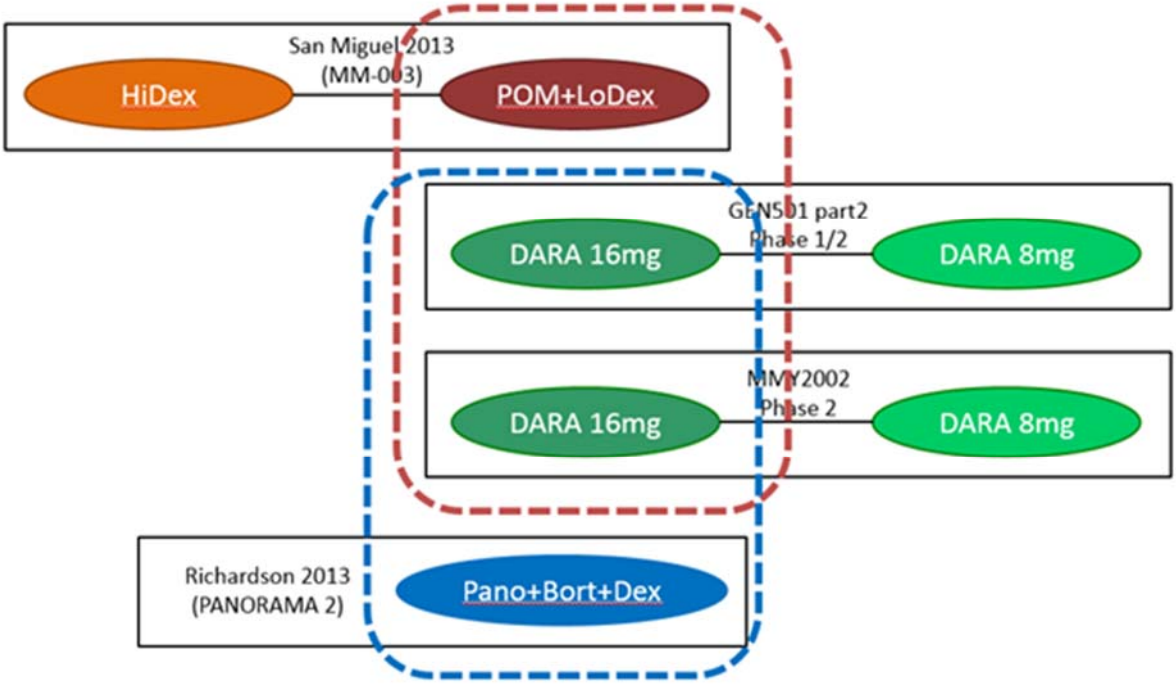
4.3.1.4 MAIC analyses

The availability of solely single-arm studies evaluating daratumumab precludes carrying out a network meta-analysis of daratumumab versus another intervention as there is no possibility of an overlapping comparator across studies. Instead, the company carried out an alternative method of indirect comparison, a MAIC, to compare daratumumab versus pano+bort+dex and versus pom+dex, which have been identified as the key comparators of relevance to the decision problem.

In a MAIC, individual patient data (IPD) for one treatment from a study or RCT are compared with aggregate data from a comparator study.[88, 89] The baseline characteristics of patients in the study for which IPD are available are matched to the average baseline characteristics of the comparator study.[88, 89] It has been reported that a MAIC accounts for cross trial differences in patients' baseline characteristics, and, thus, treatment outcomes are compared across balanced populations.[88] The company outlines that published methodology was followed to compare IPD from MMY2002 and GEN501 Part 2 versus pano+bort+dex and versus pom+dex.[88, 89]

In recognition of the increased use of population-adjusted indirect comparisons (e.g., MAIC and simulated treatment comparison [STC]) in submissions to the STA process, the NICE Decision Support Unit (DSU) published recommendations on the use of such techniques in the context of the NICE appraisal process.[90] As defined in the report from the DSU, because the network is disconnected, being based on single-arm studies, the MAIC carried out by the company is "unanchored":[90] network of evidence depicted in Figure 5.

Figure 8. Network of evidence forming MAIC (reproduced from CS, Figure 21 [pg. 117])



Abbreviations: Bort, bortezomib; CS, company submission; DARA, daratumumab; Dex, dexamethasone; HiDex, high-dose dexamethasone; LoDex, low-dose dexamethasone; MAIC, matching-adjusted indirect comparison; Pano, panobinostat; pg, page; POM, pomalidomide.

4.3.1.4.1 Methods

The CS outlines in detail the approach the company took to carry out the MAIC. In brief, the company initially compared inclusion and exclusion criteria of MMY2002 and GEN501 Part 2 against those of PANORAMA 2 and MM-003 to exclude people from the analysis who were included in the studies evaluating daratumumab but who would not have been eligible for inclusion in the comparator study. Next, using a propensity score model, IPD from the remaining patients in the daratumumab cohort were weighted such that the mean values for relevant baseline parameters reflected the means reported in the comparator study. In the propensity score model, patients from the daratumumab cohort were weighted by the inverse odds of being in the daratumumab studies, rather than MM-003 or PANORAMA 2, following methods described in the literature.[88] The company noted that "the algorithm does not directly match median values; rather, it calculates the weights such that the proportion of patients with a value below the median is matched to the proportion with a value above the median".

As noted by the company, matching of population characteristics should be "based on clinically relevant risk factors that impact the relative treatment effects". The company identified relevant baseline characteristic through a review of the literature and in consultation with clinical experts in haematology. The company identified the most important characteristics for matching as:

- Refractory status (treatment type and number of treatments);

- Number of prior treatments;
- ECOG status;
- Age;
- Cytogenetics;
- ISS staging.

The ERG's clinical experts also identified the listed characteristics as the most important for matching in the MAIC. The company acknowledged that data on baseline cytogenetics and ISS stage were not available for people enrolled in GEN501 and stated that these characteristics could not be incorporated into the MAIC for the integrated analysis. For the individual MAIC using the integrated analysis set, the company ranked the risk factors and match adjusted the analysis in order of importance, from highest to lowest priority, based on expert opinion, with adjustment being cumulative. During clarification, the company stated that "of the variables identified as potentially relevant to the outcome and, as a consequence, the relative treatment effect, cytogenetics and ISS staging were ranked lowest". The ERG's clinical experts agreed with the company in ranking refractory status as the most important factor, but ranking of remaining factors differed from those of the company, and also varied between the ERG's clinical experts. However, both advisors to the ERG ranked cytogenetics and ISS staging above age.

During clarification, the ERG requested additional MAIC analyses for MMY2002 and GEN501 Part 2 considered separately. In their response, the company set out the factors for which the population had been matched within the MAIC, and, for MMY2002 analyses, adjusting for ISS has been prioritised over ECOG status, and cytogenetics has been ranked as more important than age (depicted in Table 17 and Table 18). The ERG considers the company's rationale within the CS for the order of priority of factors to contradict the order of adjustment in their own analyses. Moreover, factors additional to those listed above have also been matched in some analyses (beta-microglobulin level; Table 17 and Table 18).

From baseline characteristics of the comparator studies, the ERG noted that the proportion of people receiving carfilzomib, lenalidomide, pomalidomide and bortezomib as subsequent therapies is much smaller in the comparator studies (MM-003 and PANORAMA 2) than in MMY2002. As discussed earlier, carfilzomib and re-treatment with lenalidomide and bortezomib are not available treatment options in the UK. Compared with subsequent therapies received in MM-003 and PANORAMA 2, the ERG considers that carfilzomib, lenalidomide and bortezomib are likely to be associated with prolonged

OS and differences in subsequent treatments received is a confounding factor in interpretation of comparative effect estimates of OS. Thus, the ERG also requested additional MAIC analyses by subsequent treatment (bortezomib, carfilzomib, lenalidomide and pomalidomide) for people whose disease progressed while receiving daratumumab for both pom+dex and pano+bort+dex. The company noted that they consider the additional requested analyses versus pom+dex and pano+bort+dex to be statistically inappropriate because of:

- "Small sample sizes, resulting in low effective sample sizes;
- Selection bias, patients are being indirectly selected based on their fitness and outcome (i.e., being fit enough and surviving long enough to receive subsequent treatment). Matching to baseline characteristics is unlikely to overcome this bias as time dependent covariates are likely to be influential;
- Insufficient overlap, daratumumab patients are being selected based on fitness and outcome, whereas patients from the comparator trials are not, this reduces the level of overlap between the datasets. The consequence of this is a reduction in the number of characteristics that can be matched thereby reducing the reliability of the MAIC."

The ERG agrees that the effective sample size in the fully adjusted data sets is small, and that, as noted by the DSU, this is indicative of poor overlap across the populations in the analysis. However, the DSU specifies that, for unanchored MAICs, all prognostic variables and effect modifiers must be included in the weighting model, the reason being that even when all observed prognostic/treatment effect modifiers are matched there will unobserved modifiers that confound the analysis. The company states that "In order to balance appropriate adjustment with reduction in effective sample size, only the most important factors were adjusted for in the base-case analyses". The ERG considers it would be more appropriate to use the fully adjusted MAIC for the base case because as many variables as possible have been matched between populations.[90]

In response to the company's comments on selection bias of the analyses, the ERG considers that the point made goes against the company's proposal that daratumumab increases the probability of a person being able to tolerate treatment after daratumumab. Considering the company's argument about insufficient overlap, the ERG considers the point made is the same as selection bias and notes that small effective sample size is indicative of insufficient overlap between studies.

In explanation of the inconsistent matching of factors across MAICs, the company states in the CS "As a consequence of the differing levels of granularity in the reported baseline characteristics across MM-003 and PANORAMA 2, the numbers of characteristics used to match MMY2002/GEN501 data with

MM-003 and with PANORAMA 2 differed". The ERG acknowledges that level of reporting of baseline characteristics in the comparator studies would determine which characteristics would be adjusted for, but considers that there are inconsistencies across variables included in MAIC analyses that are not related to reporting in the publications for pano+bort+dex and pom+dex. Factors adjusted for in individual MAICs are discussed in the comparator sub-sections below.

The ERG recognises that the DSU report summarising best practice for MAIC was not available to the company at the time of their analysis. With the release of the DSU report, the ERG wishes to highlight that there are acknowledged limitations with an unanchored MAIC and these should be borne in mind when interpreting the clinical effectiveness results discussed in this report. Of particular note:[90]

- Comparisons are not protected from imbalances in prognostic variables as they do not rely on within-study randomisation;
- Analysis assumes that all effect modifiers and prognostic factors are accounted for (this is a strong assumption that is likely to be impossible to meet);
- Failure to account for all effect modifiers and prognostics factors leads to unknown amount of bias in the estimate and, thus, uncertainty around the accuracy of the estimate;
- Strong assumption that the joint distribution of covariates and the correlation of covariates is exactly the same as the index study (i.e., the study for which IPD are available);
- Population that is modelled is dictated by the comparator trial rather than the population for which IPD data are available;
- Attempts should be made to quantify the extent of any residual systematic error arising from unobserved prognostic variables and effect modifiers.

The company does not report an assessment of likely residual bias around the effect estimates resulting from unobserved prognostic factors and effect modifiers distributed differently in the trials. The DSU highlights that quantification of the residual systematic error is an area for further research.[90]

Based on the recommendations from the DSU, the ERG considers that the most adjusted analysis set is the least biased for an unanchored comparison and so considers the most appropriate analysis set to be that incorporating adjustment for cytogenetics and ISS stage. Adjustment for all known factors is only possible in the MAIC utilising IPD from MMY2002 alone. The company carried out the MAIC using data based on only MMY2002 as a sensitivity analysis, stating that the study "had a greater number of attributes on which to match populations". In the relevant sections below, for completeness, the ERG

presents the results of MAIC of the integrated analysis for the least adjusted set, the company's base case and the most adjusted set, together with that of the MAIC that also includes adjustment for cytogenetics and ISS stage.

4.3.1.4.2 Baseline variables

Panobinostat plus bortezomib plus dexamethasone

Overview of PANORAMA 2

As touched on in Section 4.3.1.3, the company used the patient population from PANORAMA 2[81] to inform the MAIC of daratumumab versus pano+bort+dex. PANORAMA 2 (N=55 people) is a Phase II, two-stage, single-arm, open-label multicenter study of oral panobinostat in combination with bortezomib and dexamethasone (key characteristics of the study are reported in Appendix 10.4, Table 35). As a single-arm observational study, like MMY2002 and GEN501, PANORAMA 2 is associated with a high risk of bias: quality assessment for PANORAMA 2 presented in Appendix 10.2 (Table 32). As an open-label study, PANORAMA 2 is also associated with high risk of bias around outcome assessment, particularly for subjective outcomes such as ORR. It is unclear from the reporting of PANORAMA 2 whether response was evaluated by an IRC.

To be eligible for enrolment in the study, people had to:

- Be >18 years of age;
- Have relapsed and bortezomib-refractory MM (progressed on or within 60 days of the last bortezomib-containing regimen);
- Have received at least 2 prior lines of therapy;
- Have been exposed to an IMiD;
- Have measurable disease (defined as M protein >10 g/L or urine M protein >200 mg per 24 hours);
- Have an ECOG performance status score of ≤2;
- Have absolute neutrophil count ≥1.0 x 10^9/L, platelet count >70 x 10^9/L, electrolyte levels within normal limits and transaminase levels ≤2.5x the upper limit of normal.

Comparison of the baseline characteristics of people enrolled in PANORAMA 2 (presented in Appendices 10.7, Table 36) and MMY2002 indicates that people in PANORAMA 2 were less heavily pre-treated than in MMY2002, receiving a median of four previous therapies compared with five prior

treatments in MMY2002. In addition, there are key differences between the populations in the prior therapies received. In the baseline characteristics reported for PANORAMA 2, neither pomalidomide nor carfilzomib is listed as a prior therapy. Information on therapies given on progression is not reported in the full publication for PANORAMA 2. In terms of refractory status, information on only refractoriness to bortezomib is available from PANORAMA 2. A similar proportion of people was refractory to bortezomib in each study (approximately 90% in MMY2002 and PANORAMA 2).

Differences between populations in ECOG score and ISS stage were also noted. Considering ECOG performance status, the largest proportion of people in PANORAMA 2 had a baseline ECOG score of 0 (47.3%), whereas most people in MMY2002 had an ECOG score of 1 (65.1%). Similar variation was noted in ISS stage at baseline, with a larger proportion of people in MMY2002 (37.7%) categorised as ISS stage III compared with PANORAMA 2 (23.6%). The differences in ECOG score and ISS stage could suggest that the population in MMY2002 had a poorer overall health status compared with those in PANORAMA 2. Other baseline characteristics were well matched across the studies. Differences across the populations should be accounted for in the MAIC.

The primary objective of PANORAMA 2 was to evaluate ORR as defined by European Group for Blood and Marrow Transplantation (EBMT) criteria.[91] It should be noted that the criteria for response developed by the IMWG are similar to those presented by the EBMT but differ in the listed areas:[2]

- IMWG criteria include FLC response and progression criteria for patients without measurable disease;
- Definition for disease progression for people who achieve CR;
- IMWG includes additional response categories of VGPR and sCR;
- IMWG omits minor response, and the mandatory 6-week wait time to confirm response as specified in EBMT system.

A key difference between IMWG criteria and EBMT criteria for response is inclusion in IMWG criteria of a definition for progression for people without measurable disease. The ERG considers that this issue does not impact on the MAIC for daratumumab versus pano+bort+dex as an inclusion criterion in both studies was that people have measurable disease at baseline.

The outcome of VGPR was assessed in PANORAMA 2 as an exploratory outcome and evaluated as such per IMWG criteria.[81] Secondary outcomes captured in PANORAMA 2 were MR, TTR, DOR, PFS, OS and safety and tolerability

Variables matched in MAIC analysis

The prognostic factors identified and adjusted for by the company in their MAIC analyses for the comparison of daratumumab versus pano+bort+dex are listed in Table 17: there are differences across MAICs in the factors matched and, thus, for which the comparative PFS and OS have been adjusted. The baseline variables are recorded in the first column of the table, and are listed in order of ranking of adjustment as reported across MAIC analyses (Table 17), from highest to lowest priority. The number of characteristics within a specific variable that are matched and adjusted are also listed. Within each column representing an adjusted data set, the "tick" symbol denotes that the population has been matched to PANORAMA 2 baseline characteristics for that variable. Adjustments are made sequentially, reading down the column for that data set (Table 17). For example, in MMY2002, the fully adjusted data set forming the MAIC has been population matched and adjusted for 17 characteristics (not 18 characteristics as the populations have not been matched for IgM). By contrast, fully adjusted MAIC utilising GEN501 Part 2 and the integrated analysis are not matched to PANORAMA 2 for ISS or cytogenetics and so are matched for only 13 characteristics.

Within the CS, for the MAIC of daratumumab versus pano+bort+dex, the company states that it was not possible to adjust for refractory status, with the exception of people refractory to bortezomib, or to adjust for creatinine clearance.

Table 17. Baseline characteristics (in order of relevance to effect on OS and order of adjustment) available for matching for daratumumab versus pano+bort+dex (adapted from CS, Table 35 [pg. 122] and company's response to clarification [Tables 1–7])

Baseline variable	Number of characteristics in the baseline variable to match	MMY2002	GEN501 Part 2	Integrated analysis of MMY2002 and GEN501 Part 2
Refractory to bortezomib (%)	1	✓	✓	✓
Median number of prior regimens: Median number of prior regimens >3 prior regimens (%)	2	✓	✓	✓
ISS stage: ISS 1 (%) ISS 2 (%) ISS 3 (%)	3	✓		
ECOG status: ECOG 0 (%) ECOG 1 (%) ECOG 2 (%)	3	✓	✓	✓
Cytogenetics: (Modified) high cytogenetic risk (%)	1	✓		

Median time since diagnosis (years)	1	✓	✓	✓
Myeloma subtype: IgA (%) IgG (%) IgM (%)	3	✓ (only IgA and IgG)	✓	✓
Beta-microglobulin: beta-microglobulin <2.5 (%)	1	✓		
Prior ASCT (%)	1	✓	✓	✓
Age: Median age (years) ≥65 years (%)	2	✓	✓	✓
Total number of characteristics to match	**18**	**17**	**13**	**13**
Abbreviations: ASCT, autologous stem-cell transplant; CS, company submission; ECOG, Eastern Cooperative Oncology Group; Ig, immunoglobulin; pano+bort+dex, panobinostat plus bortezomib plus dexamethasone; pg, page.				

Pomalidomide plus dexamethasone

Overview of MM-003

The population of MM-003 forms the basis for the company's MAIC of daratumumab versus pom+dex. MM-003 (N=455) is an open-label, multicentre RCT designed to compare clinical effectiveness of pom+dex (low dose) versus high-dose dexamethasone alone in people with rrMM and not responding to treatment with bortezomib and lenalidomide.[82] In line with the quality assessment of MM-003 as part of another STA, the ERG considers MM-003 to be a well conducted study.[92]

To be eligible for inclusion in MM-003, people had to:

- Be refractory to their previous treatment;
- Be judged to have refractory or relapsed and refractory disease;
- Have received at least two previous consecutive cycles of bortezomib and lenalidomide, alone or in combination;
- Have adequate alkylator treatment (at least six cycles of alkylator treatment, or progressive disease after at least two cycles of alkylator treatment, or received alkylator treatment as part of a stem-cell transplant);
- Be older than 18 years;
- Have failed treatment with bortezomib or lenalidomide (treatment failure defined as progressive disease on or before 60 days of treatment, progressive disease ≤6 months after achieving partial response, or intolerance to bortezomib).

People were categorised as having refractory MM if they had progressed on or within 60 days of treatment with bortezomib and lenalidomide (and had developed progressive disease on or within 60 days after completing their last treatment). By contrast, people were classified as having rrMM if they had achieved at least a partial response to previous treatment with bortezomib or lenalidomide, or both, but progressed within 6 months (and had developed progressive disease on or within 60 days after completing their last treatment). MM-003 also included people who developed treatment intolerance after a minimum of two cycles of bortezomib and had developed progressive disease on or before 60 days after completing their last treatment.

Comparison of baseline characteristics of MM-003 and MMY2002 show that the populations in the relevant groups (pom+dex arm from MM-003) are well matched in terms of number of prior therapies received, with both groups undergoing a median of five previous rounds of therapy: baseline characteristics for MM-003 are presented in Appendix 10.8, Table 38. However, there are key differences between the populations in the prior therapies received. An exclusion criterion of MM-003 was prior exposure to pomalidomide. Additionally, carfilzomib is not listed as a prior therapy for those enrolling into MM-003. On progression in MM-003, the most commonly used subsequent therapies were dexamethasone, cyclophosphamide, bortezomib and bendamustine, which may have been used alone or in combination.[85] Compared with MMY2002 and GEN501 Part 2, a considerably smaller proportion of people in MM-003 received carfilzomib, lenalidomide and bortezomib as a subsequent therapy (proportion of MM-003 vs MMY/GEN501 Part 2 receiving therapy: 2% vs 28% for carfilzomib; 5% vs 15% for lenalidomide and 18% vs 24% for bortezomib). The ERG considers that the subsequent treatments given in MMY2002 are likely to be associated with increased OS compared with the most common treatments given on progression in MM-003.

In terms of refractory status, populations were well matched in proportion of people refractory to lenalidomide, bortezomib and thalidomide. Considering other baseline factors, the studies were also well matched in age, median time since diagnosis, and the proportion of people categorised as ISS stage I/II. Minor differences in ECOG scores are noted between MMY2002 and MM-003. Most people in MMY2002 and MM-003 had an ECOG score of 1, but the proportion in that category was larger in MMY2002 compared with MM-003 (65.1% in MMY2002 versus 45.7%), with corresponding differences between studies in ECOG scores of 0 and 2 (larger proportion of people in each category in MM-003).

The primary outcome for MM-003 was PFS, with OS, ORR (proportion of patients achieving at least a PR as set out by IMWG criteria or EBMT criteria for minor response only), and safety, amongst other endpoints, captured as secondary outcomes. PFS and ORR were based on investigator assessment of

response and progressive disease in accordance with IMWG criteria. As acknowledged by the authors of the full publication of MM-003, the lack of a masked investigator introduces bias into the study.[82]

Variables matched in MAIC analysis

The prognostic factors identified and adjusted for by the company in their MAIC analyses for the comparison of daratumumab versus pom+dex are listed in Table 18. The format of the table is as described in the MAIC analysis discussion in the section covering daratumumab versus pano+bort+dex (Section 4.3.1.4.2).

As noted by the ERG in Section 3.1, to generate as representative a population to UK clinical practice as possible from MMY2002 and MM-003 for the purposes of the MAIC, it is important to adjust for prior exposure to pomalidomide. The company reports that excluding people who had received prior pomalidomide from the daratumumab integrated dataset (to match the population of MM-003) resulted in a much smaller effective sample size: in the integrated analysis of MMY2002 and GEN501 Part 2, 82 out of 148 people had received prior treatment with pomalidomide. Because of the resulting small sample size for pomalidomide-naïve people, the company chose to include pom+dex experienced people in their base case analysis. However, the company carried out a sensitivity analysis using the integrated analysis dataset adjusted for exposure to pomalidomide before trial entry (n=66). Despite the small effective sample size, the ERG considers that the MAIC adjusted for prior pomalidomide treatment would have been a more appropriate choice by the company. Furthermore, as discussed earlier, the ERG's preferred MAIC is that also adjusting for cytogenetics and ISS stage (utilises data from MMY2002 alone).

During clarification, the ERG omitted to ask the company to carry out the MAIC utilising the MMY2002 dataset excluding those exposed to pomalidomide before enrolment. The ERG discusses results of the MAIC based on the integrated dataset, but reiterates that this is not the ERG's preferred analysis.

Table 18. Baseline characteristics (in order of relevance to effect on OS and order of adjustment) available for matching for daratumumab versus pom+dex (adapted from CS, Table 35 [pg. 122] company's response to clarification [Tables 1–7])

Baseline variable	Number of characteristics to match	MMY2002	GEN501 Part 2	Integrated analysis of MMY2002 and GEN501 Part 2	Integrated analysis of MMY2002 and GEN501 Part 2: pom+dex naïve people
Refractory status:	3	✓	✓	✓	✓

Refractory to lenalidomide (%) Refractory to bortezomib (%) Refractory to both (%)					
Mean number of prior regimens: Mean number of prior regimens >2 prior regimens (%)	2	✓	✓	✓	✓
ISS stage: ISS 2 (%) ISS 3 (%)	2	✓			
Creatinine clearance: <30 (%) 30–60 (%) ≥60 (%)	3	✓	✓	✓	✓
ECOG status: ECOG 0 (%) ECOG 1 (%) ECOG 2 (%)	3	✓	✓	✓	✓
Cytogenetics (Modified) high cytogenetic risk (%)	1	✓			
Median time since diagnosis (years)	1	✓	✓	✓	✓
Myeloma subtype: IgA (%) IgG (%) IgM (%) IgD (%) Light chain Kappa (%) Light chain lambda (%)	6	✓ (excluding IgM)	✓	✓	✓
Beta-microglobulin: beta-microglobulin <3.5 (%) beta-microglobulin ≥3.5–<5.5 (%) beta-microglobulin ≥5.5 (%)	3	✓			
Ethnicity: White (%) Asian (%) Black (%)	3	✓		✓	
Bone lesions (%)	1	✓		✓	
Prior ASCT (%)	1	✓		✓	
Age (years): Mean age (years) >65 years (%) Age >75 years (%)	3			✓	
Total number of characteristics to match	**32**	**28**	**18**	**26**	**18**
Abbreviations: ASCT, autologous stem-cell transplant; CS, company submission; ECOG, Eastern Cooperative Oncology Group; Ig, immunoglobulin; pg, page; pom+dex, pomalidomide plus dexamethasone.					

4.3.1.4.3 Results from MAIC

Progression-free survival

Using the ERG's preferred dataset (that adjusted for the most characteristics), the results generated by MAIC show no significant difference between daratumumab and pano+bort+dex (HR 0.85, 95% CI: 0.39 to 1.88) or pom+dex (HR 1.14, 95% CI: 0.64 to 2.03) in PFS (Table 19). The direction of the effect favours daratumumab compared with pano+bort+dex, but not when compared with pom+dex. However, it should be noted that the effective sample size in each MAIC was small, indicating poor overlap across populations: 13 in the MAIC versus pano+bort+dex and of 19 in the MAIC versus pom+dex. In addition, as a result of the small effective sample size, the estimates are likely to be unstable and there is considerable uncertainty around the results, as illustrated by the change in direction of effect with increasing number of factors adjusted for and the widening 95% CIs (Table 19). For the comparison of daratumumab and pom+dex, the ERG considers the effect estimate in people without prior exposure to pomalidomide to be particularly relevant to the decision problem. As noted earlier, results for an MAIC utilising the MMY2002 study population are not available. In the MAIC of the integrated dataset, there was no statistically significant difference in PFS between daratumumab and pom+dex in pomalidomide-naïve people (HR 0.51, 95% CI: 0.24 to 1.06; Table 20).

The ERG notes that there is considerable variation in effect estimates across the MAIC reported by the company in the CS and during clarification. For example, the most adjusted MAIC based on the integrated dataset of MMY2002 and GEN501 Part 2 generated a HR of 0.96 (95% CI: 0.60 to 1.55; Table 20) for daratumumab versus pano+bort+dex and a HR of 0.72 (95 CI: 0.50 to 1.05) for daratumumab versus pom+dex, which are markedly different from the estimates generated using solely MMY2002. The ERG mentions these results to emphasise the uncertainty around the estimates from the MAIC and that results should be interpreted with caution.

Table 19. Summary of PFS for the MAIC of daratumumab versus pano+bort+dex and versus pom+dex for MMY2002 alone (reproduced from Tables 4 and 5 of the company's response to clarification)

Number of matched characteristics	N	Neff	HR (95% CI)
Pano+bort+dex			
Non-bortezomib refractory included Unadjusted	106	–	1.22 (0.84 to 1.76)
Non-bortezomib refractory excluded Unadjusted	95	–	1.26 (0.87 to 1.84)
2	95	68	1.40 (0.94 to 1.09)
8[a]	95	56	1.20 (0.77 to 1.87)
16[b]	**84**	**13**	**0.85 (0.39 to 1.88)**

Pom+dex			
Unadjusted	106	–	1.03 (0.79 to 1.35)
3	106	75	0.97 (0.69 to 1.37)
13[a]	106	55	0.95 (0.64 to 1.40)
28[b]	**93**	**19**	**1.14 (0.64 to 2.03)**

[a] Company's base case.

[b] Estimate adjusted for all listed prognostic factors, including cytogenetics and ISS stage.

Abbreviations: CI, confidence interval; CS, company submission; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; Neff, net effective sample size; pano+bort+dex, panobinostat + bortezomib + dexamethasone; PFS, progression-free survival; pg, page; pom+dex, pomalidomide + dexamethasone.

Table 20. Summary of PFS for the MAIC of daratumumab versus pano+bort+dex and versus pom+dex for the integrated analysis of MMY2002 and GEN501 Part 2 (reproduced from CS, Tables 40 [pg. 132], 41 [pg. 135] and 42 [pg. 137])

Number of matched characteristics	N	Neff	HR (95% CI)
Pano+bort+dex			
Non-bortezomib refractory included Unadjusted	148	–	1.05 (0.75 to 1.47)
Non-bortezomib refractory excluded Unadjusted	125	–	1.09 (0.77 to 1.56)
2	125	91	1.19 (0.83 to 1.72)
5[a]	125	80	1.09 (0.74 to 1.61)
12	125	46	0.96 (0.60 to 1.55)
Pom+dex			
Unadjusted	148	–	0.88 (0.69 to 1.12)
3	148	110	0.84 (0.64 to 1.11)
11[a]	148	84	0.81 (0.60 to 1.09)
26	136	55	0.72 (0.50 to 1.05)
Integrated analysis excluding people with prior exposure to pom+dex			
Unadjusted	66	–	0.77 (0.55 to 1.09)
3	66	51	0.78 (0.53 to 1.16)
11[a]	66	29	0.57 (0.31 to 1.05)
18	66	19	0.51 (0.24 to 1.06)

[a] Company's base case.

Abbreviations: CI, confidence interval; CS, company submission; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; Neff, net effective sample size; pano+bort+dex, panobinostat + bortezomib + dexamethasone; PFS, progression-free survival; pg, page; pom+dex, pomalidomide + dexamethasone.

Overall survival

Using the ERG's preferred dataset (fully adjusted), the results generated by MAIC show no significant difference between daratumumab and pano+bort+dex (HR 0.61, 95% CI: 0.25 to 1.45) or pom+dex (HR 0.88, 95% CI 0.44 to 1.77) in OS (Table 21). The direction of the effect favours daratumumab compared with pano+bort+dex and with pom+dex. However, as with PFS, it should be noted that the effective sample size in each MAIC was small, indicating poor overlap across populations and likely

unstable estimates of effect. For the comparison of daratumumab and pom+dex, the ERG considers the effect estimate in people without prior exposure to pomalidomide to be particularly relevant to the decision problem. As noted earlier, results for an MAIC utilising the MMY2002 study population are not available. In the MAIC of the integrated dataset, in people without prior exposure to pomalidomide, daratumumab was associated with a statistically significant reduction in risk of mortality compared with pom+dex (HR 0.33, 95% CI: 0.17 to 0.66; Table 18).

Again, the ERG notes considerable variation in effect estimates across the MAIC reported by the company in the CS and during clarification. The most adjusted MAIC based on the integrated dataset of MMY2002 and GEN501 Part 2 generated an HR of 0.76 (95% CI 0.44 to 1.30; Table 22) for daratumumab versus pano+bort+dex and an HR of 0.56 (95% CI 0.38 to 0.83) for daratumumab versus pom+dex, with the latter result suggesting that daratumumab is statistically significantly more effective than pom+dex at improving OS. The ERG mentions these results to emphasise the uncertainty around the estimates from the MAIC and that results should be interpreted with caution.

During clarification, the ERG requested MAIC analysis for the integrated dataset based on subsequent treatment received on progression (bortezomib, carfilzomib, lenalidomide and pomalidomide). The results provided by the company in their response are presented in Table 22. Considering the comparison of daratumumab versus pano+bort+dex and versus pom+dex, the ERG notes [redacted] HRs and 95% CIs generated for the individual subsequent treatments compared with the result for a [redacted] integrated dataset. The ERG notes the [redacted] in the analyses and [redacted].

Table 21. Summary of OS for the MAIC of daratumumab versus pano+bort+dex and versus pom+dex for MMY2002 alone (reproduced from Tables 4 and 5 of the company's response to clarification)

Number of matched characteristics	N	Neff	HR (95% CI)
Versus pano+bort+dex			
Non-bortezomib refractory included Unadjusted	106	–	0.96 (0.61 to 1.51)
Non-bortezomib refractory excluded Unadjusted	95	–	1.03 (0.65 to 1.63)
2	95	68	1.03 (0.63 to 1.68)
8[a]	95	56	0.92 (0.56 to 1.52)
16[b]	**84**	**13**	**0.61 (0.25 to 1.45)**
Versus pom+dex			
Unadjusted	106	–	0.72 (0.54 to 0.98)

3	106	75	0.69 (0.48 to 0.99)
13[a]	106	55	0.65, (0.41 to 1.04)
28[b]	**93**	**19**	**0.88 (0.44 to 1.77)**

[a] Company's base case.

[b] Estimate adjusted for all listed prognostic factors, including cytogenetics and ISS stage.

Abbreviations: CI, confidence interval; CS, company submission; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; Neff, net effective sample size; OS, overall survival; pano+bort+dex, panobinostat + bortezomib + dexamethasone; pg, page; pom+dex, pomalidomide + dexamethasone.

Table 22. Summary of OS for the MAIC of daratumumab versus pano+bort+dex and versus pom+dex for the integrated analysis of MMY2002 and GEN501 Part 2 (reproduced from CS, Tables 40 [pg. 132], 41 [pg. 135] and 42 [pg. 137] and from response to clarification, Tables 11-18)

Number of matched characteristics	N	Neff	HR (95% CI)
Versus pano+bort+dex			
Non-bortezomib refractory included Unadjusted	148	–	0.82 (0.53 to 1.26)
Non-bortezomib refractory excluded Unadjusted	125	–	0.93 (0.60 to 1.44)
2	125	91	0.91 (0.57 to 1.45)
5[a]	125	80	0.84 (0.52 to 1.37)
12	125	46	0.76 (0.44 to 1.30)
Subgroup of people receiving bortezomib as a subsequent treatment after progression			
Non-BORT refractory included Unadjusted	[redacted]	[redacted]	[redacted]
Non-BORT refractory excluded Unadjusted	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Subgroup of people receiving carfilzomib as a subsequent treatment after progression			
Non-BORT refractory included Unadjusted	[redacted]	[redacted]	[redacted]
Non-BORT refractory excluded Unadjusted	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
Subgroup of people receiving lenalidomide as a subsequent treatment after progression			
Non-BORT refractory included Unadjusted	[redacted]	[redacted]	[redacted]
Non-BORT refractory excluded Unadjusted	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]

5	[redacted]	[redacted]	[redacted]
Subgroup of people receiving pomalidomide as a subsequent treatment after progression			
Non-BORT refractory included Unadjusted	[redacted]	[redacted]	[redacted]
Non-BORT refractory excluded Unadjusted	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Versus pom+dex			
Unadjusted	148	–	0.61 (0.46 to 0.81)
3	148	110	0.61 (0.45 to 0.83)
11[a]	148	84	0.57 (0.41 to 0.81)
26	136	55	0.56 (0.38 to 0.83)
Integrated dataset excluding people with prior exposure to pom+dex			
Unadjusted	66	–	0.38 (0.25 to 0.60)
3	66	51	0.47 (0.30 to 0.74)
11[a]	66	29	0.40 (0.20 to 0.80)
18	66	19	0.33 (0.17 to 0.66)
Subgroup of people receiving bortezomib as a subsequent treatment after progression			
Unadjusted	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
Subgroup of people receiving carfilzomib as a subsequent treatment after progression			
Unadjusted	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]
Subgroup of people receiving lenalidomide as a subsequent treatment after progression			
Unadjusted	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
Subgroup of people receiving pomalidomide as a subsequent treatment after progression			
Unadjusted	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]

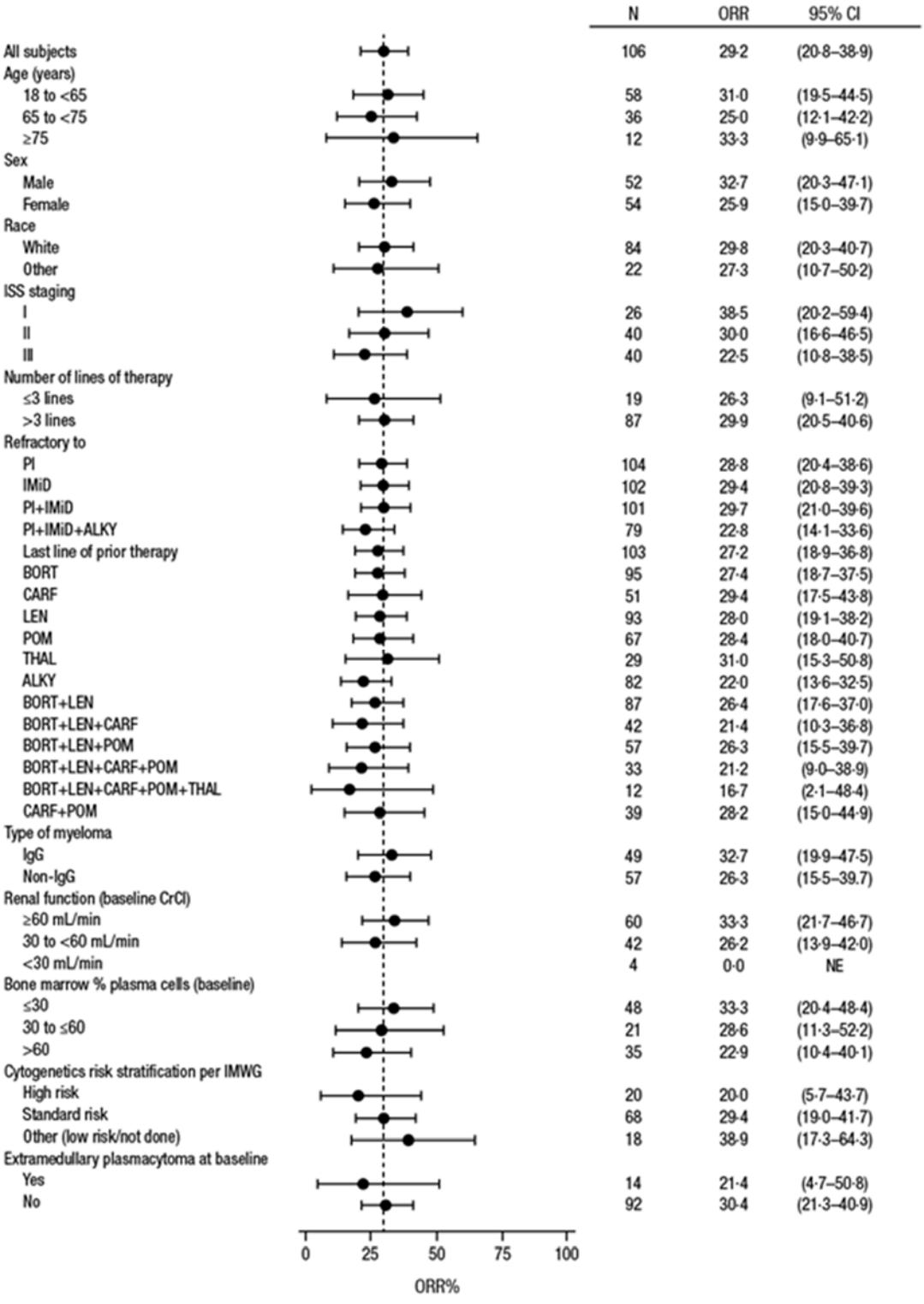
[a] Company's base case.

Abbreviations: CI, confidence interval; CS, company submission; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; Neff, net effective sample size; OS, overall survival; pano+bort+dex, panobinostat + bortezomib + dexamethasone; pg, page; pom+dex, pomalidomide + dexamethasone.

4.3.2 Subgroup analyses

No subgroup of interest to the decision problem was identified in the final scope issued by NICE.[1] For information, the ERG considers it noteworthy that the ORR was reasonably consistent across various subgroups analysed in MMY2002 and GEN501 Part 2, with ORRs of greater than 20% reported across most subgroups, with the exception of people in MMY2002 who were refractory to all of bortezomib, lenalidomide, carfilzomib, pomalidomide, and thalidomide (Figure 9). A poor response in people refractory to five different treatments would be expected.

Figure 9. ORR by subgroups for MMY2002 (based on IRC assessment, 9 January data cut-off; reproduced from CS, Appendix 5, Figure 1 [pg. 60])



Abbreviations: ALKY, alkylating agents, including autologous stem cell transplant; BORT, bortezomib; CARF, carfilzomib; CI, confidence interval; CrCl, creatinine clearance; CS, company submission; IMiD, immunomodulatory drug; LEN, lenalidomide; ORR, overall response rate; pg, page; PI, proteasome inhibitor; POM, pomalidomide; THAL, thalidomide.

The CSR for MMY2002 also presents a subgroup analysis of PFS and OS based on response to treatment with daratumumab (responders versus non-responders).[53] For PFS, at the time of the primary

analysis (median follow-up of 9.3 months), and based on IRC assessment, 54.8% of the responders had progressed or died, compared with 77.3% of those who did not respond to daratumumab (Table 23). Median PFS was 8.3 months (95% CI: 6.5 months to NE) in responders versus 2.1 months (95% CI: 1.64 months to 2.79 months) in non-responders. In addition, the PFS rate at various time points was considerably larger for responders (Table 23).

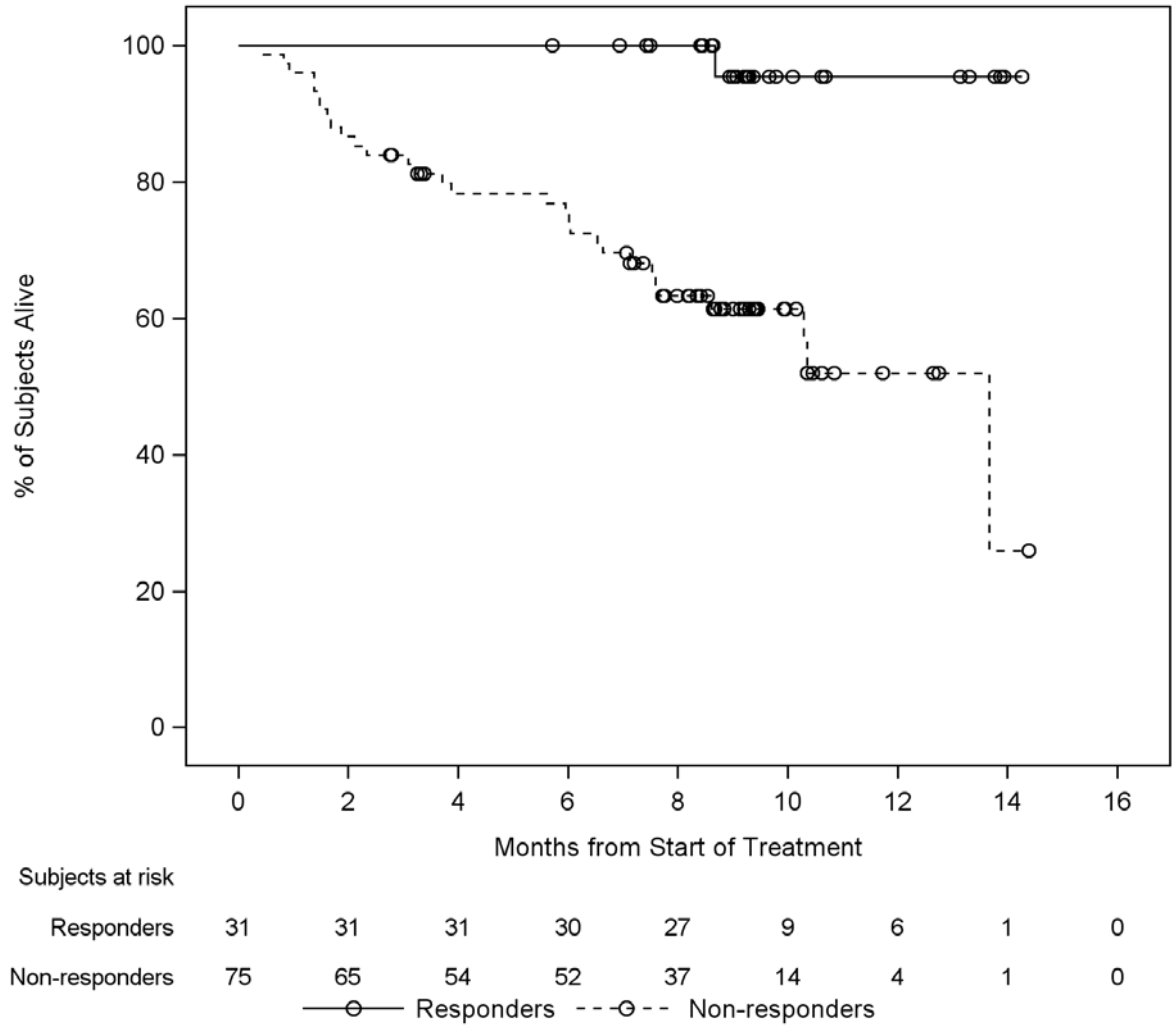
Table 23. Summary of PFS (based on IRC assessment) for responder versus non-responder in MMY2002 (adapted from CSR, Table 24, pg. 85)

	Responder	Non-responder
Analysis set: all treated	31	75
Progression-free survival		
Number of events (%)	17 (54.8%)	58 (77.3%)
Number of censored (%)	14 (45.2%)	17 (22.7%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	5.55 (3.71 to 7.39)	0.95 (0.92 to 1.41)
Median (95% CI)	8.34 (6.51 to NE)	2.10 (1.64 to 2.79)
75% quantile (95% CI)	NE (8.54 to NE)	3.71 (2.79 to 7.39)
3-month progression free survival rate % (95% CI)	93.5 (76.6 to 98.3)	29.2 (18.5 to 40.8)
6-month progression free survival rate % (95% CI)	74.2 (55.0 to 86.2)	18.2 (9.6 to 29.1)
12-month progression free survival rate % (95% CI)	42.4 (24.2 to 59.4)	NE (NE to NE)

Abbreviations: CI, confidence interval; CSR, clinical study report; IRC, independent review committee; NE, not estimable; PFS, progression-free survival; pg, page.

A marked difference in OS between responders and non-responders is also noted, with 29 (94%) of 31 responders remaining alive at time of primary analysis (median follow-up of 9.3 months) compared with 45 (60%) of 75 non-responders.[53] For responders, the 6-month and 12-month OS rate was 100% and 96%, respectively: corresponding data for non-responders are not reported in the CSR. The KM plot for responders versus non-responders for OS is presented in Figure 10.

Figure 10. KM plot for OS (based on IRC assessment) for responder versus non-responder in MMY2002 (all treated population) (reproduced from CSR, Figure 8, pg. 88)



Abbreviations: CSR, clinical study report; IRC, independent review committee; KM, Kaplan-Meier; OS, overall survival; pg, page.

4.3.3 Adverse effects

The company presents safety data in the CS from the integrated analysis of MMY2002 and GEN501 Part 2 at the December 2015 data cut-off. [93] The ERG also considered safety in the two daratumumab studies, MMY2002 and GEN501 Part 2, separately. The data summarising treatment emergent adverse events (TEAEs) (Table 24 and Table 27) and infusion-related reactions (IRRs) (Table 21) for the individual studies were obtained from the CSRs.[53, 55]

According to the company, daratumumab was well tolerated and resulted in no patient death or treatment discontinuation due to drug toxicity. Three deaths occurred due to TEAEs, one case each of viral HIN1 infection, pneumonia and aspiration pneumonia. In the integrated analysis, 79% of people experienced a drug-related TEAE, but only 8.8% of people had a serious drug-related TEAE. The majority of AEs were Grade 2 or 3 (approximately 37%). The ERG notes there were some differences

between MMY2002 and GEN501 Part 2 in the grades of reported AEs. MMY2002 had a higher proportion of Grade 3 events compared with GEN501 Part 2 (45.3% and 19%, respectively; Table 24). The ERG suggests that variations in AEs are likely related to the differences reported in efficacy and baseline characteristics of the two studies (further discussed in Section 4.2.2), with the population in MMY2002 being more heavily pre-treated compared with that of GEN501 Part 2.

Table 24. Summary of TEAEs for MMY2002, GEN501 Part 2 and the integrated analysis of MMY2002 and GEN501 Part 2 (data for MMY2002 and GEN501 taken from CSRs, data for integrated analysis reproduced from CS, Table 29 [pg. 104])

	MMY2002[53] [a] (N=106)	GEN501 Part 2[55] [a] (N=42)	Integrated analysis of MMY2002 and GEN501 Part 2 (N=148)
Any TEAE, n %	105 (99.1)	41 (97.6)	147 (99.3)
Drug-related	81 (76.4)	33 (78.6)	117 (79.1)
Any serious TEAE, n %	32 (30.2)	14 (33.3)	48 (32.4)
Drug-related	8 (7.5)	5 (11.9)	13 (8.8)
Maximum severity of any TEAE, n %			
Grade 1	8 (7.5)	2 (4.8)	9 (6.1)
Grade 2	26 (24.5)	28 (66.7)	55 (37.2)
Grade 3	48 (45.3)	8 (19.0)	56 (37.8)
Grade 4	14 (13.2)	2 (4.8)	17 (11.5)
Grade 5	9 (8.5)	1 (2.4)	10 (6.8)
Discontinuation due to TEAE, n %	5 (4.7)	1 (2.4)	6 (4.1)
Drug-related	0	0	0
Death due to TEAE, n %	2 (1.9)	1 (2.4)	3 (2.0)
Drug-related	0	0	0

[a] Data reported for all-treated analysis set, which comprised all enrolled people who received at least one dose of study drug.
Abbreviations: CS, company submission; CSR, clinical study report; pg, page; TEAE, treatment-emergent adverse event.

The most common TEAEs for daratumumab across all grades were fatigue (41.9%), nausea (29.7%), anaemia (28.4%), back pain (27%) and cough (25.7%) as reported from the integrated analysis (summary in Table 25). According to the company, the common AEs were consistent with the underlying disease state of advanced MM. The most common AEs of Grade 3 or higher were those related to blood and lymphatic system disorder such as thrombocytopenia, anaemia and neutropenia, which were managed with platelet transfusions, red blood cell (RBC) transfusions and prophylactic use of granulocyte colony-stimulating factor (GCSF). A total of 46 patients (31%) required 199 transfusions; of those 14 (20%) patients received platelet transfusion and 44 patients (30%) received the RBC transfusion. Twelve patients (8%) required prophylactic treatment with GCSF. The ERG notes differences between the two studies in the number of TEAEs, particularly in relation to Grade 3/4 blood and lymphatic system disorders, with 42% of patients in MMY2002 experiencing a TEAE affecting the blood and lymph system compared with only 9.5% of patients in GEN501 Part 2.

Table 25. Summary of TEAEs by organ class for MMY2002, GEN501 Part 2 and the integrated analysis of MMY2002 and GEN501 Part 2 (data for MMY2002 and GEN501 taken from CSRs, data for integrated analysis reproduced from CS, Table 30 [pgs 105–106])[a]

	MMY2002[53] b,c (N=106)		GEN501 Part 2[55] b,d (N=42)		Integrated analysis of MMY2002 and GEN501 Part 2 (N=148)		
	Any grade	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3**	**Grade 4**
Total TEAEs, n (%)	105 (99.1)	70 (66.0)	41 (97.6)	11 (26.2)	147 (99.3)	61 (41.2)	21 (14.2)
General disorders and administration site conditions	74 (69.8)	7 (6.6)	27 (64.3)	2 (4.8)	103 (69.6)	9 (6.1)	0
Fatigue	42 (39.6)	3 (2.8)	17 (40.5)	0	62 (41.9)	3 (2.0)	0
Pyrexia	17 (16.0)	0	7 (16.7)	1 (2.4)	29 (19.6)	1 (0.7)	0
Chills	N/R	N/R	5 (11.9)	0	15 (10.1)	0	0
Respiratory, thoracic, and mediastinal disorders	65 (61.3)	7 (6.6)	28 (66.7)	1 (2.4)	98 (66.2)	8 (5.4)	0
Cough	22 (20.8)	0	9 (21.4)	0	38 (25.7)	0	0
Nasal congestion	19 (17.9)	0	6 (14.3)	0	29 (19.6)	0	0
Dyspnoea	16 (15.1)	1 (0.9)	6 (14.3)	0	25 (16.9)	1 (0.7)	0
Musculoskeletal and connective tissue disorders	64 (60.4)	10 (9.4)	24 (57.1)	1 (2.4)	97 (65.5)	10 (6.8)	2 (1.4)
Back pain	23 (21.7)	3 (2.8)	10 (23.8)	0	40 (27.0)	4 (2.7)	0
Arthralgia	20 (18.9)	0	5 11.9)	0	27 (18.2)	0	0
Pain in extremity	18 (17.0)	1 (0.9)	5 (11.9)	0	26 (17.6)	1 (0.7)	0

Musculoskeletal chest pain	13 (12.3)	2 (1.9)	N/R	N/R	19 (12.8)	2 (1.4)	0
Bone pain	N/R	N/R	5 (11.9)	1 (2.4)	15 (10.1)	1 (0.7)	0
Musculoskeletal pain	N/R	N/R	N/R	N/R	15 (10.1)	1 (0.7)	0
Gastrointestinal disorders	64 (60.4)	3 (2.8)	20 (47.6)	0	88 (59.5)	3 (2.0)	1 (0.7)
Nausea	31 (29.2)	0	9 (21.4)	0	44 (29.7)	0	0
Diarrhoea	18 (17.0)	0	6 (14.3)	0	27 (18.2)	1 (0.7)	0
Constipation	17 (16.0)	0	N/R	N/R	22 (14.9)	0	0
Vomiting	19 (17.9)	0	N/R	N/R	21 (14.2)	0	0
Infections and infestations	54 (50.9)	12 (11.3)	27 (64.3)	2 (4.8)	87 (58.8)	13 (8.8)	2 (1.4)
Upper respiratory tract infection	19 (17.9)	1 (0.9)	7 (16.7)	0	32 (21.6)	1 (0.7)	0
Nasopharyngitis	8 (7.5)	N/R	10 (23.8)	0	22 (14.9)	0	0
Blood and lymphatic system disorders	61 (57.5)	44 (41.5)	N/R	4 (9.5)	76 (51.4)	37 (25.0)	11 (7.4)
Anaemia	35 (33.0)	25 (23.6)	N/R	1 (2.4)	42 (28.4)	26 (17.6)	0
Thrombocytopenia	27 (25.5)	20 (18.9)	N/R	1 (2.4)	32 (21.6)	13 (8.8)	8 (5.4)
Neutropenia	24 (22.6)	13 (12.3)	N/R	2 (4.8)	31 (20.9)	11 (7.4)	4 (2.7)
Metabolism and nutrition disorders	53 (50.0)	11 (10.4)	N/R	2 (4.8)	62 (41.9)	9 (6.1)	4 (2.7)

Decreased appetite	19 (17.9)	1 (0.9)	N/R	N/R	23 (15.5)	1 (0.7)	0
Hypercalcaemia	18 (17.0)	5 (4.7)	N/R	0	18 (12.2)	3 (2.0)	2 (1.4)
Nervous system disorders	37 (34.9)	6 (5.7)	N/R	1 (2.4)	55 (37.2)	6 (4.1)	1 (0.7)
Headache	10 (9.4)	2 (1.9)	N/R	N/R	18 (12.2)	2 (1.4)	0
Vascular disorders	25 (23.6)	9 (8.5)	N/R	1 (2.4)	30 (20.3)	9 (6.1)	0
Hypertension	12 (11.3)	7 (6.6)	N/R	1 (2.4)	15 (10.1)	7 (4.7)	0

[a] Data for the integrated analysis are labelled within the CS as common TEAEs occurring in ≥10% of people. Corresponding data for MMY2002 and GEN501 are taken from tables within the CSRs presenting most common TEAEs occurring in ≥10% of people and most common TEAEs of Grade3/4 (≥1%).

[b] Data reported for all-treated analysis set, which comprised all enrolled people who received at least 1 dose of study drug.

[c] Data taken from Tables 28 and 29 in the CSR for MMY2002.

[d] Data taken from Tables 30 and 31 in the CSR for GEN501.

Abbreviations: CS, company submission; CSR, clinical study report; N/R, not reported; pgs, pages; TEAE, treatment-emergent adverse event.

Infusion related reactions (IRRs) are a known AE of daratumumab, as reported in the SmPC.[51] In the integrated analysis, 48% of patients experienced IRRs, with most IRRs (95.6%) occurring at the first infusion. The company reported the most common IRRs (experienced by ≥5% of patients) based on the integrated analysis of MMY2002 and GEN501 Part 2, which are summarised in Table 26. Respiratory, thoracic and mediastinal disorder (nasal congestion, cough, allergic rhinitis, throat infection and dyspnoea) were the most common group of IRR, occurring in 36.5% of patients across all infusions. The number of IRRs reduced with each subsequent infusion. According to the company, IRRs were managed with pre- and post-infusion medications that included antihistamines, corticosteroids and paracetamol/ acetaminophen. All patients who experienced IRRs were able to continue daratumumab therapy at a full dose with these supportive treatments.

There was some disparity between the two studies in relation to IRR occurrence: 42% of patients in MMY2002 experienced IRRs compared to a much larger proportion of 73% in GEN501 Part 2 (Table 27). There was also a notable difference in mean time to IRR onset, 86.4 minutes in GEN501 Part 2 compared with 108.6 minutes in MMY2002. It is unclear why there are differences between MMY2002 and GEN501 Part 2 in IRR-related events.

The safety profile of daratumumab highlights that the drug has high tolerability with low occurrence of Grade 4 and higher AEs, with no dose reductions or patients discontinuing due to study drug toxicity. Considering the AE profile of the comparator treatments for people with MM, both panobinostat and pomalidomide are known to be associated with more serious AEs. Adverse events for panobinostat reported in PANOROMA 2[81] and for pomalidomide reported in MM-003[82] indicate that Grade 3/4 haematological events are relatively common; thrombocytopenia was reported in 63.6% of people receiving panobinostat and 22% of people given pomalidomide compared with 14.2% of people treated with daratumumab.

Panobinostat was also associated with higher rates of diarrhoea (70.9%), fatigue (69.1%) and nausea (60%) across all grades compared with daratumumab.[81] People receiving pomalidomide had higher rates of anaemia (52%) and neutropenia (51%) across all grades compared with daratumumab.[82] Pomalidomide had a particularly toxic profile, causing serious AEs, with 61% of patients reported to have had a Grade 5 event (requiring hospitalisation or resulted in disability or incapacity) and 4% to have had treatment-related death (eight cases of infections and infestations, two cases of multi-organ failure or sudden death and one nervous system disorder).

The ERG agrees with the company that daratumumab seems to offers a favourable safety profile compared with pomalidomide and panobinostat, although this naïve comparison across single arms should be interpreted with caution.

Table 26. Summary of IRRs by system organ class for the integrated analysis of MMY2002 and GEN501 (reproduced from CS, Table 31 [pgs 107–108])

	Integrated analysis of MMY2002 and GEN501 Part 2 (N=148)			
	First infusion (N=148)	**Second infusion (N=145)**	**Subsequent infusions (N=141)**	**Total (N=148)**
Total IRRs, n (%)[a]	68 (45.9)	5 (3.4)	5 (3.5)	71 (48.0)
Respiratory, thoracic and mediastinal disorders	53 (35.8)	4 (2.8)	0	54 (36.5)
Nasal congestion	17 (11.5)	1 (0.7)	0	17 (11.5)
Cough	11 (7.4)	1 (0.7)	0	12 (8.1)
Rhinitis allergic	10 (6.8)	0	0	10 (6.8)
Throat irritation	8 (5.4)	1 (0.7)	0	9 (6.1)
Dyspnoea	7 (4.7)	1 (0.7)	0	8 (5.4)
General disorders and administration site conditions	15 (10.1)	1 (0.7)	1 (0.7)	16 (10.8)
Chills	10 (6.8)	0	0	10 (6.8)
Gastrointestinal disorders	10 (6.8)	1 (0.7)	1 (0.7)	11 (7.4)
Nausea	7 (4.7)	1 (0.7)	1 (0.7)	8 (5.4)

Abbreviations: CS, company submission; IRR, infusion related reaction; pg, page.

Table 27. Summary of number of IRRs and time to onset of IRR for MMY2002 and GEN501 (adapted from CSR MMY2002, pg. 114 [Table 114] and CSR GEN501, pg. 138 [Table 36])

	MMY2002[53] (N=106)				GEN501 Part 2[55] (N=42)			
	Total	**First infusion**	**Second infusion**	**Subsequent infusions**	**Total**	**First infusion**	**Second infusion**	**Subsequent infusions**
Total number of people experiencing an IRR, n (%)	45	40 (88.9)	3 (6.7)	8 (17.8)	31	30 (96.8)	3 (9.7)	1 (3.2)
Total number of IRRs, n (%)	92	80 (87.0)	4 (4.3)	8 (8.7)	52	45 (86.5)	6 (11.5)	1 (1.9)
Time to onset of IRR (mins)								
N[a]	81	76	3	2	52	45	6	1
Mean time to onset (SD)	108.6 (86.99)	107.1 (84.33)	183.0 (155.88)	53.5 (21.92)	86.4 (53.85)	85.4 (54.36)	106.7 (43.67)	10 (–)
Median time to onset (range)	90.0 (1 to 470)	90.0 (1 to 470)	93.0 (93 to 363)	53.5 (38 to 69)	82.5 (10 to 190)	75.0 (10 to 181)	100.0 (60 to 190)	10.0 (10 to 10)

[a] IRRs for which the onset time is missing have been excluded from the analysis.

Abbreviations: CS, company submission; IRR, infusion related reaction; pg, page; SD, standard deviation.

4.3.4 Summary of clinical effectiveness

In support of the submission to NICE, the company presented data on the clinical effectiveness of daratumumab from two studies, MMY2002 and GEN501 Part 2, together with an integrated analysis that pooled data from the two studies. Daratumumab has a European marketing authorisation for the treatment of people with rrMM, whose prior therapy included a PI and an IMiD and who demonstrated disease progression on the last therapy.[50]

The population of interest to the decision problem as set out in the final scope issued by NICE is those with rrMM previously treated with a PI and an IMiD and who have demonstrated disease progression on the last therapy. In the CS, the company positions daratumumab as a fourth-line treatment in the rrMM setting, which is narrower than the final scope issued by NICE. The ERG's clinical experts support, to an extent, the positioning of daratumumab as a fourth-line treatment, feeding back that their likely preference would be to use daratumumab after len+dex but before pano+bort+dex, with the caveat that treatment choice at this stage of rrMM is tailored to the patient based on available options and is determined on a case-by-case basis.

As discussed in Section 4.2, the ERG notes key differences in baseline characteristics of the populations enrolled in MMY2002 and GEN501 Part 2. Given the differences between the studies, the ERG has chosen to focus reporting on MMY2002, as information on ISS and cytogenetics is available and the study was designed and planned to record ORR. The ERG recognises that with five median lines of prior therapy, the population is likely to be more heavily pre-treated than those who would be eligible for treatment with daratumumab in the UK and the results are biased against daratumumab in that setting.

At the time the ERG started this STA, pom+dex, was undergoing review by NICE through the STA process (subsequently approved) for treatment of rrMM after lenalidomide, the ERG considers people without prior pomalidomide to be a subgroup of interest to the decision problem.

In MMY2002, daratumumab was associated with an ORR (people achieved at least a PR) of 29.2% (95% CI: 20.8% to 38.9%). The median time taken to achieve the first response was 0.99 months, ranging from 0.9 to 5.6 months. Based on TTR, for people who respond to treatment with daratumumab, response is rapid, and shrinkage of tumours typically occurs within the first month of treatment. Median DOR in MMY2002 was 6.82 months (95% CI: 5.55 months to 11.07 months). Median PFS and OS were 3.7 months (95% CI: 2.8 months to 4.6 months) and 18.6 months (95% CI: 13.7 months to not reached), respectively, in MMY2002. In pomalidomide-naive people, median PFS was 3.98 months (95% CI: 2.60 months to 7.39 months). Median OS could not be determined for those without prior

exposure to pomalidomide. Results for pomalidomide-naïve people are *post hoc* analyses and should be interpreted with caution.

The ERG considered that the OS benefit reported for daratumumab in MMY2002 was substantially longer than would be expected based on the comparatively short PFS, given the typically poor prognosis of people at this stage of MM. The company proposes that the large difference between PFS and OS is not unexpected and is likely as a result of daratumumab's novel mode of action and immunomodulatory activity. However, a longer OS compared with PFS has been reported in other studies in people with rrMM, with one potential explanation proposed to be progression in disease being diagnosed biochemically, with clinical manifestation of relapse not occurring until months later.[82]

Confounding of OS due to subsequent therapy given at disease progression is recognised in studies evaluating treatments in oncological conditions. In MMY2002, people who progressed received carfilzomib and re-treatment with lenalidomide or bortezomib, none of which are available treatment options in the UK. Carfilzomib, lenalidomide and bortezomib are likely to be associated with prolonged OS compared with other treatment options available in the UK setting for the population of interest, and, hence, the OS benefit reported for daratumumab in MMY2002 is likely to be an overestimate of what would be expected in UK clinical practice.

The company reports that 71% of people (n=73) in MMY2002 went on to receive another intervention subsequent to treatment with daratumumab, which, as acknowledged by the company and its experts, is a large proportion and is likely to be smaller in clinical practice should daratumumab be approved (~55%). The ERG notes that the estimate of 55% of people going on to receive further therapy after daratumumab is similar to the proportion of people receiving subsequent treatment in MM-003 (44%). The company proposes that the high number of people receiving additional treatment after daratumumab is attributable to the "...novel and unique MoA associated with daratumumab, alongside the favourable safety profile, that culminate in an improved health status of patients". As the company outlines in their response to clarification, the more favourable adverse effect profile of daratumumab gives people "time to recover from the cumulative toxicity of previous treatments allowing a greater proportion of patients to receive subsequent therapy." Additionally, the company proposes that the "novel MoA of daratumumab, which includes immune-mediated mechanisms, increases the likelihood of benefitting from subsequent therapy". To evaluate the potential impact of confounding in OS due to therapies received after daratumumab, during clarification the ERG requested OS for MMY2002 and GEN501 Part 2 based on those receiving no subsequent treatment, and those receiving any subsequent treatment. Median OS of those receiving [redacted].

In terms of safety, daratumumab was well tolerated and resulted in no patient death or treatment discontinuation due to drug toxicity. Three deaths occurred due to TEAEs, one case each of viral HIN1 infection, pneumonia and aspiration pneumonia. IRRs are a known AE of daratumumab, as reported in the SmPC.[51] In the integrated analysis of MMY2002 and GEN501 Part 2, 48% of people experienced IRRs, with most IRRs (95.6%) occurring at the first infusion. Respiratory, thoracic and mediastinal disorder (nasal congestion, cough, allergic rhinitis, throat infection and dyspnoea) were the most common group of IRR, occurring in 36.5% of patients across all infusions. The number of IRRs reduced with each subsequent infusion. According to the company, IRRs were managed with pre- and post-infusion medications that included antihistamines, corticosteroids and paracetamol/ acetaminophen. All patients who experienced IRRs were able to continue daratumumab therapy at a full dose with these supportive treatments.

To address the lack of evidence from RCTs on comparative effectiveness of daratumumab, the company carried out a MAIC comparing daratumumab versus the identified relevant comparators of pom+dex and pano+bort+dex for PFS and OS. The company followed reported methods. The ERG's preferred dataset from the MAIC differs from that of the company. Based on guidance from the DSU, the ERG considers that the most adjusted dataset to be the most appropriate, which included adjustment for ISS and cytogenetics (therefore based on MMY2002 alone). For pomalidomide-naïve people, results for the MAIC are based on the dataset from the integrated analysis of MMY2002 and GEN501 Part 2. The ERG highlights that there were inconsistencies across analyses in factors adjusted for within the MAIC.

For PFS, results from the MAIC show no significant difference between daratumumab and pano+bort+dex (HR 0.85, 95% CI: 0.39 to 1.88) or pom+dex (HR 1.14, 95% CI: 0.64 to 2.03). The direction of the effect favours daratumumab compared with pano+bort+dex, but not when compared with pom+dex. In people without prior exposure to pomalidomide (based on integrated analysis), the MAIC found no statistically significant difference in PFS between daratumumab and pom+dex (HR 0.51, 95% CI: 0.24 to 1.06).

For OS, using the ERG's preferred dataset, the results generated by MAIC show no significant difference between daratumumab and pano+bort+dex (HR 0.61, 95% CI: 0.25 to 1.45) or pom+dex (HR 0.88, 95% CI 0.44 to 1.77). In the MAIC of the integrated dataset, in people without prior exposure to pomalidomide, daratumumab was associated with a statistically significant reduction in risk of mortality compared with pom+dex (HR 0.33, 95% CI: 0.17 to 0.66).

Again, the ERG considers it important to note that OS data are confounded by differences between MMY2002 and the comparator studies that have not been adjusted for. For example, in MM-003, which informs the MAIC versus pom+dex, the most commonly used subsequent therapies were dexamethasone, cyclophosphamide, bortezomib and bendamustine, which may have been used alone

or in combination.[85] Compared with MMY2002 and GEN501 Part 2, a considerably smaller proportion of people in MM-003 received carfilzomib, lenalidomide and bortezomib as a subsequent therapy (proportion of MM-003 vs MMY2002/GEN501 Part 2 receiving therapy: 2% vs 28% for carfilzomib; 5% vs 15% for lenalidomide and 18% vs 24% for bortezomib). The ERG considers that the subsequent treatments given in MMY2002 are likely to be associated with increased OS compared with the most common treatments given on progression in MM-003.

The ERG advises that the results of the MAIC are interpreted with caution. The most adjusted sets had small effective sample sizes, which indicates poor overlap between studies and that the estimates are likely to be unstable. In addition, there is considerable uncertainty around the results, as illustrated by the change in direction of effect within some MAIC and the wide 95% CIs.

4.4 Conclusions of the clinical effectiveness section

- Daratumumab (Darzalex®) has a European marketing authorisation for the treatment of people with rrMM, whose prior therapy included a PI and an IMiD and who demonstrated disease progression on the last therapy.

- Evidence on clinical effectiveness of daratumumab derived from two studies, MMY2002 and GEN501 Part 2, together with an integrated analysis that pooled data from the studies.

- ERG chooses to focus reporting on results for daratumumab from MMY2002. Daratumumab was associated with an ORR (people achieved at least a PR) of 29.2% (95% CI: 20.8% to 38.9%). The median time taken to achieve the first response was 0.99 months, ranging from 0.9 to 5.6 months. Based on TTR, for people who respond to treatment with daratumumab, response is rapid, and shrinkage of tumours typically occurs within the first month of treatment. Median DOR in MMY2002 was 6.82 months (95% CI: 5.55 months to 11.07 months). Median PFS and OS were 3.7 months (95% CI: 2.8 months to 4.6 months) and 18.6 months (95% CI: 13.7 months to not reached), respectively, in MMY2002.

- Those with no prior exposure to pomalidomide is a subgroup of interest to the decision problem. In pomalidomide-naive people, median PFS was 3.98 months (95% CI: 2.60 months to 7.39 months). Median OS could not be determined for those without prior exposure to pomalidomide. Results for pomalidomide-naïve people are *post hoc* analyses and should be interpreted with caution.

- MAIC for PFS found no significant difference between daratumumab and pano+bort+dex (HR 0.85, 95% CI: 0.39 to 1.88) or pom+dex (HR 1.14, 95% CI: 0.64 to 2.03) in PFS. In people without prior exposure to pomalidomide, MAIC found no statistically significant difference in PFS between daratumumab and pom+dex (HR 0.51, 95% CI: 0.24 to 1.06).

- MAIC for OS found no significant difference between daratumumab and pano+bort+dex (HR 0.61, 95% CI: 0.25 to 1.45) or pom+dex (HR 0.88, 95% CI 0.44 to 1.77) in OS. Daratumumab was associated with a statistically significant reduction in risk of mortality compared with pom+dex in pomalidomide-naïve people (HR 0.33, 95% CI: 0.17 to 0.66).

- The adverse effects reported for the integrated analysis dataset were consistent with the SmPC for daratumumab. IRRs are a known AE associated with use of daratumumab. In the integrated analysis of MMY2002 and GEN501 Part 2, 48% of people experienced IRRs, with most IRRs (95.6%) occurring at the first infusion. Respiratory, thoracic and mediastinal disorder (nasal congestion, cough, allergic rhinitis, throat infection and dyspnoea) were the most common group of IRR, occurring in 36.5% of patients across all infusions.

4.4.1 Clinical issues

- Evidence on clinical effectiveness of daratumumab is derived from long-term follow up of a single-arm from two separate studies, and thus is based on observational data and is at a high risk of bias.

- Single-arm studies are not considered appropriate design to capture time to event outcomes such as PFS and OS.

- Based on differences in baseline characteristics between MMY2002 and GEN501 Part 2, the ERG considers it inappropriate to combine data from the two studies for the purposes of estimating clinical effectiveness of daratumumab.

- ERG has concerns around the validity of the methods used by the company to carry out the reported integrated analysis of MMY2002 and GEN502 Part 2 to estimate clinical effectiveness of daratumumab.

- No estimates of clinical effectiveness from head-to-head studies.

- Long-term follow-up of a key study omitted from company's report. The ERG cannot definitively conclude that all relevant evidence has been identified.

- The ERG has concerns around the generalisability of MMY2002 and GEN501 Part 2 to UK clinical practice. Some treatments given as prior therapies and as subsequent treatments on progression are not available treatment options to clinicians in the UK in this setting.

- OS data are confounded by the use of subsequent treatment. Although this is the case in most studies, the ERG thinks it particularly noteworthy in the context of the decision problem

because some of the treatments given on progression in MMY2002 are not available as an option to clinicians in the UK. In addition, subsequent treatment could not be adjusted for in the MAIC.

- The ERG considers that results of the MAIC should be interpreted with caution as a result of small effective sample size, which can lead to unstable estimates.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and the *de novo* economic evaluation submitted by the company. Due to mistakes or discrepancies identified before and during the clarification process, the company provided two versions of the written submissions of the economic evidence along with three electronic versions of the Microsoft Excel® based economic model. The focus of the ERG report is therefore on the updated company submission (CS) and the third version, updated, economic model.

5.2 Summary of the company's key results

The company presented results for the pairwise analysis of daratumumab compared with pom+dex, pano+bort+dex and bendamustine. The base case and probabilistic results are presented in Table 28 and Table 29, respectively, for daratumumab at list price.

Table 28. Pairwise base case results from the company's updated model (CS, addendum to company evidence submission, Table 2)

Treatment	Total			Incremental			ICER (Dara vs comparator) at list prices
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Daratumumab	£81,422	1.31	2.54				
Pom+dex	£49,921	0.75	1.46	£31,501	0.56	1.07	£55,766
Pano+bort+dex	£74,530	1.10	2.14	£6,892	0.21	0.39	£32,593
Bendamustine-based therapy	£38,327	0.55	1.10	£43,095	0.76	1.44	£56,574
Abbreviations in table: bort, bortezomib; dex, dexamethasone; dara, daratumumab; year; ICER, incremental cost-effectiveness ratio; LY, life year; pano, panobinostat; pom, pomalidomide; QALY, quality-adjusted life year.							

Table 29. Mean PSA from company's updated model (CS, addendum to company's evidence submssion, Table 7)

Treatment	Total			Incremental			ICER (Dara vs Comparator)
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Daratumumab	£80,197	1.32	2.55				
Pom+dex	£49,653	0.76	1.50	£30,544	0.56	1.06	£54,987
Pano+bort+dex	£74,516	1.14	2.22	£5,681	0.18	0.33	£31,079
Bendamustine-based therapy	£39,313	0.56	1.13	£40,884	0.76	1.43	£54,149
Abbreviations in table: dex, dexamethasone; pano, panobinostat; bort, bortezomib; LY, life years; pom, pomalidomide; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; dara, daratumumab							

5.3 ERG comment on company's review of cost-effectiveness evidence

The company reports carrying out a systematic literature review to identify studies assessing the cost-effectiveness of daratumumab for treating multiple myeloma (MM). An overview of the search is presented in Section 5.1 of the CS with the search strategy and results being presented in Appendix 10 of the CS. The search strategies and terms used to identify cost-effectiveness studies are reasonable and in line with published guidelines by the Scottish Intercollegiate Guidelines Network[73].The company searched the following electronic databases:

- MEDLINE and MEDLINE In-Process;
- EMBASE;
- Health Technology Assessment (HTA) database;
- National Health Service Economic Evaluation Database (NHS EED);
- EconLit.

The search was conducted in January 2016 and was restricted based on intervention to identify only studies assessing the cost-effectiveness of daratumumab for treating MM. The inclusion and exclusion criteria applied in the search are presented in Table 30. Although the majority of the inclusion and exclusion criteria are reasonable, the ERG disagrees with the company's decision of excluding cost-effectiveness studies of treatments other than daratumumab for MM. Given that the only intervention considered was daratumumab, it is not surprising that the company concludes that no NICE submissions met the inclusion criteria for cost-effectiveness studies.

Table 30. Inclusion and exclusion criteria for search for cost-effectiveness studies (CS Appendix 10, page 99, Table 29)

Criteria	Inclusion	Exclusion
Study population	Adult patients with MM	No adult MM patients
Intervention	Daratumumab	None
Outcome	Studies will include a comparison of costs between the intervention and comparator arms. Results should also include either incremental QALYs (or another measure of health outcome/clinical effectiveness), or be structured with a cost-minimisation argument.	Cost-only outcomes (without a cost-minimisation argument, e.g. burden of illness studies).
Study types	Economic evaluations (including cost-consequence, cost-minimisations, cost-effectiveness, cost-utility and cost-benefit evaluations)	None
Publication Types	None	Letters and comment articles.
Language	Studies reported in English	Studies not reported in English

Other	Studies must present sufficient detail of the methodology used and provide extractable results.	Publications that fail to present sufficient methodological detail or extractable results.
Abbreviations in table: MM, multiple myeloma; QALY, quality-adjusted life year; multiple myeloma.		

A total of 10 studies were identified from the search which were excluded after abstract review due to not meeting the inclusion criteria for study type. The company proceeded to search the Scottish Medicines Consortium (SMC) and NICE websites, and reported that no evaluations met the inclusion criteria.

In conclusion, the ERG disagrees with the company's approach of limiting the cost-effectiveness search to a specific intervention (daratumumab), as this led the company to exclude relevant sources of data unnecessarily. Issues identified in previous cost-effectiveness studies and TA submissions of comparator treatments would have enabled the company to explore methodological uncertainty further and strengthen the *de novo* cost-effectiveness analysis for daratumumab. For example, the company did not identify the TA submission for pomalidomide to the SMC which included a more recent publication of the analysis of EQ-5D data from the MM-003 trial.

The ERG notes that the company carried out separate searches to identify quality of life data and resource use for patients with MM, which were not limited to specific interventions and included economic evaluations if these reported data on either. Therefore, some but not all economic evaluations have been identified. Furthermore, the company refers to two TAs [94, 95] in Section 5.4.5 and Section 5.4.6, yet there is no mention of how they were identified as relevant appraisals. This is further explored in Section 5.5.8 and Section 5.5.9 of the ERG report.

5.4 Overview of company's economic evaluation

Upon a brief initial review of the company's model, the ERG identified implementation errors, related with the fact that the model cycles had been changed from daily to seven-day cycles before the company submitted the final analysis. Furthermore, several of the company's scenario analysis (whether using alternative data or methodologies) were also found to not work properly. The ERG was concerned that this reflected a poor level of internal quality assessment of the model by the company before the submission date and invited the company to amend the economic model at that stage. As a result of this, the company provided the ERG with an updated model before the end of the clarification stage. Upon the ERG's initial alert to the mistakes in the model, the company advised that since submission the model had undergone further consistency checks and had been reviewed by the vendor who had built the model; a different vendor and Janssen internally.

Despite this, the ERG identified further mistakes in the second model submitted by the company and so the company submitted a third model after the clarification stage, as a reply to the ERG's request for clarification related with new errors identified. After the submission of the third model, the ERG still found a considerable amount of serious errors in the economic model (described throughout the report).

Furthermore, the references included in the original CS were incorrectly labelled or missing. Upon a request for revision of the references and respective sources by the ERG, the company submitted new references and an updated CS. The ERG still found mislabelled references after the company's attempt to correct these. This added to the burden of the ERG's review process and increased the likelihood of mistakes as the sources provided for the respective references were not always correct or available to the ERG.

The company also submitted new data (as a response to the ERG's request). The ERG encountered several errors and discrepancies in the data forwarded by the company to the ERG at the clarification stage. For example, all the overall survival Kaplan-Meier curves for subsequent treatments were labelled with the incorrect treatment (for instance, what the company reported as being the subsequent pomalidomide overall survival Kaplan-Meier curve, was actually the subsequent lenalidomide overall survival Kaplan-Meier curve, as the ERG discovered later).

As a consequence, the ERG lacks overall confidence in the Excel model and in the company analysis of data. The specificities of this STA allied with the submission of multiple model versions and the limited time available for the ERG review, make it very likely that some mistakes were not detected by the ERG. The key specificities of this STA are as follows:

- The absence of RCT evidence;

- The possible permutations for the data analysis (three datasets for daratumumab – MMY2002; GEN501 and integrated; two different trials for the two comparator; two subgroups of relevance related with subsequent therapies and pre-treatment received by patients; two possible modelling approaches – dependent or independent fit and finally the variation in the adjustment factors included in the MAIC).

Furthermore, the ERG had to make several data assumptions due to lack of clarity in the model and in the CS. The fact that the ERG kept finding mistakes in data handling and labelling increases the probability that some other similar mistakes were not identified. It is impossible to foresee the impact of such potentially uncovered mistakes on the final ICER. It is the ERG's opinion that the company's model and data analysis need further internal consistency checks and a thorough quality check before a reliable final ICER can be determined for daratumumab.

5.4.1 Model structure

In this Section, the ERG presents the model developed by the company. A detailed discussion and critique of the model structure and modelling approach is included in Section 5.5.

The company developed a *de novo* model in Microsoft Excel® to assess the cost-effectiveness of daratumumab in comparison with pom+dex and in comparison with pano+bort+dex in relapsed refractory multiple myeloma (rrMM) patients whose prior therapy included a proteasome inhibitor (PI) and an immunomodulatory (IMiD) agent and who have demonstrated disease progression on the last therapy. The company also assessed the cost-effectiveness of daratumumab when compared with bendamustine.

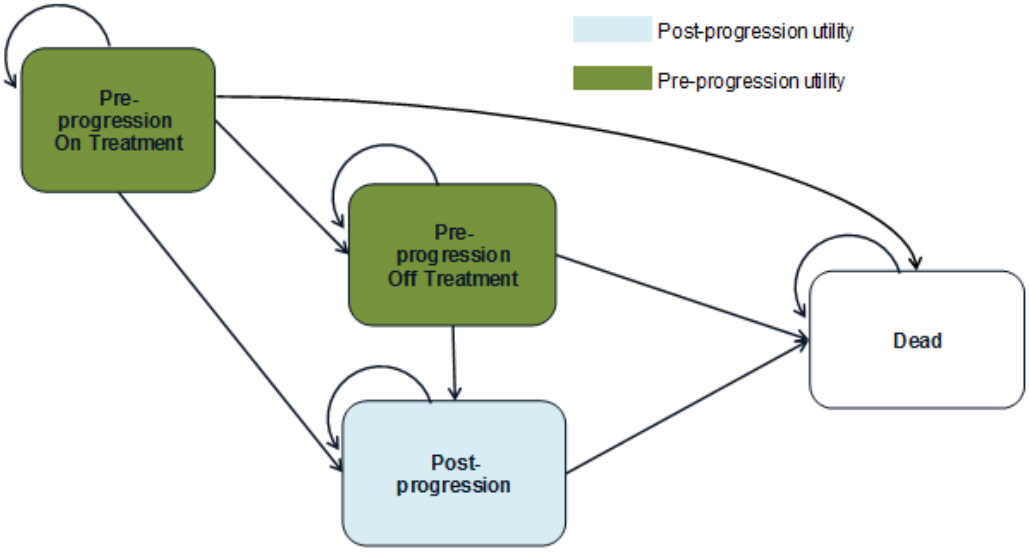
The company developed a cohort-based partitioned survival model (presented in Figure 11) which includes four health states: progression-free on treatment (PFT), progression-free off treatment (PFOT), progressed disease (PD), and death. The company reports that rrMM patients may withdraw from active treatment before disease progression therefore disaggregating the progression-free (PF) state into PFT and PFOT to allow treatment costs to be captured more accurately in the economic analysis.

The cohort is allocated to the PFT state at the beginning of the economic analysis and is assumed to initiate treatment with daratumumab or with one of the three comparators. Patients occupying the PFT state are at risk of disease progression or death and can also discontinue treatment before disease progression. Patients in the PFOT state can move to the PD state or die. Patients occupying the PD state are also at risk of death and can receive further treatment lines in the model. After entering the PD state patients cannot enter remission.

The partitioned survival (or area under the curve [AUC]) approach means that the proportion of patients modelled in each health state is based on parametric survival curves for each clinical outcome. A

description of how the survival curves were estimated and implemented in the model is provided in detail in Section 5.4.2.

Figure 11. Model structure



A life time horizon of 15 years is adopted in the model, and time is discretised into weekly cycles with a half-cycle correction not applied. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.[96]

5.4.2 Treatment effectiveness

The CS reports that daratumumab is associated with unprecedented survival benefit for responding or partially responding patients. The company adds that the survival benefits for rrMM patients observed in MMY2002 and GEN501 may be underestimated given the poor prognosis of patients enrolled in both trials compared with the potential survival that could be achieved with daratumumab monotherapy in a less heavily pre-treated and refractory population.

The company also explains that due to daratumumab's immunomodulatory mode of action, a relatively short progression-free survival (PFS) compared with OS is not unexpected. It is noted that trial assessment methods for disease progression can be misleading as patients can have biochemical progression (as measured by the International Myeloma Working Group criteria) without clinical progression. The results of the MAIC conducted by the company and reported in Section 4 of the ERG report show that PFS for daratumumab is not statistically significantly different from the PFS observed with pano+bort+dex or with pom+dex.

The company also reports that daratumumab is well tolerated and has a favourable safety profile, which is particularly important for rrMM patients who have been exposed to the continuous toxicity associated with other rrMM treatments. In fact, the company states that the unique mechanism of action associated with daratumumab monotherapy appears to change the natural course of disease in rrMM as its favourable safety profile is potentially associated with a disease reset. This culminates in an improved health status of patients, allowing them to receive further active treatments (and retreatment with drugs received previously) to re-stabilise their disease.

Treatment effectiveness within the model was implemented through a partitioned survival method, which uses the estimated OS and PFS data from the MMY2002/GEN501 integrated trial analysis to determine mortality and disease progression at each cycle of the economic model. Treatment effectiveness was also included in the model through the observed lower rates of adverse events (AEs) related with daratumumab. The clinical impact of subsequent treatments received after daratumumab was implicitly included in the economic model through the use of overall OS data from MMY2002 and GEN501, given that patients received further rrMM treatment after daratumumab. Disease progression on subsequent therapy is not captured within the economic model.

5.4.2.1 Statistical approach

In this section the ERG provides an overview of the statistical approach undertaken to estimate parametric survival models using OS, PFS and time to treatment discontinuation (TTD) data from MMY2002 and GEN50 and the process of deriving the occupancy for the PFT, PFOT, PD and death states of the model in the base case analysis. The ERG also reports the results of the company analysis of PFS and TTD data. The mortality section of the ERG report (Section 5.4.4) describes the results of the company analysis of OS data in the base case economic analysis.

In their base case analysis, the company decided to use the integrated patient-level data from MMY2002 and GEN501 (described in Section 4 of the ERG report). In order to extrapolate OS, PFS and TTD data into the model time horizon the company fitted a variety of parametric curves to the integrated data. The company reports fitting clinical data from the trials with exponential, Weibull, log-logistic, lognormal and generalised gamma models in accordance with guidance from NICE Technical Support Document (TSD) 14.[97] The company adds that the fit of each parametric model was compared with the observed KM data and that statistical fit was assessed using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). It is also reported that the clinical plausibility of each extrapolation was assessed by a consultant haematologist practicing within the NHS in England.

Once the best-fitting model was selected, survival curves were derived through the use of survival functions and were then used to estimate the proportion of patients in each health state for every cycle of the economic model. The company did not report how the estimated survival curves for daratumumab

were used to derive the proportion of patients in each health state of the model, therefore the ERG investigated the economic model and reports the formulae used by the company below. The company's model used the following equations:

- PFT = P(PFS);
- PFOT = P(PFS)-P(TTD);
- PD = P(OS)-P(PFS);
- Death = 1-P(OS).

Where P(PFS) is the proportion of progression-free patients taken from the PFS curve, P(OS) is proportion of patients alive taken from the OS curve and P(TTD) is the proportion of patients on treatment taken from the TTD curve.

To derive the survival curves for pom+dex and pano+bort+dex the weighted HRs derived from the MAIC (Section 4) were applied to the estimated unadjusted survival curves derived from MMY2002/GEN501 for daratumumab for OS and PFS. The company estimated TTD curves for daratumumab using the integrated data from MMY2002/GEN501. For pom+dex, only mean and median TTD could be obtained from the literature, therefore the TTD curves for daratumumab were calibrated to match the observed mean and median from MM-003. The company could not find TTD data for pano+bort+dex or bendamustine therefore patients were assumed to be treated until progression, or when the maximum number of treatment cycles was reached for these two treatments.

As reported by the company, trial data for bendamustine-based therapy in the rrMM patient population are scarce and of low quality. Therefore, the company used real-world data sources to provide efficacy estimates for bendamustine. As explained in Section 4 of this report, clinical expert opinion provided to the ERG confirmed that bendamustine is not an appropriate comparator for daratumumab. Furthermore, bendamustine does not have a marketing authorisation in the UK for rrMM although it is currently funded through the CDF. Given this and the added complexity of the company's analysis of the relative effectiveness of bendamustine vs daratumumab, the ERG decided to not include bendamustine in its review of the company's analysis of treatment effectiveness within the economic model. The costs and adverse events related with bendamustine are still reported in Section 5.4.6 and Section 5.4.3, respectively, for inclusiveness purposes.

The company's base case model assumes that the proportional hazards (PH) assumption holds for the comparison of daratumumab against pom+dex and pano+bort+dex, for OS and PFS data. In Appendix 11 of the CS, the company reports the tests undertaken for the validation of the PH assumption for OS

data. Validation of the PH assumption for PFS data were not initially reported by the company. There was no assessment of the proportional odds (PO) or accelerated failure time (AFT) assumptions. Upon a clarification request by the ERG, the company submitted various plots to aid the assessment of PH for PFS and assessment of PO and AFT for PFS and OS. However, the company did not carry out the assessment itself to arrive at a conclusion (for example, through examination of the log-log plots) as requested by the ERG. This is further explored in Section 5.5.5.

The company's original model included an option to run the cost-effectiveness analysis using independently fitted curves for OS but not for PFS. Upon clarification, the company submitted an updated model which allowed the estimation of OS as well as PFS through an independent fit approach. The option to model curves independently uses the integrated MAIC-adjusted daratumumab data (for OS or PFS) and the unadjusted OS or PFS curves from MM-003 for pom+dex and from PANORAMA2 for pano+bort+dex.

The company's model also includes an option to run the cost-effectiveness analysis using the MMY2002 and the GEN501 data separately. Nonetheless the combination of running individual trial data with independently fitted curves is not an option in the model. In summary, the options to run the model using different statistical approaches consist of:

5. Dependently fitted curves, with application of the MAIC HRs to the unadjusted daratumumab integrated curves to obtain the pom+dex and the pano+bort+dex OS and PFS curves;

6. Dependently fitted curves, with application of the MAIC HRs to the unadjusted daratumumab MMY2002 curves to obtain the pom+dex and the pano+bort+dex OS and PFS curves;

7. Dependently fitted curves, with application of the MAIC HRs to the unadjusted daratumumab GEN501 curves to obtain the pom+dex and the pano+bort+dex OS and PFS curves;

8. Independently fitted curves, using the integrated MAIC-adjusted daratumumab OS and PFS curves and the unadjusted fitted OS and PFS curves taken from MM-003 for pom+dex and from PANORAMA2 for pano+bort+dex.

5.4.2.2 Progression-free survival

The company used the independent review committee (IRC) integrated KM data to model PFS for daratumumab in the base case economic model. Goodness of fit was assessed through analysis of AIC and BIC statistics together with clinical plausibility of the curves. Based on the AIC and BIC criteria reported (Table 31) and clinical plausibility of the curves, the company concluded that the best fitting model is the lognormal. Initially the company did not report the Gompertz AIC and BIC statistics in

their assessment of curve fit. Nonetheless the economic model reported these estimates which are also reported in Table 31.

Table 31. Goodness-of-fit statistics for daratumumab integrated PFS data

	Log-normal	Log-logistic	Exponential	Weibull	Generalised Gamma	Gompertz*
AIC	394.21	399.16	413.61	415.39	388.38	602.31
BIC	400.21	405.15	416.61	421.38	397.37	608.30

AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.
*The company provided AIC and BIC statistcis on a different scale for the Gompertz distribution. See text below for more information.

The lognormal model used by the company together with the integrated PFS KM data for daratumumab is shown in Figure 12. Figure 13 shows the fitted curves and the PFS KM curve for a shorter time horizon (26 months). Visual inspection of Figure 13 shows that all curves, expect the exponential, provide a similar fit to the KM curve for the trial period, with the Gompertz and the Gamma distribution being a closer fit to the KM data. Given the good visual fit of the Gompertz distribution, the ERG requested the company to explain the high AIC and BIC values reported for the Gompertz distribution (Table 31). The company replied that, "*there is a discrepancy in the AIC/BIC statistics submitted, due to different SAS procedures being used to derive these estimates. The AIC/BIC statistics for the Gompertz distribution are on the original scale whereas; the AIC/BIC for other distributions tested are on the log scale. As noted by the ERG the Gompertz distribution is indeed a better statistical fit to the PFS data than the lognormal. However […] clinical validation of the extrapolations resulted in the lognormal being chosen as the base case.*"

The company concluded that even though the generalised gamma and Gompertz models are the best fit to the PFS integrated daratumumab data, these project a plateau in PFS of around 5% of patients, from around 5 years onwards. The company's clinical experts did not find this plausible, therefore the lognormal model was used. The lognormal model predicts that around 3% of patients will be progression-free three years after treatment with daratumumab with 1% of patients still free from disease progression by year 5.

Figure 12. Parametric curves fit to PFS data of the integrated MMY2002/GEN501 cohort (15 years time horizon)

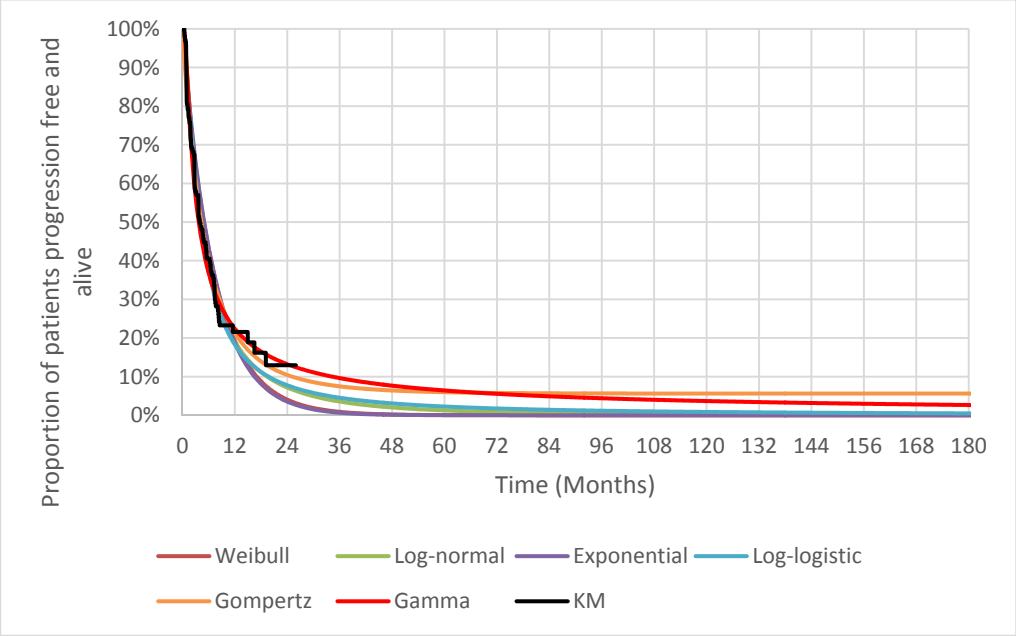
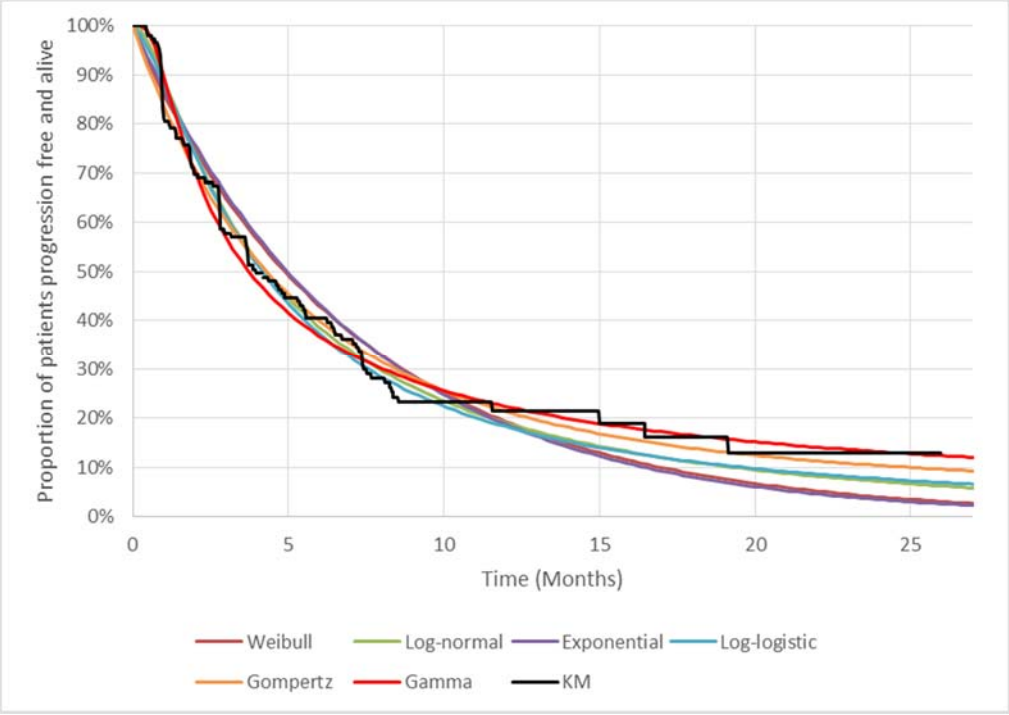


Figure 13. Parametric curves fit to PFS data of the integrated MMY2002/GEN501 cohort (2 years time horizon)



To estimate the PFS curves for pom+dex and pano+bort+dex, the company applied the weighted HRs from the MAIC analysis (Section 4) to the unadjusted integrated daratumumab PFS curve modelled with the lognormal distribution. The weighted HRs used in the analysis are reported in Table 32. The weighted PFS HR for pom+dex was derived through the MAIC when matching the top 11

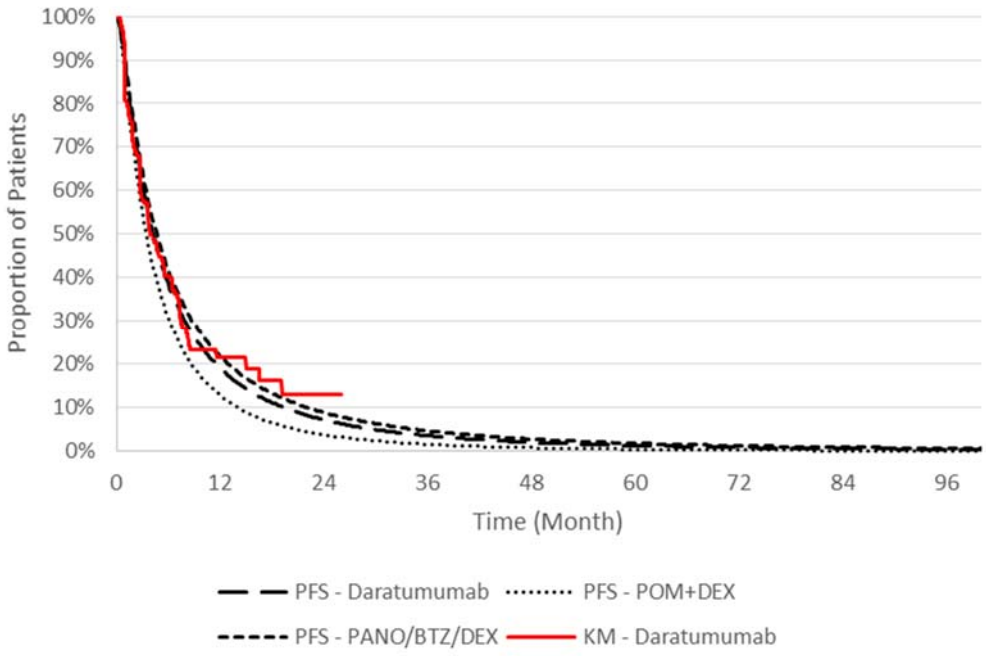
characteristics, while the PFS HR for pano+bort+dex was derived when matching the five top baseline characteristics across patients in the daratumumab trials and PANORAMA2. Figure 14 shows the PFS curves for daratumumab, pom+dex and pano+bort+dex, together with the unadjusted KM curve for the integrated daratumumab data.

The HRs reported in Table 32 show that PFS is not statistically significantly different between daratumumab and pom+dex and between daratumumab and pano+bort+dex, after adjusting for differences across trials. The company explains that the analysis against pano+bort+dex is based on small patient numbers (n=55) and so it is challenging to demonstrate statistical significance. The company adds that as a consequence of lack of data available from PANORAMA2 it was not possible to adjust for refractory status (other than to bortezomib). The refractory status of patients is a key prognostic factor and given the generally more refractory nature of patients enrolled in MMY2002/GEN501 the company considers that it is likely that the lack of adjustment for refractory status would introduce bias against daratumumab. The company did not provide any potential explanation for the lack of statistical significance in the PFS HR between daratumumab and pom+dex.

Table 32. Progression-free survival HRs for pom+dex and pano+bort+dex

Daratumumab compared with	Weighted HR from MAIC	95% confidence interval	Number of characteristics matched
Pom+dex	1.241	(0.920; 1.675)	11
Pano+bort+dex	0.920	(0.623; 1.357)	5
Abbreviations in table: bort, bortezomib; dex, dexamethasone; MAIC, matched adjusted indirect comparison; pano, panobinostat; pom, pomalidomide.			

Figure 14. Progression-free survival curves for daratumumab, pom+dex and pano+bort+dex



The company included an option to fit PFS curves independently in the model. Nonetheless several errors were identified in the implementation of this option in the model, together with several unjustified assumptions. The formulae in the model were incorrect and used the MAIC HR to derive the pom+dex curve (dependent fit) when an option to independently fit the PFS curves was chosen. The models used to fit the daratumumab MAIC-adjusted PFS curves were also incorrectly applied in the model as the formulae linked these to the models chosen for OS instead of PFS, which resulted in the daratumumab PFS curves being fit with exponential curves and the pom+dex and pano+bort+dex curves being fit with lognormal curves.

Figure 15 and Figure 16 report the independently fitted curves for daratumumab vs pom+dex (in a longer and shorter time horizons) and for daratumumab vs pano+bort+dex, respectively. Figure 15 shows that daratumumab is associated with a higher PFS than pom+dex (however there is no analysis of the statistical significance of this difference). Figure 16 shows that daratumumab is associated with a lower PFS than pano+bort+dex until month 6 and a higher PFS than pano+bort+dex after that (however there is no analysis of the statistical significance of this difference). To note is that when the curves are fitted together (Figure 14) daratumumab is associated with a higher PFS than pom+dex overall and a lower PFS than pano+bort+dex for the entire time horizon of the model. Even though from a statistical point of view, there might be no overall difference across the curves, the relative positioning of the PFS curves has a crucial impact on the estimation of treatment costs and consequently on the final ICER. The appropriateness of fitting treatment curves together or independently is also related with the assessment of the PH, PO and AFT assumptions. These issues are further explored in Section 5.5.5 of the ERG report.

It should also be noted that when fitting PFS curves independently, the company did not report any formal process of curve fitting or model selection. The same curve selection used for the dependently fitted curves was applied (i.e. using a lognormal model). Visual assessment of the KM and the fitted curves in Figure 15 and Figure 16 suggest that while the curves fitted for pom+dex may be a reasonable fit, the pano+bort+dex curves do not seem to fit the KM data well. AIC and BIC statistics were reported in the Excel model.

Finally, it should be considered that the CS does not explicitly state how many characteristics are adjusted for in the MAIC-adjusted daratumumab curves for use in the independent fit approach. The ERG assumes that the same 11 characteristics were matched and adjusted for in relation to pom+dex, while the PFS adjusted curve for daratumumab in comparison with pano+bort+dex adjusted for the same five baseline characteristics across patients in the daratumumab trials and PANORAMA2 as for the dependent fit approach.

Figure 15. Indepedently fitted PFS curves for daratumumab vs pom+dex

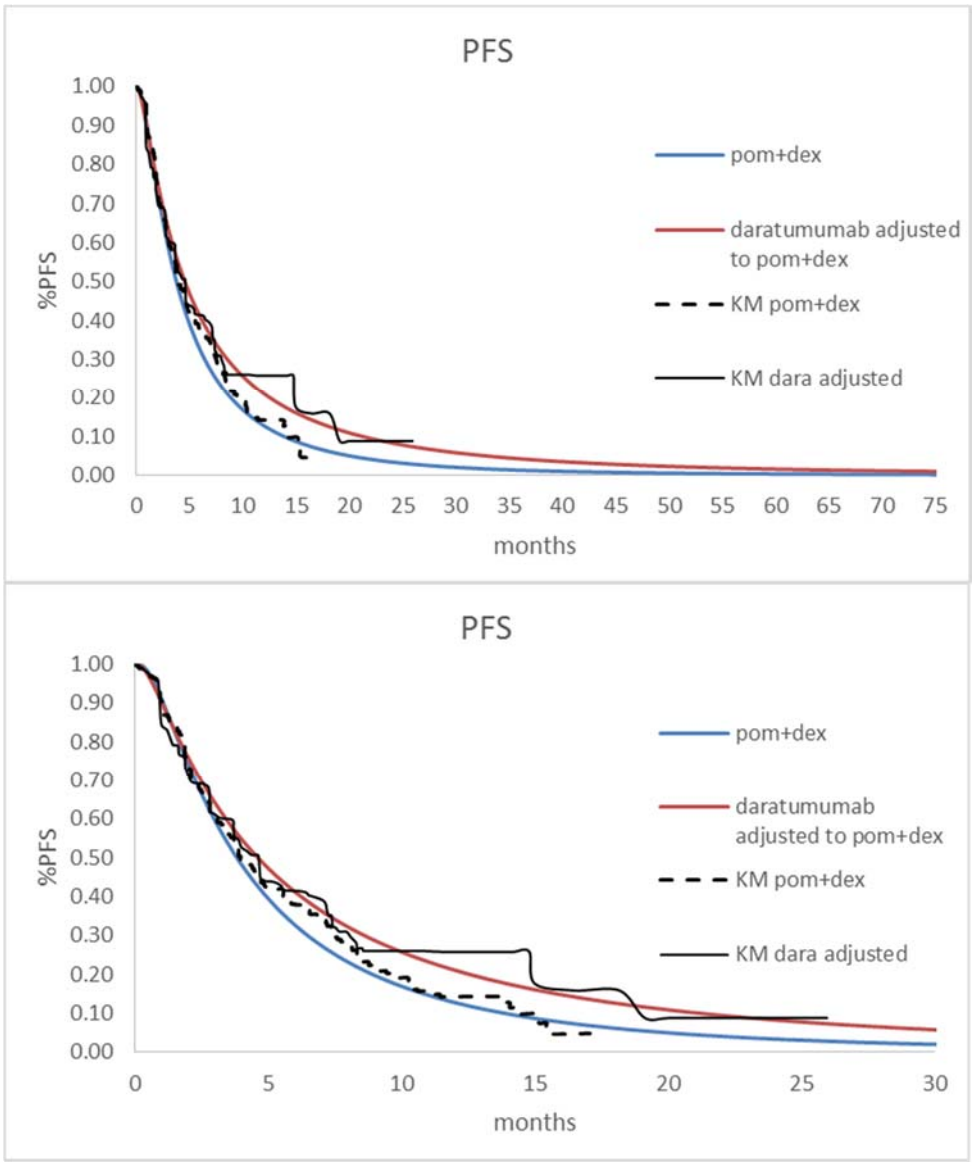
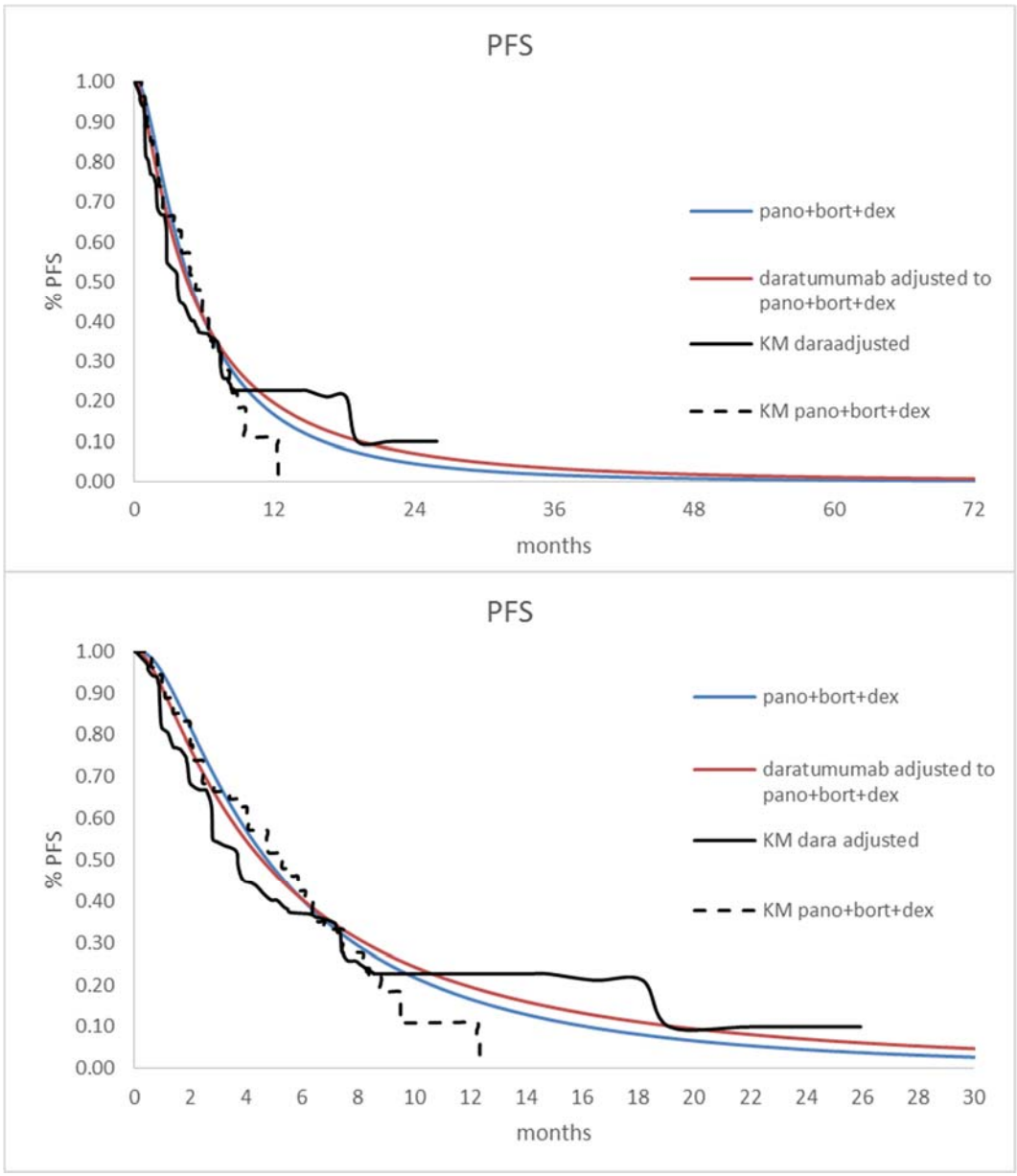


Figure 16. Indepedently fitted PFS curves for daratumumab vs pano+bort+dex



5.4.2.3 Time to treatment discontinuation

Time to treatment discontinuation is used by the company to model treatment costs for daratumumab and pom+dex. This is done by subtracting the PFS curve from the TTD curve for each treatment, to obtain time on treatment for daratumumab and pom+dex patients (TOT = P(PFS)-P(TTD)). The company estimated TTD curves for daratumumab using the integrated data from MMY2002 and GEN50. For pom+dex, only mean and median TTD could be obtained from the literature, therefore the TTD curves for daratumumab were calibrated to match the observed mean and median from MM-003. The company could not find TTD data for pano+bort+dex or bendamustine therefore patients were assumed to be treated until progression, or when the maximum number of treatment cycles was reached for these two treatments.

The ERG could not find TTD as a specified outcome in the MMY2002 clinical study report (CSR) or in GEN501 CSR. After a request for clarification, the company explained that TTD was not a pre-specified outcome in the MMY2002 or in the GEN501 trials and so the company carried out a *post-hoc* analysis of the patient level data available in the two trials to derive the clinical outcome measure.

The company assessed the goodness of fit of parametric curves to daratumumab TTD data by analysing AIC and BIC statistics. The log-logistic curve was considered by the company to have the best statistical fit and therefore was used in the economic model. The ERG has several concerns with the use and estimation of TTD data which are explored in Section 5.5.5.3.

5.4.3 Adverse events

Adverse event rates for daratumumab were estimated by calculating a weighted average of treatment-emergent adverse events (TEAEs) in the MMY2002 and GEN501 trials. The AE rates for pano+bort+dex are based on what seems to be TEAEs observed in the PANORAMA 2[(81)] while AEs for pom+dex have been estimated based on treatment-related adverse events (TRAEs) from the MM-003 trial[(82)]. The company reports that due to the lack of published data on AEs for bendamustine, these were assumed to be the same as those observed for pom+dex in MM-003. [(82)]. This assumption is reported to be in line with the views of the company's clinical experts.

Adverse events are considered in the model based on their severity, frequency and perceived importance according to the company's clinical experts. Due to their clinical experts' advice, the company included nausea, peripheral neuropathy, and upper respiratory tract infections regardless of severity (grade), if encountered in ≥ 1% of patients in any of the trials. The remaining AEs included in the analysis were based on all Grade 3/4 TEAEs observed in ≥5% of patients receiving treatment in the respective trials. The rates of AEs considered in the model are presented in Table 33. The costs of managing AEs are considered in the model as reported in Section 5.4.6. Utility decrements are applied to capture the impact of AEs on patients' quality of life as reported in Section 5.4.5 of the ERG report.

Table 33. Adverse event rates used in the economic model (adapted from CS, page 200-202, Table 59)

Adverse event	Daratumumab AE incidence rate, % MMY2002/GEN501, Jan 2015	Pano+bort+dex AE incidence rate, % PANORAMA 2	Bendamustine incidence rate, % Assumed to be equal to POM+DEX	Pom+dex AE incidence rate, % MM-003
Febrile neutropenia	0%	NR	9%	9%
Neutropenia	10%	15%	48%	48%
Anaemia	19%	15%	33%	33%
Thrombocytopenia	17%	64%	22%	22%
Lymphopenia	6%	NR	NR	NR
Leukopenia	2%	NR	9%	9%
Upper respiratory infection (all grades)	20%	NR	16%	16%
Pneumonia	6%	15%	14%	14%
Hypophosphatemia	NR	6%	NR	NR
Nausea (all grades)	6%	60%	15%	15%
Diarrhoea	NR	20%	NR	NR
Fatigue	2%	20%	5%	5%
Asthenia	NR	9%	NR	NR
Dyspnoea	0%	NR	5%	5%
Back pain	4%	NR	5%	5%
Peripheral neuropathy (all grades)	NR	14%*	23%	23%*
Flatulence	NR	5.50%	NR	NR
Abdominal Pain	NR	5.50%	NR	NR
Abdominal distention	NR	7.30%	NR	NR
Hypokalaemia	NR	7.27%	NR	NR
Dehydration	NR	5.45%	NR	NR
Hypotension	NR	9.09%	NR	NR
Septic Shock	NR	5.50%	NR	NR
Syncope	NR	9.10%	NR	NR
Sepsis	NR	9.09%	NR	NR

Abbreviations in table AE, adverse event; bort, bortezomib; dex, dexamethasone; pano, panobinostat; pom, pomalidomide. Notes:*These numbers were reported incorrectly in the CS as NR for pano+bort+dex, and 2% for pom+dex, and bendamustine-based therapy.

5.4.4 Mortality

In order to fit OS curves for daratumumab the company undertook an assessment of goodness of fit through analysis of AIC and BIC statistics together with judgment of clinical plausibility of the extrapolated curves. The company notes that given the lack of maturity for OS data (only 55% of OS KM data were complete by the time of the analysis), clinical expert validation of the tails of the survival curves is particularly important in this case.

Based on the AIC and BIC criteria reported (Table 34) and clinical plausibility of the curves, the company concluded that the best fitting model was the exponential. Initially the company did not report the Gompertz AIC and BIC statistics in their assessment of curve fit. Nonetheless the economic model reported these estimates which are also reported in Table 34.

Table 34. Goodness-of-fit statistics for daratumumab integrated OS data

	Exponential	Weibull	Log-normal	Log-logistic	Generalised Gamma	Gompertz*
AIC	361.69	363.33	363.78	363.67	364.89	647.68
BIC	364.32	369.32	369.77	369.66	373.89	653.67

AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.
*The company provided the AIC and BIC statistcis on a different scale for the Gompertz distribution. See Section 5.4.2.2 for more details.

The exponential model used by the company together with the integrated unadjusted OS KM data for daratumumab is shown in Figure 17. Figure 18 shows the fitted curves and the OS KM curve for a shorter time horizon (30 months). Visual inspection of Figure 18 shows that all curves, expect the Gompertz, provide a similar fit to the KM curve for the trial period. The company concluded that neither the lognormal nor the log-logistic curves gave clinically plausible long-term survival estimates as these predicted that around 10% of patients would still be alive at 10 years. The exponential curve gives a survival estimate of 2% at year 10, while the Gompertz and the Weibull show that 1% of patients are alive then. The Gamma curve predicts that 5% of patients are alive 10 years after treatment.

Figure 17. Parametric curves fit to OS data of the integrated MMY2002/GEN501 cohort (15 years time horizon)

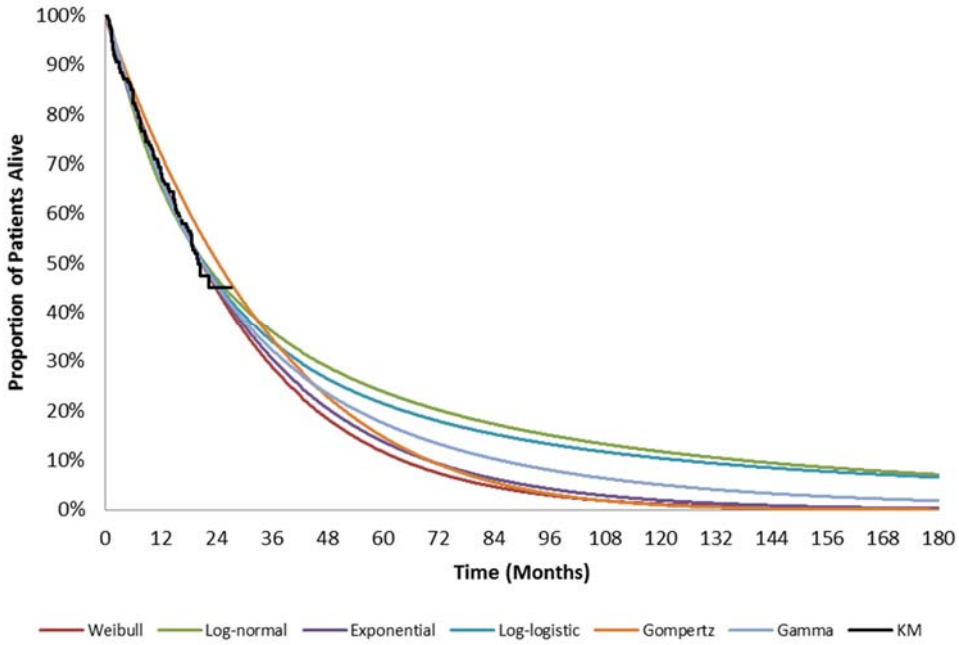
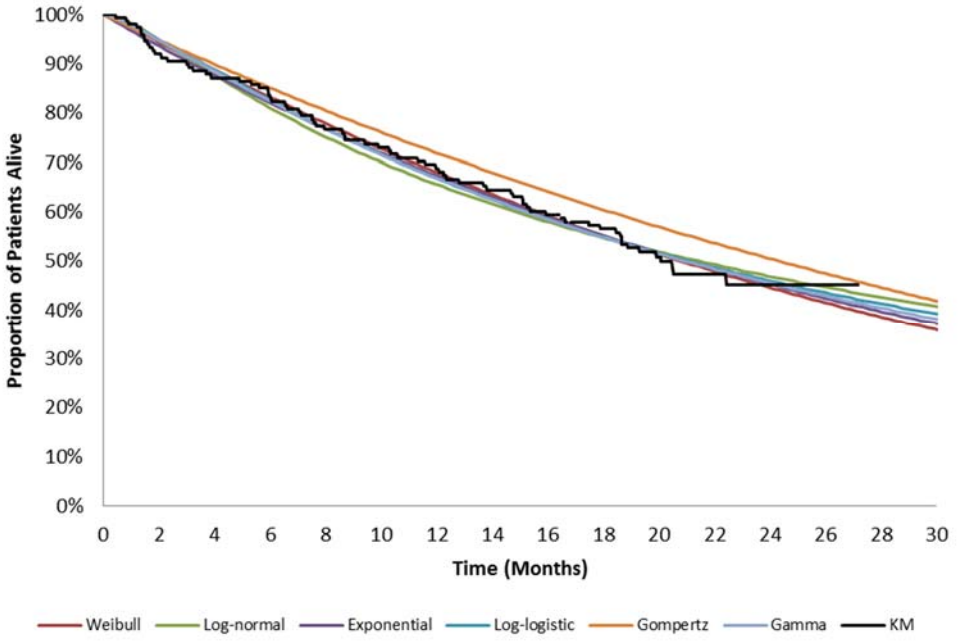


Figure 18. Parametric curves fit to OS data of the integrated MMY2002/ GEN501 cohort (30 months time horizon)



To estimate the OS curves for pom+dex and pano+bort+dex, the company applied the weighted HRs from the MAIC analysis (Section 4) to the unadjusted integrated daratumumab OS curve modelled with the exponential distribution. The weighted HRs used in the analysis are reported in Table 35. The weighted OS HR for pom+dex was derived through the MAIC when matching the top 11 characteristics

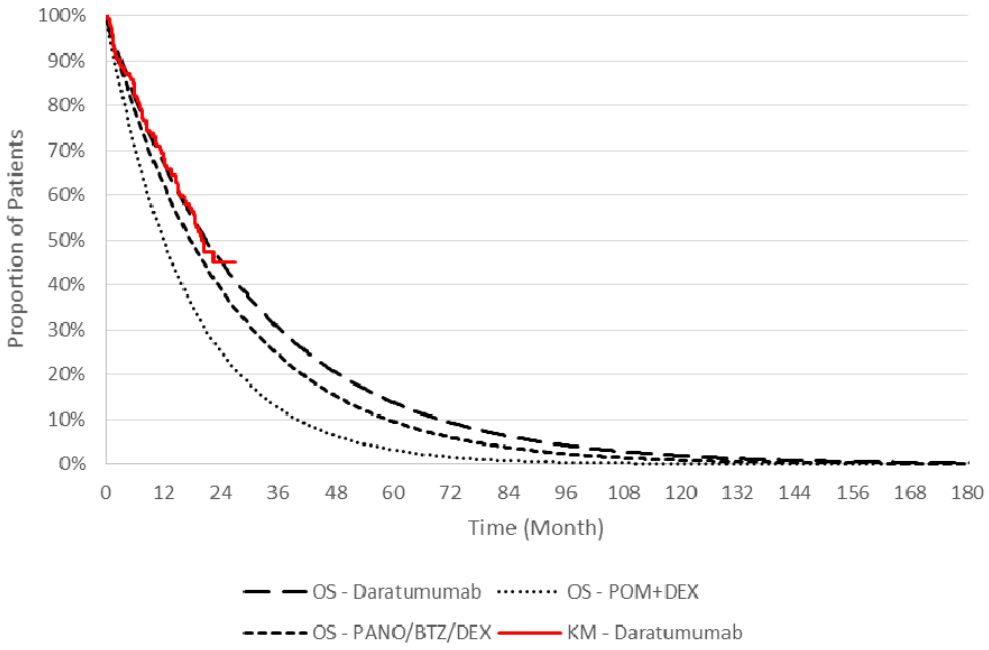
while the OS HR for pano+bort+dex was derived when matching the five top baseline characteristics across patients in the daratumumab trials and PANORAMA2. Figure 19 shows the OS curves for daratumumab, pom+dex and pano+bort+dex, together with the KM curve for the integrated daratumumab data.

The HRs reported in Table 35 show that OS is not statistically significantly different between daratumumab and pano+bort+dex, after adjusting for differences across trials. Figure 19 shows that the OS curve estimated for daratumumab is associated with a considerable survival benefit compared with pom+dex and to a smaller extent with pano+bort+dex.

Table 35. Overall survival HRs for pom+dex and pano+bort+dex

Daratumumab compared with	Weighted HR from MAIC	95% confidence interval	Number of characteristics matched
Pom+dex	1.742	(1.238; 2.457)	11
Pano+bort+dex	1.186	(0.733; 1.919)	5
Abbreviations in table: bort, bortezomib; dex, dexamethasone; HR, hazard ratio; MAIC, matched adjusted indirect comparison; pano, panobinostat; pom, pomalidomide.			

Figure 19. Overall survival curves for daratumumab, pom+dex and pano+bort+dex



The company included an option to fit OS curves independently in the model. Figure 20 and Figure 21 report the independently fitted curves for daratumumab vs pom+dex (in a longer and shorter time horizons) and for daratumumab vs pano+bort+dex, respectively. Figure 20 shows that daratumumab is associated with a higher OS when compared with pom+dex for the whole time period of the analysis, even though the KM curves seems to cross at around month 4. Similarly, Figure 21 shows that daratumumab is associated with a higher OS than pano+bort+dex for the entire analysis, even though

the KM curves cross at around month 4. The relative positioning of the OS is maintained from the dependent fit to the independent fit (i.e. there is a consistent OS benefit with daratumumab compared with the other treatments). The appropriateness of fitting treatment curves together or independently is also related with the assessment of the PH, PO and AFT assumptions. This issue is further explored in Section 5.5.5 of the ERG report.

It should also be noted that when fitting OS curves independently, the company also undertook an assessment of goodness of fit, reported in the Appendix 11 to the CS. Nonetheless the assessment was not complete, as the Gompertz distribution was left out of the assessment with no justification, as happened with the analysis of OS and PFS (dependent fit). The company concluded that the same curves used for the dependently fitted models were the best fit for the individual curves, having fitted an exponential function to the different OS curves. Visual inspection of the KM and the fitted curves in Figure 20 and Figure 21 suggest a considerable overestimation of daratumumab OS curve in the pom+dex comparison in the first six months and an underestimation of the OS curve for pano+bort+dex in the first four months.

Finally, it should be considered that the CS does not explicitly state how many characteristics are adjusted for in the MAIC-adjusted daratumumab curves for use in the independent fit approach. The ERG assumes that the same 11 characteristics were matched and adjusted for in relation to pom+dex, while the OS adjusted curve for daratumumab in comparison with pano+bort+dex would have been adjusted for the same five baseline characteristics across patients in the daratumumab trials and PANORAMA2 as for the dependent fit approach.

Figure 20. Indepedently fitted OS curves for daratumumab vs pom+dex

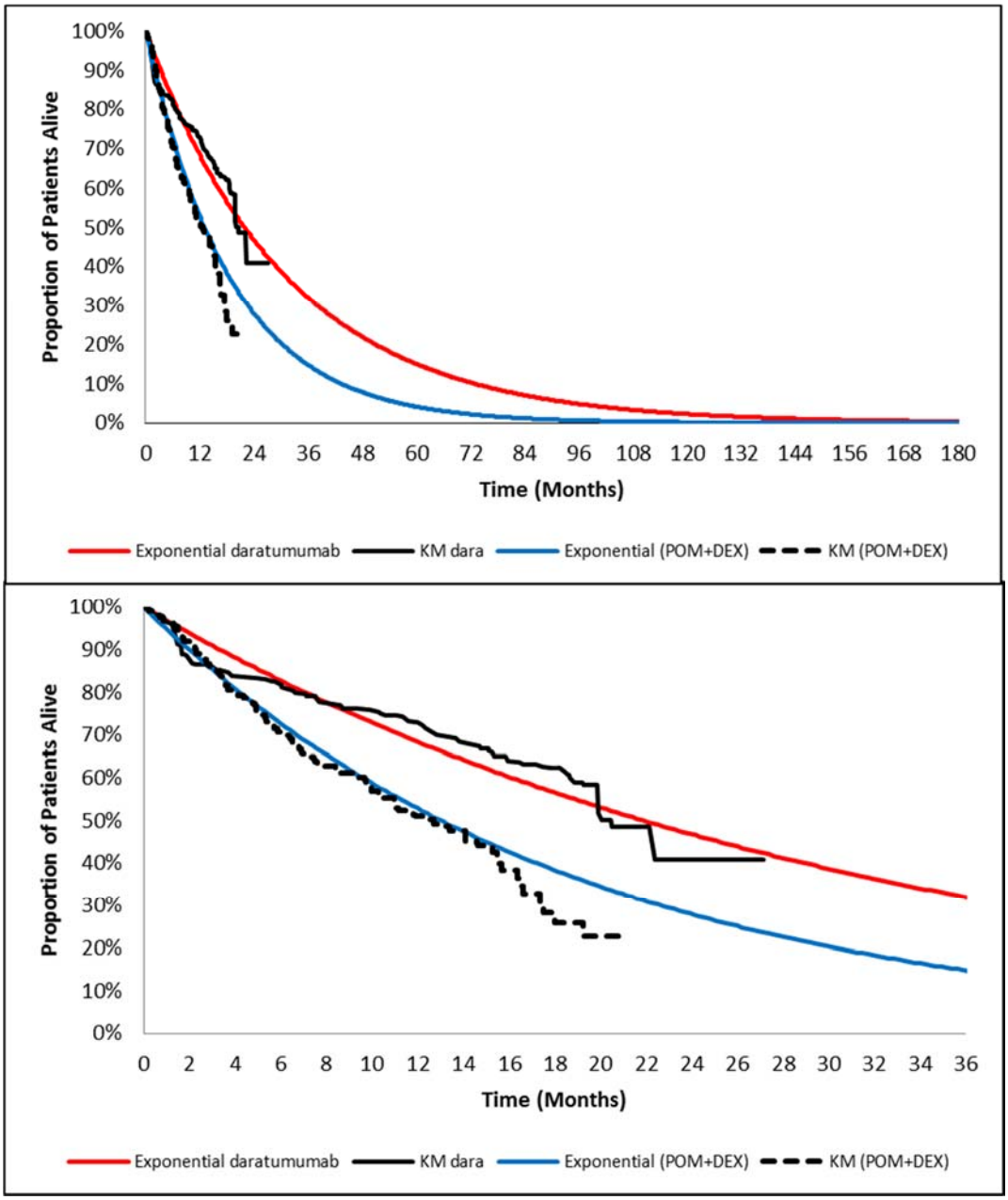
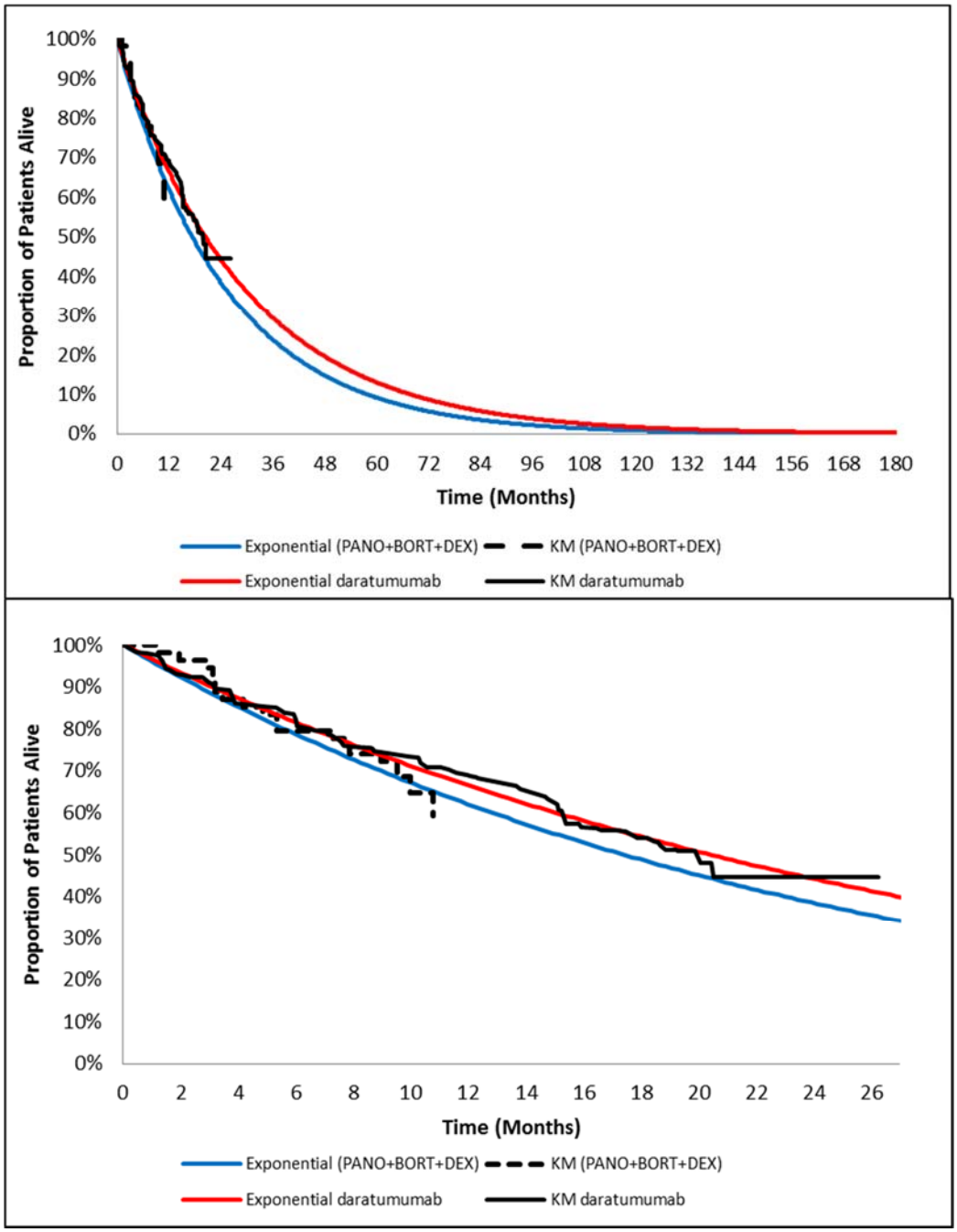


Figure 21. Indepedently fitted OS curves for daratumumab vs pano+bort+dex



5.4.4.1 Subsequent treatments received

The CS reports that daratumumab is associated with unprecedented survival benefit for responding or partially responding patients. It is also stated that due to daratumumab's immunomodulatory mode of action, a relatively short PFS compared with OS is not unexpected. The considerable difference between the large estimated survival benefit associated with daratumumab and the small (if any) gain in progression-free survival of daratumumab compared with the other treatments leads to the need of a

careful examination of the impact of subsequent treatments received on patients' survival. This issue is fully explored in Section 5.5.7.2.

5.4.5 Health-related quality of life

5.4.5.1 HRQoL systematic literature review

The company reports carrying out a systematic literature review to identify studies reporting the health-related quality of life (HRQoL) of patients with MM or rrMM. An overview of the search is presented in Section 5.4.3 of the CS and the search details are presented in and Appendix 12 of the CS. The searches were carried out in January 2016 and the following electronic databases were searched:

- MEDLINE and MEDLINE In-Process;
- EMBASE;
- HTA database;
- NHS EED;
- EconLit.

A total of 4,952 papers were identified through the searches, of which 722 publications were selected for full-text screening following abstract review. Out of those, 703 studies were excluded for the following reasons; "non-relevant study type" (n=163); "non-relevant publication type" (n=40); "non-relevant population" (n=57); "non-relevant outcomes" (n=423); "language" (n=12); "duplicate" (n=7); and "other" (n=1). A total of 19 studies were finally included and extracted. The inclusion and exclusion criteria applied in the search are presented in Table 36, and the included studies are summarised in Table 37.

The ERG considers the search strategy and terms used to be reasonable. The search was not limited by intervention, therefore making it more inclusive than the cost-effectiveness search strategy. The company refers to two technology appraisals, (TA338 and TA380) [94, 95]as sources identified for utility data. The company describes these two appraisals as, "key NICE submissions", but no detail was provided on the approach taken to identify and include NICE submissions and why other submissions were not considered relevant. As the cost-effectiveness search was limited by the intervention (daratumumab) and the ERG is unware of how the company searched for TA submissions, it is difficult to predict why some relevant data on QoL (identified through the SMC pomalidomide submission) were missed by the company.

Table 36. Inclusion and exclusion criteria for systematic search for HRQoL studies (CS, Appendix 12, Table 44)

Criteria	Inclusion	Exclusion
Study population	Adult patients with MM	No adult MM patients
Intervention	No restriction by treatment. Untreated patients included.	None
Outcome	Utility values produced using generic, preference-based measures of patient utility, disease-specific measures or vignettes Instrument responses should be elicited from patients Valuations of utilities should be based on general population preferences	Disease specific and non-preference-based measures not converted to utilities Proxy questionnaire responses
Study types	Quality of life studies Economic evaluations reporting patient utility values	None
Publication Types	None	Letters and comment articles.
Language	Studies reported in English	Studies not reported in English
Other	Studies must present sufficient detail of the methodology used and provide extractable results.	Publications that fail to present sufficient methodological detail or extractable results.

Abbreviations in table: MM, multiple myeloma; NHS, National Health Service; rrMM, relapsed/refractory multiple myeloma.

Table 37. Summary of HRQoL studies identified in systematic literature search (CS, Appendix 12, Table 38)

Reference	Study Type	Brief Description of Study	Population	Setting	Method of elicitation/ Instrument used	Utility Values reported
Delea et al. 2011[98]	Cost-effectiveness Study	Partitioned survival model to evaluate the cost-effectiveness of zol vs clo and zol vs pam in patients with newly-diagnosed MM	Newly diagnosed MM	Canada	EQ-5D	PFS at baseline = 0.485, PPS = 0.485. Mean EQ-5D at baseline was 0.49 (± 0.38) for zoledronic acid and 0.48 (± 0.37) for clodronate. From baseline to 3 months after initial randomisation, the mean utility value was 0.55 ± 0.30 in the zoledronic acid and clodronate group. At 3 months after maintenance randomisation, the mean utility value increased to 0.66 ± 0.26 in the zoledronic acid group and 0.67 ± 0.27 in the clodronate group.
Crott et al. 2013[99, 100]	Mapping Study	Assessed the external validity of mapping EORTC-QLQ-C30 to EQ-5D preferences	MM	NR	EORTC-QLQ-C30 mapped to EQ-5D	Mean EQ-5D utility = 0.68 SD = 0.26
Van Agthoven et al. 2004[101]	Economic evaluation	A prospective randomised Phase III study in patients 465 years old with previously untreated MM, intensive chemotherapy followed by myeloablative chemotherapy and autologous stem-cell rescue was compared with intensive chemotherapy alone. This economic evaluation was based on detailed data from patient charts and hospital information systems	Stage II/III MM	The Netherlands	EQ-5D	For patients who were not in remission, a correction factor was applied to the general population utility value (0.8) to give a utility value 0.644.
Fragoulakis et al. 2013[102]	Economic evaluation	DES model assessing cost-effectiveness of therapies for patients suffering from rrMM	rrMM	Greece	EQ5D	Non responders with PD = 0.64, all other response levels = 0.81
Gooding et al. 2011[14]	Economic evaluation	Cost-effectiveness evaluation of therapies in the DRMM setting	Double-relapse and/or refractory	NR	NR	Utility = 0.58 and assumed to remain constant through the patient's lifetime.

		involving non-clinical trial and real world MRU data from relevant patients	MM			
Uyl-De Groot et al. 2005[103]	Prospective longitudinal questionnaire study	Prospective longitudinal questionnaire study	MM undergoing transplantation	The Netherlands	EQ-5D	Mean baseline 0.52 (0.33) Baseline - Patients who preceded to 12 months follow-up = 0.60 (0.33) 12 months follow-up - Patients with baseline = 0.77 (0.13) 12 months follow-up - All patients = 0.79 (0.18)
Kharroubi at al. 2015[104]	Mapping study	Mapped EORTC-QLQ-C30 and EORTC-QLQ-MY20 to EQ5D utilities in patients with MM	MM	UK, New Zealand and South Africa	EORTC-QLQ-C30 and EORTC-QLQ-MY20 mapped to EQ5D	Mean EQ5D 0.52 (0.26–0.76)
Acaster et al. 2013[105]	Quality of life study	Assessed if (1) a treatment-free interval (TFI) is associated with a better HRQL vs other treatment phases and (2) the length of the TFI influences HRQL in patients with MM	MM	UK	EQ-5D	First-line treatment = 0.63 (0.26) First TFI = 0.72 (0.26) Second-line treatment = 0.67 (0.25) Later stage = 0.63 (0.29)
Rowen et al. 2012[106]	Mapping study	Examined how different methods of eliciting health states and utility values compare, and thus aimed to inform researchers and policymakers in their choice of the source of utility values and the interpretation of these values regarding discrimination across severity groups, responsiveness, and agreement	Newly Diagnosed MM	UK	EQ5D	EQ-5D by Karnofsky Performance Scale: 50-60;0.171±0.363, 60-70;0.320±0.344, 70-80; 0.481±0.303, 80-90; 0.618±0.251, 90-100; 0.724±0.217, 100; 0.810±0.179 McKenzie and van der Pol–mapped EQ-5D estimates by Karnofsky Performance Scale: 50-60; .235±0.249 60-70; 0.392±0.235, 70-80; 0.487±0.238, 80-90; 0.581±0.230, 90-100; 0.693±0.223, 100; 0.791±0.192 Kontodimopoulos et al.–mapped EQ-5D estimates by Karnofsky Performance Scale:50-60; 0.286±0.239, 60-70; 0.448±0.237, 70-80; 0.571±0.227, 80-90; 0.672±0.209, 90-100; 0.792±0.211, 100; 0.879±0.195 Crott and Briggs–mapped EQ-5D estimates by Karnofsky Performance

						Scale:50-60; 0.390±0.209, 60-70; 0.563±0.219, 70-80; 0.670±0.199, 80-90; 0.748±0.172, 90-100:0.811±0.141, 100; 0.857±0.116 EQ5-D values by Overall quality of life (EORTC QLQ-C30 item) 1-2,2-3, 3-4,4-5, 5-6, 6, 7: −0.025± 0.309, 0.197±0.340, 0.437±0.294, 0.608±0.230, 0.705±0.210, 0.813±0.176, 0.885±0.184, respectively McKenzie and van der Pol–mapped EQ-5D estimates by Overall quality of life (EORTC QLQ-C30 item) 1-2,2-3, 3-4,4-5, 5-6, 6, 7: 0.061±0.191, 0.239±0.218, 0.397±0.197, 0.561±0.186, 0.692±0.174, 0.841±0.142, 0.930±0.135, respectively Kontodimopoulos et al.–mapped EQ-5D estimates by Overall quality of life (EORTC QLQ-C30 item) 1-2,2-3, 3-4,4-5, 5-6, 6, 7: 0.079±0.162, 0.271±0.172, 0.455±0.149, 0.638±0.136, 0.793±0.130, 0.960±0.114, 1.080±0.126, respectively Crott and Briggs–mapped EQ-5D estimates by Overall quality of life (EORTC QLQ-C30 item) 1-2,2-3, 3-4,4-5, 5-6, 6, 7: 0.315±0.227, 0.488±0.225, 0.635±0.202, 0.751±0.158, 0.807±0.131, 0.856±0.100, 0.870±0.095, respectively
Quinn et al. 2015[107]	Mapping study	Patient-level EORTC QLQ-C30 and EORTC QLQ-MY20 data were collected in a clinical trial of RRMM patients and mapped to EQ-5D scores using published algorithms	rrMM	NR	EORTC QLQ-C30 and EORTC QLQ-MY20	Overall mean estimate of PFD= 0.733 PFD with response= 0.744 PFD with no response= 0.704 Grade 3 adverse events suggested a difference in HSUV of -0.029
Proskorovsky et al. 2014[108]	Mapping study	Mapped EORTC-QLQ-C30 and EORTC-QLQ-MY20 to EQ-5D utilities in patients with MM	MM	UK and Germany	EORTC-QLQ-C30 and EORTC-QLQ-MY20 mapped	Subgroups: Asymptomatic: 0.923 Mildly symptomatic: 0.806 Moderately symptomatic: 0.675

					to EQ-5D	Severely symptomatic: 0.501
Naik et al. 2014[109]	Quality of life study	Assessed utility in a range of cancers, including MM (abstract only)	Myeloma	Canada	EQ-5D	Patients with PRO-ECOG scores of 0, 1, 2 and 3 had HSUVs of 0.90±0.14, 0.77±0.11, 0.65±0.14 and 0.59±0.19, respectively (p<0.0001) In patients with solid tumours, those with local disease had HSUVs of 0.82±0.15; metastatic disease, 0.80±0.15; p=0.015
Delforge et al. 2015[110]	Quality of life	Assessed the HRQL of newly diagnosed MM patients from FIRST III trial	Newly diagnosed MM or transplant ineligible	18 countries in Europe, North America and Asia-Pacific region	EQ-5D, EORTC QLQ-C30 and EORTC QLQ-MY20	Time: [Len/dex mean (SD) Baseline: 0.5 (0.36) Month 1: 0.6 (0.34) Month 3: 0.7 (0.27) Month 6: 0.7 (0.25) Month 12: 0.7 (0.23) Month 18: 0.7 (0.24)
Cella et al. 2015[111]	Quality of life	Preliminary report of the impact on quality of life of multiple myeloma in the preamble trial	rrMM	NR	EQ-5D	Lines of previous treatment: 1: 0.69; 2: 0.69; >2: 0.76; 3: 0.76; >3: 0.76
Ashaye et al. 2015[112]	Mapping	A review of the algorithms available for mapping EORTC-QLQ-C30 to EQ-5D and application of those mappings to the results of the ASPIRE trial	Relapsed MM	NR	EORTC-QLQ-C30 mapped to EQ5D	Mapped to EQ-5D using algorithm by Versteegh 2010: 0.59 (0.27) Mapped to EQ-5D using algorithm by Proskorovsky 2014: 0.71 (0.20)
Ashaye et al. 2015[113]	Quality of life	Estimated EORTC-8D values from EORTC-QLQ-C30 in a randomised open label phase III trial	rrMM	NR	EORTC-QLQ-C30 mapped to EORTC-8D	Baseline = 0.7851 (0.1266) carf+ len + dex = 0.7816 len + dex = 0.7816
Moller et al. 2011[114]	Cost-effectiveness study	Cost-effectiveness study to estimate the cost per QALY of len+dex compared to BORT for patients with rrMM in Norway	rrMM	Norway	EQ5D	Progressive disease = 0.64 Responding patients = 0.81
Usmani et al. 2016[115]	Cost-effectiveness study	Cost-effectiveness study to estimate the cost per QALY of len+ dex compared to bort, for newly diagnosed or transplant ineligible patients in the US	Newly diagnosed MM, or transplant ineligible	US	EQ5D and EORTC-QLQ-C30	Baseline =0.53 Maximum Pre-progression utility = 0.67 for RD, 0.59 for VMP PD = 0.59
Palumbo et	Quality of Life	Estimated utility in RRMM	rrMM	UK	EQ5D and	EQ-5D

al. 2013[116]		patients receiving either pom+LoDex or HiDex by progression status and by treatment and time.			EORTC-QLQ-C30	Pre-progression; Mean 0.61 SD: 0.31 Post-progression; Mean 0.57 SD: 0.30 EORTC-8D Pre-progression; Mean 0.74 SD: 0.13 Post-progression; Mean 0.69 SD: 0.14 EQ5D Baseline Mean 0.59 SD: 0.33 EORTC-8D Baseline Mean 0.74 SD: 0.15 EQ-5D 12 weeks pom+LoDEX; Mean 0.66 SD: 0.24 HiDex; Mean 0.59 SD: 0.31 EORTC-8D 12 weeks pom+LoDEX; Mean 0.75 SD: 0.12 HiDex; Mean 0.74 SD: 0.11
Abbreviations in table: bort, bortezomib; carf, carfilzomib; clo, clodronate; DES, discrete event simulation; dex, Dexamethasone; DRMM, double relapsed and/or refractory multiple myeloma; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQoL 5-Dimension; HRQL, health-related quality of life; HSUV, health state utility values; len, lenalidomide; MM, multiple myeloma; MRU, medical resource utilisation; NR, not reported; QALY, quality-adjusted life year; PD, progressive disease; PFD, progression-free disease; PFS, progression-free survival; PPS, post-progression survival; rrMM, relapsed and refractory multiple myeloma; SD, standard deviation; TFI, treatment-free interval; VMP, bortezomib, melphalan, prednisone; zol, zoledronic acid.						

5.4.5.2 HRQoL in the cost-effectiveness analysis

The company assumes that patients' quality of life varies according to progression status and whether or not patients experience adverse reactions to the different treatments received. The health state utility values (HSUVs) used in the base case analysis are taken from a paper by Palumbo *et al.* which analyses EQ-5D data collected in the MM-003 trial. The study looks at a total of 445 patients with rrMM enrolled in the MM-003 trial and respective EQ-5D data collected at baseline and after 12 weeks of treatment. The patients completed 1,406 EQ-5D questionnaires, 89% of which were complete prior to progression. The EQ-5D data were valued using the UK general population time trade-off values, which resulted in the HSUVs reported in Table 38. Patients experience a utility of 0.61 before progressing, which decreases by 0.04 to 0.57 once they progress. [117]

Table 38. HSUVs used in the model (CS, pages 203-204, Table 60)

State	Utility value	95% confidence interval	Source
Pre-progressive disease	0.61	(0.59; 0.63)	Palumbo 2013[117, 118][5]
Progressive disease	0.57	(0.55; 0.59)	

The utility decrements attributed to AEs in the model are based on published estimates and the company's clinical experts' input, as summarised in Table 39. The highest decrements are associated with febrile neutropenia, anaemia and thrombocytopenia. The final adjusted disutility value used in the economic analysis is estimated based on the AE specific utility decrement, the proportions of patients experiencing the event in each treatment arm and the duration of the AE episode. In cases where the duration of the AE on patients' QoL was not reported in literature, the duration of the AE was assumed to be 28 days. The utility decrement is applied in the first model cycle.

Table 39. Utility decrements associated with adverse reactions (CS, page 203-204, Table 60)

Adverse event	Utility decrement	Duration (Days)	QALY decrement	95% confidence interval	Source
Febrile neutropenia	-0.39	28	-0.03	-0.24, -0.55	Launois 1996
Neutropenia	-0.15	28	-0.01	-0.09, 0.21	Brown 2013[119]/Partial Review TA171[71]
Anaemia	-0.31	180	-0.02	-0.20, 0.44	Brown 2013[119]/Partial Review TA171[71]
Thrombocytopenia	-0.31	28	-0.02	-0.20, 0.44	Brown 2013[119]/Partial Review TA171[71]
Lymphopenia	-0.07	28	0.00	-0.04, -0.09	Assume lowest in range (Partial Review TA171)[71]
Leukopenia	-0.07	28	0.00	-0.04, -0.09	Assume lowest in range (Partial Review TA171)[71]
Upper respiratory infection (all grades)	-0.19	7	-0.01	-0.12, -0.27	Assume the same as pneumonia

Pneumonia	-0.19	7	-0.01	-0.12, -0.27	Brown 2013[119]/Partial Review TA171[71]
Hypophosphatemia	-0.07	28	0.00	-0.04, -0.09	Partial Review TA171[71]
Nausea (all grades)	-0.10	28	-0.01	-0.07, -0.15	Lloyd 2006[120]
Diarrhoea	-0.10	28	-0.01	-0.07, -0.15	Lloyd 2006[120]
Fatigue	-0.12	28	-0.01	-0.07, -0.16	Lloyd 2006[120]
Asthenia	-0.12	28	-0.01	-0.07, -0.16	Assumed the same as fatigue
Dyspnoea	-0.12	28	-0.01	-0.07, -0.16	Assume the same as fatigue
Back pain	-0.07	28	0.00	-0.04, -0.09	Assumed the same as peripheral neuropathy
Peripheral neuropathy (all grades)	-0.10	28	-0.01*	NR	Clinical Opinion
Flatulence	0.00	28	0.00	0,0	Assumed
Abdominal Pain	-0.05	28	0.00	-0.03, -0.07	Sullivan et al. 2011[121]
Abdominal distention	-0.05	28	0.00	-0.03, -0.07	Sullivan et al. 2011[121]
Hypokalaemia	-0.20	0.02	0.00		Clinical Opinion
Dehydration	0.00	28	0.00	0,0	Assumed
Hypotension	-0.07	0.01	0.00		Clinical Opinion
Septic Shock	-0.20	28	-0.01*	-0.12, -0.28	Tolley et al. 2013[122]
Syncope	-0.10	28	-0.01*		Clinical Opinion
Sepsis	-0.20	28	-0.01*	-0.12, -0.28	Tolley et al. 2013[122]

Abbreviations in table: AE, adverse event; QALY, quality-adjusted life year.
*These values were incorrectly applied initially as positive values in the model, and were corrected by the company at clarification stage.

5.4.6 Resources and costs

5.4.6.1 Systematic literature review for resource use

The company reports carrying out a systematic literature search to identify evidence on resource use for the management of patients with rrMM or MM in the NHS in England. An overview of the search, and the search details are presented in section 5.5.1 and Appendix 13 of the CS, respectively. The searches were carried out in January 2016, and the following electronic databases were searched:

- MEDLINE and MEDLINE In-Process;
- EMBASE;
- HTA database;
- NHS EED;
- EconLit.

A total of 801 papers were identified through the searches, out of which 73 publications were selected for full-text screening following abstract review. Out of those, 67 studies were excluded for the following reasons; "non-relevant study type" (n=32); "non-relevant publication type" (n=18); "non-relevant population" (n=6); and "non-relevant outcomes" (n=4). Six studies were finally included and extracted. The inclusion and exclusion criteria applied in the search are presented in Table 40, and the included studies are summarised in Table 41.

The ERG considers the search strategy and terms used to be reasonable. The search was not limited by intervention, and included untreated patients. The company refers to two technology appraisals, (TA338 and TA380) [94, 95]as sources identified for costs data but does not mention the criteria used to search and include relevant technology appraisals

Table 40. Inclusion and exclusion criteria for systematic search of resource use and costs (CS, Appendix 13, Table 44)

Criteria	Inclusion	Exclusion
Study population	Adult patients with MM	No adult MM patients
Intervention	No restriction by treatment. Untreated patients included.	None
Outcome	Any outcomes quantifying the costs and/or resource use requirements of advanced melanoma and its management. Any outcomes quantifying the costs and/or resource use associated with disease or treatment related adverse events. Costs should be reported as incurred by the NHS in the UK.	None
Study types	Cost and/or resource use studies and economic evaluations.	None
Publication Types	None	Letters and comment articles.
Language	Studies reported in English	Studies not reported in English
Other	Studies must present sufficient detail of the methodology used and provide extractable results.	Publications that fail to present sufficient methodological detail or extractable results.

Abbreviations in table: MM, multiple myeloma; NHS, National Health Service; rrMM, relapsed/refractory multiple myeloma.

Table 41. Included resource use and costs studies (CS, Appendix 13, Table 45)

Reference	Study type	Brief description of study	Population	Setting	Methods used	Costs	Resource use
Janssen Cilag, 2006	Manufacturer submission for HTA	Manufacturer submission for the technology appraisal of bortezomib (Velcade) monotherapy.	Patients with MM at first relapse	UK	Interviews with 11 haematologists conducted to gather resource use information.	Treatment Costs Drug cost per patient: £19,060 Admin cost per patient per dose: £79.00 Total cost per patient: £21,035 Resource use costs Hospitalisation: £5,367 Outpatient visits: £4,722 Procedures: £2,821 Community care: £954 Laboratory tests: £925 Chemotherapy: £894 Hospice care: £611 Other drugs: £215 Anti-emetics: £188 Mean total costs £16,697 £348 per month, £443 per month when inflated to 2006 costs	Resource use per patient Outpatient clinic, hours: 82.40 Hospital ward, days: 19.72 Hospice, days: 1.85 Laboratory tests, tests: 93.37 Blood transfusion, units: 8.11 Skeletal survey, procedures: 3.9
Gooding et al., 2015[14]	Patient records study (Retrospective case series study)	Examined patient records to calculate the costs associated with double relapsed and/or refractory multiple myeloma (DRMM) treatment and medical resource utilisation (MRU) costs.	Double Refractory MM	UK	Resource use was taken from healthcare records. Costs were calculated using NHS reference costs 2012-2013. The costs and resources were combined using a micro-costing approach to give an MRU cost from the start of DRMM therapy to death or censoring.	Costs per patient per 28-day cycle 1st DRMM therapy Bortezomib based treatment: £4,022 Lenalidomide based treatment: £3,913 DT-PACE chemotherapy: £946 Bendamustine based: £1,332 No active treatment: £0 Average: £2,532 2nd DRMM therapy Bendamustine/Thalidomide/Dexamethasone: £853 Melphalan/Dexamethasone: £133 Thalidomide: £298	MRU occurrences during DRMM period (SD) Inpatient admissions Night as inpatient: 9.3 (7.9) Outpatient: 4.2 (4.1) Attendances Day therapy unit: 12.8 (9.7) Triage, not admitted: 0.4 (0.9) Invasive and radiological procedures

						Pomalidomide/Dexamethasone: £8,887 No 2nd DRMM treatment: £0 Average: £294 <u>3rd DRMM therapy</u> Bortezomib/cyclophosphamide/dexamethasone: £4,118 Bortezomib/Melphalan/Prednisone: £3,847 Bendamustine/Thalidomide/Dexamethasone: £1,983 No 3rd DRMM treatment: £0 Average: £361 <u>Cost per patient</u> <u>Inpatient admissions</u> Night as inpatient: £2,463 Outpatient: £630 <u>Attendances</u> Day therapy unit: £4,331 Triage, not admitted: £46 <u>Invasive and radiological procedures</u> CT scan: £42 MRI scan: £57 X-ray: £31 Maxillofacial: £21 Other: £172 <u>Supportive therapies</u> Bisphosphonate: £217 Radiotherapy: £1,237 <u>Transfusions</u> Red blood cells: £1,684 Platelets: £1,200 Full blood count: £65 <u>Blood tests</u> Biochemistry: £26 Immunology: £22	CT scan: 0.4 (0.8) MRI scan: 0.3 (0.6) X-ray: 1.1 (2.7) Maxillofacial: 0.1 (0.2) Other: 0.3 (0.5) <u>Supportive therapies</u> Bisphosphonate: 2.6 (2.5) Radiotherapy: 1.1 (3.6) <u>Transfusions</u> Red blood cells (units): 5.9 (6.0) Platelets (units): 2.3 (3.8) Full blood count: 21.6 (13.0) <u>Blood tests</u> Biochemistry: 20.6 (15.6) Immunology: 4.4 (2.9) Microbiology: 5.6 (7.0)

						Microbiology: £38 Total other MRU costs per patient: £12,281 Total drug costs other MRU costs per patient: £23,472	
Green et al., 2009[123]	Summary of ERG report	A summary of the ERG report for NICE TA129.	Population was based on patients with MM at first relapse	UK	NR	Cost of bortezomib per course £21,035 Cost of other care – bortezomib pre-progression £470 Cost of other care – pre and post progression £470 Cost of HDD per course £82	NR
Ross et al., 2004[124]	Systematic Review	Systematic review of bisphosphonate use as therapy in breast cancer and prostate cancer to stop or reduce metastasis to the bone and its resultant effects.	Multiple Myeloma	UK	Skeletal morbidity: Resource use from the model was calculated from the literature to give incidence rates per year. Resource use was not expressed in terms of days or units, but rather as events. These events were: vertebral fracture non-vertebral fracture hypercalcaemia Radiotherapy Hypercalcaemia: Assumptions were made from clinical practice and put in the model:	Hypercalcaemia regimens: Pamidronate 90mg: £155.80 Pamidronate 60mg: £109.60 Pamidronate 30mg: £54.53 Clodronate 1500mg: £68.90 Zoledronate 8mg: £390.00 Zoledronate 4mg: £195.00 Ibandronate 6mg: £261.24 Ibandronate 4mg: £174.16: Ibandronate 2mg £87.08 Skeletal morbidity: Vertebral fracture: £2017 Non-vertebral fracture: £2017 Hypercalcaemia: £3503 Radiotherapy: £708 <u>Bone pain costs, skeletal morbidity:</u> <u>[Cost per unit, cost per year]</u> <u>Year 1:</u> Oncology outpatient visit: £92, £368 Coproxamol (4 × 2 tablets): £0.1, £35 Tramadol (4 × 100g): £0.79, £289 Codanthramer (2 × 2 capsules): £1.71, £626	Patients receiving bisphosphonate treatment would spend 7 days in hospital/hospice. From the model; (per patient) [Resource use/event biphosphonate, Resource use/event no bisphosphonate, increment] Bisphosphonate therapy (months): 28.2, 0, 28.2 Non-vertebral fracture: 0.3, 0.58, –0.28 Vertebral fracture: 1.36, 2.1, –0.74 Hypercalcaemia: 0.67, 0.69, –0.02 Radio/Chemotherapy: 2.04, 2.62, –0.58 Total: 4.37, 5.99, –1.62

						Haloperidol (1.5 mg nocte): £0.04, £14 Total cost per year = £1331 Cost per month = £111 <u>Year 2:</u> Oncology outpatient visit: £92, £368 Palliative chemotherapy (day case): £232, £1392 Palliative nurse visit (1 hour): £67.1, £1745 GP clinic consultation 26 Monthly: £12, £et District nurse (0.5 hours): £28.6, £1487 Codanthramer (2 × 2 capsules): £1.71, £626 Haloperidol (1.5 mg nocte): £0.04, £14 Morphine (6 × 20 mg, tablets): £0.65, £236 Total cost per year = £6179 Cost per month = £515 <u>Year 3:</u> As for year 2: £6179 Palliative nurse visit (1 hour): £67.1, £1745 Palliative medicine outpatient visit: £96.34, £1156 Hospice day visit (including 1-hour physiotherapy): £84, £4368 Hospice stay (nights): £235, £3290 Occupational therapist (1 hour): £47.1, £47 Total cost per year = £6785 Cost per month = £1399 <u>Costs of pathological bone fracture in the community</u>	Pain reduction (months): 4.1, 0, 4.1

						[Cost per unit, units per month, cost per month] Home care - lower cost package: Oncology outpatient visit: £92, 1, £92 Palliative nurse visit (1 hour): £67.1, 4, £268 District nurse (1 hour): £56.1, 4, £224 Social services (1 hour/day for shopping/cleaning): £10.31, 36, £371 Social services (1 hour/day for personal care): £10.31, 36, £371 Total cost per month =: £1327 Home care - higher cost package: Palliative nurse visit (1 hour): £67.1, 4, £268 GP home visit (1/2 hour): £99.69, 4, £399 District nurse (1 hour - morning & twilight service): £57.2, 30, £1716 Social services (1 hour/day for shopping/cleaning): £10.31, 36, £371 Social services (3 hours/day for personal care): £10.31, 108, £1113 Occupational therapist (2 hours): £93.1, 0.17, £16 Wheelchair, unpowered: £54, 0.08, £5 Hoist: £235, 0.08, £20 Pressure-relieving mattress: £38.93, 0.08, £3 Commode (mobile): £40.36, 0.08, £3 Mattress variator: £127.97, 0.08, £11 Hospital bed (fixed height): £166.57, 0.08, £14 Total cost per month =: £3939 Results from MM Skeletal morbidity model:	

						[cost biphosphonate, cost no-bisphosphonate, increment] Bisphosphonate therapy (months): £6710, £0, £6710 Non-vertebral fracture: £567, £1100, £–533 Vertebral fracture: £2567, £3961, £–1394 Hypercalcaemia: £2209, £2263, £–55 Radio/Chemotherapy: £1352, £1738, £–386 Total: £6694, £9063, £–2368 Pain reduction (months): £–1946, £–, £–1946 Total cost (per patient): £11458, £9063, £2396	
Brown et al., 2013[119]	Cost-effectiveness Study	A simulation model to evaluate the cost effectiveness of a lenalidomide dexamethasone combination.	MM patients who have received one prior treatment.	UK	Costs were taken from NHS cost information. Medication costs, for treatments and AE management, were obtained from the British National Formulary V.60. The resources used in the management and treatment of rrMM were obtained via a structured questionnaire completed by 15 UK haematologists who specialised in the treatment of MM. A monthly cost was estimated post-progression for monitoring and palliative care.	Lenalidomide/dexamethasone cycle cost: £4,073 Dexamethasone cycle cost: £37 Monthly monitoring cost while on treatment: £43 Monthly monitoring cost while off treatment: £11 Monthly cost post-progression: £144 Costs of adverse events: Adverse event: [£Grade3/4] Neutropenia: £262/560 Thrombocytopenia: £136/623 Pneumonia: £1275/1289 Deep-vein thrombosis: £390/1195 Anaemia: £425/722 Peripheral neutropenia: £186/332 Diarrhoea: £1072/1783 Hypercalcaemia: £668/873 Constipation: £764/1632	NR

					All resource use was costed using the National Schedule of Reference Costs (2008–2009) and inflated using medical inflation to 2010. Future costs and outcomes were discounted at 3% for the model.		
Palumbo et al., 2009[116]	Clinical review, making treatment and management recommendations.	Lenalidomide in combination with dexamethasone for the treatment of relapsed or refractory multiple myeloma	rrMM	UK	NR	NR	Monitoring of full blood count and, in some cases, interruption of treatment or dose reductions (see Table 5 for dosing levels), is recommended (Table 6). Moreover, in some patients with neutropenia Additional treatment with granulocyte colony-stimulating factor is recommended. Some patients with anaemia may require treatment with erythropoiesis-stimulating agents.
Abbreviations in table: AE, adverse event; CT, computerised tomography; DRMM, double relapsed and refractory multiple myeloma; DT-PACE, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide; ERG, evidence review group; GP, general practitioner; HTA, health technology assessment; mg, milligrams; MM, multiple myeloma, MRI, magnetic resonance imaging; MRU, medical resource utilisation; NHS, National Health Service; NR, not reported, rrMM, refractory and relapsed multiple myeloma; RU, resource use; TA, Technology Appraisal.							

The costs considered in the economic model consist of pharmacological costs (treatment acquisition, administration and concomitant treatment costs), disease management costs, AEs costs, subsequent therapy costs and end of life costs. These are now described in turn.

5.4.6.2 Pharmacological costs

In order to estimate the mean number of vials of daratumumab, bortezomib, and bendamustine administered per patient in the model, the company used the method of moments which assumes a normal weight distribution for patients. The dosage used for daratumumab is weight-based while body surface area is used to calculate the number of vials of bortezomib and bendamustine used in the model. Mean patient weight is assumed to be 73.91 kg, which is the average weight of European patients across the MMY2002 and GEN501 trials. The Dubois formula[125] was used to estimate patients' mean body surface area (1.84m^2 in the model) based on the average weight of European patients across the trial (i.e. 73.91 kg) and the average height of patients from the whole dataset (i.e. pooled height data from the MMY2002 and GEN501 regardless of location). The dosage assumptions and specific treatment duration applied in the model are summarised in Table 42 while the treatment acquisition costs are summarised in Table 43. The company includes wastage (i.e. no vial sharing) for IV treatments in the base case analysis, and explores the impact of excluding it in a scenario analysis reported in Section 5.6.2. Treatment administration costs are included in the model for all treatment arms as summarised in Table 44. The first infusion of daratumumab and bendamustine are assumed to take longer and cost more than subsequent infusions, while for bortezomib the cost of infusion is assumed to be the same regardless of treatment cycle number. An administration cost is applied only for the first dose of orally administered drugs (i.e. pom+dex, panobinostat, and thalidomide).

The company searched for TTD trial data related with the intervention and comparator drugs in order to accurately estimate treatment duration in the model. Time to treatment discontinuation data for daratumumab and pom+dex were available and analysed as described in Section 5.4.2.3. However, no TTD data were identified for pano+bort+dex or for bendamustine so pano+bort+dex patients were assumed to be treated until progression, or when 16 cycles of treatment were reached, while those in the bendamustine arm receive treatment until progression.

Table 42. Treatment regimens and durations assumed in the model

Drug	Dose per administration	Administration method	Dosing cycle	Dosing schedule*	Treatment duration
Daratumumab	16mg/kg	Complex chemotherapy with prolonged infusion	28 days	Days 1, 8, 15 and 22 of each cycle in Cycles 1-2, then Days 1 and 15 of each cycle in Cycles 3-6, then Day 1 of each cycle for subsequent cycles	TTD data from pooled MMY2002 and GEN501
Pomalidomide	4mg	Oral	28 days	Days 1-21 of each cycle	TTD data from MM-003
Dexamethasone (with pom)	40mg	Oral	28 days	Days 1, 8, 15 and 22 of each cycle	TTD data from MM-003
Dexamethasone (with pano)	20mg	Oral	21 days	Days 1, 2, 4, 5, 8, 9, 11 and 12 for first 8 cycles, Days 1, 2, 8 and 9 for cycles 9 – 16	Maximum of 16 treatment cycles or until progression
Panobinostat	20mg	Oral	21 days	Days 1, 3, 5, 8, 10 and 12 for first 8 cycles, Days 1, 3, 5, 8, 10 and 12 for cycles 8 – 16	Maximum of 16 treatment cycles or until progression
Bortezomib (with pano)	1.3mg/m²	Injection	21 days	Days 1, 4, 8 and 11 for cycles 1 - 8. Days 1 and 8 for cycles 9-16.**	Maximum of 16 treatment cycles or until progression
Bendamustine (alone or with steroids)	150mg/m²	Complex chemotherapy	28 days	Bendamustine is administered as an IV treatment on days 1 and 2 of a 28-day cycle	Until progression
Bendamustine (with thal+dex)	60mg/m^2	Complex Chemotherapy	28 days	Bendamustine is administered as an IV treatment on days 1 and 8 of a 28-day cycle	Until Progression
Thalidomide (with benda)	50mg	Oral	28 days	Daily	Until Progression
Dexamethasone (with benda)	40mg	Oral	28 days	Days 1, 8, 15 and 22	Until Progression

Abbreviations in table: bort, bortezomib; dex, dexamethasone; EMA, European Medicines Agency; EPAR, European public assessment report; m, metre; mg, milligrams; pano, panobinostat; pom, pomalidomide; SmPC, summary of product characteristics; TTD, Time to treatment discontinuation.

Notes: *Dosing schedules are applied until disease progression or unacceptable toxicity unless stated otherwise. The dosing schedule for daratumumab reflects that in Study MMY2002 and draft EMA product label; the dosing schedule for pomalidomide plus dexamethasone reflects that in the EMA EPAR for pomalidomide.[126] The dosing schedule for pano + bort + dex reflects that in the EMA EPAR for panobinostat.[127] The dosing schedule for bendamustine and chemotherapy are consistent with the corresponding SmPCs.[128]

** There was a mistake in the dosage described for bortezomib (with pano) described in the CS. This is the correct dosage applied in the model.

Table 43. Treatment acquisition costs (CS, page 210, Table 63)

Drug	Formulation	Cost per vial/pack (at list price)	Vials/tabs per pack	Cost per mg	Cost per administration
Daratumumab	100mg	£360.00[129]	1	£3.60	£4,437.39
	400mg	£1,440.00[129]		£3.60	
Pomalidomide	4mg	£8,884.00[129]	21	£105.76	NA
Dexamethasone	2mg	£78.00[130]	100	£0.39	NA
Panobinostat	10mg	£3,492.00[129]	6	£58.20	NA
	15mg	£3,492.00[129]		£38.80	
	20mg	£4,656.00[129]		£38.80	
Bortezomib	3.5mg*	£762.38**[129]	1	£217.82	£762.38
Bendamustine	25mg	£347.26[129]	5	£2.78	£991.33 (150mg/m^2) £388.51 (60mg/m^2)
	100mg	£1,379.04[129]		£2.76	

Abbreviations in table: m, metre; mg, milligrams.
Notes: *Incorrectly reported in CS as 4mg; ** Incorrectly reported in the CS as £217.82.

Table 44. Treatment administration costs (CS, page 215, Table 65)

Regimen	Type of administration	Doses applied	Cost	NHS Reference Costs 2014-15 Code[131]
Daratumumab	First complex infusion	1st dose only	£414	SB14Z Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance
	Subsequent complex infusions	All subsequent doses	£362	SB15Z Deliver subsequent elements of a chemotherapy cycle
Pom+dex	Oral drug initiation	1st dose only	£192	SB11Z Deliver Exclusively Oral Chemotherapy
Panobinostat	Oral drug initiation	1st dose only	£192	SB11Z Deliver Exclusively Oral Chemotherapy
Bortezomib	Injection	Per dose	£257	SB12Z Deliver simple Parenteral Chemotherapy at first attendance
Bendamustine	First complex infusion	1st dose only	£329*	SB13Z Deliver more complex Parenteral Chemotherapy at first attendance*

	Subsequent infusions	All subsequent doses	£257*	SB12Z Deliver simple Parenteral Chemotherapy at first attendance*
Thalidomide	Oral	1st dose only	£192	SB11Z Deliver Exclusively Oral Chemotherapy
* Incorrectly reported in CS.				

All patients in the daratumumab, pom+dex and bendamustine arms of the model receive concomitant medications while receiving the specific active treatments. The dosage and unit costs of concomitant medications included in the model are presented in Table 45 and Table 46, respectively. Patients in the daratumumab arm of the model receive corticosteroids, antipyretics and antihistamines, while those in the pom+dex arm receive acetylsalicylic acid. Patients in the bendamustine arm also receive corticosteroids. The costs of concomitant medications are applied in each cycle of the model together with the costs of the active treatment.

Table 45. Dosage assumptions for concomitant medications included in the model (CS, page 214, Table 66)

Treatment	Co-medication	Dose per administration*	Cost per treatment administration[132]
Daratumumab	Corticosteroid (methylprednisolone IV)	60mg	£2.28
	Antipyretic (acetaminophen)	1000mg	£0.01
	Antihistamine (cetirizine hydrochloride)	10mg	£0.01
Pom+dex	Acetylsalicylic acid	325mg	£0.02
Bendamustine	Corticosteroid (methylprednisolone IV)	60mg	£2.28
Pano+bort+dex	None		

Abbreviations in table: bort, bortezomib; dex, dexamethasone; IV, intravenous; mg, milligrams; pano, panobinostat; pom, pomalidomide.

Table 46. Unit costs of concomitant medications (CS, page 214, Table 67)

Co-medication	Formulation	Cost per vial/pack*	Vials/tabs per pack	Cost per mg
Corticosteroid (methylprednisolone IV)	125mg	£4.75	1	£0.04
Antipyretic (acetaminophen)	500mg	£0.43	100	£0.00
Antihistamine (cetirizine hydrochloride)	10mg	£0.19	30	£0.00
Acetylsalicylic acid	75mg	£0.47	100	£0.00

Abbreviations in table: IV, intravenous.
Notes: *Latest Drugs and pharmaceutical electronic market information (eMIT) estimates [132].

In addition to concomitant medications, patients may also require treatments like granulocyte stimulating factor (GCSF), red blood cell and platelet transfusions while receiving active treatment. When available, trial data were used to inform the number of patients in the model receiving these treatments. The proportion of transfusions and GCSF treatments received by patients in the daratumumab arm of the model are taken from the pooled MMY2002 and GEN501 dataset, while for the pom+dex arm of the model these are based on the pom+dex arm of the MM-003 trial.[133] The company reports that data on concomitant treatments for the PANORAMA2 trial were not available, so 20% of patients in the pano+bort+dex arms of the model are assumed to receive concomitant treatments, based on the company's clinical experts' opinion.[134] The proportion of patients in the bendamustine

arm of the model receiving concomitant treatments is assumed to be the same as that for patients receiving daratumumab. This is reported to be in line with expert feedback received by the company. The costs associated with concomitant treatments are applied as one-off costs in the first cycle of the economic model and are summarised in Table 47.

Table 47. Summary of concomitant therapies included in the model (CS, page 215, Table 68)

Treatment	Concomitant treatment	Proportion of patients	Number per patient	Unit cost	One-off cost applied
Daratumumab	GCSF	8%	1.00	£52.70	£202.38
	RBC Transfusion	30%	3.00	£121.85[135]	
	Platelet Transfusion	10%	4.79	£196.96[135]	
Pom+dex	GCSF	43%[133]	1.00	£52.70	£390.30
	RBC Transfusion	49%[133]	3.00	£121.85[135]	
	Platelet Transfusion	20%[133]	4.79	£196.96[135]	
Pano+bort+dex	GCSF	20%[134]	1.00	£52.70	£272.17
	RBC Transfusion	20%[134]	3.00	£121.85[135]	
	Platelet Transfusion	20%[134]	4.79	£196.96[135]	
Bendamustine	GCSF	8%	1.00	£52.70	£202.38
	RBC Transfusion	30%	3.00	£121.85[135]	
	Platelet Transfusion	10%	4.79	£196.96[135]	

Abbreviations in table: bort, bortezomib; dex, dexamethasone; GCSF, granulocyte colony-stimulating factor; pom, pomalidomide; pano, panobinostat; RBC, red blood cell.

5.4.6.3 Disease management costs

Resource use associated with disease management in the model is based on estimates reported in the NICE technology appraisal (TA338) which assessed pomalidomide in the treatment of rrMM. Patients are assumed to have physician visits and blood tests (complete blood count and biochemistry) regardless of disease stage or treatment status. The frequency of visits and blood tests are assumed to increase after disease progression as reported in Table 48. The NHS Reference costs associated with disease management are summarised in Table 49.

Table 48. Resource use according to model health states (CS, page 216, Table 69)

Health state	Resource	Frequency per week	Source
PFS (on treatment)	Physician visit	0.23	NICE TA338[133]
	Complete blood count test	0.21	
	Biochemistry	0.19	
PFS (off treatment)	Physician visit	0.08	
	Complete blood count test	0.21	

	Biochemistry	0.19	
PPS, subsequent active treatment	Physician visit	0.08	
	Complete blood count test	0.39	
	Biochemistry	0.33	
PPS, BSC	Physician visit	0.08	
	Complete blood count test	0.39	
	Biochemistry	0.33	
Abbreviations in table: BSC, best supportive care; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; PPS; post-progression survival; TA, Technology Appraisal.			

Table 49: Disease management unit costs (CS, page 2016, Table 70)

Health resource	Cost	Source[131]
Physician visit	£162.02	National Schedule of Reference Costs - Year 2014-15 - NHS trusts and NHS foundation trusts – Chemotherapy (Total National Average Costs) Services Code 303: Clinical Haematology
Complete blood count test	£3.01	National Schedule of Reference Costs - Year 2014-15 - NHS trusts and NHS foundation trusts – Chemotherapy (Total National Average Costs) DAPS05: Haematology
Blood chemistry	£1.19	National Schedule of Reference Costs - Year 2014-15 - NHS trusts and NHS foundation trusts – Chemotherapy (Total National Average Costs) DAPS04: Clinical biochemistry
Abbreviations in table: NHS, National Health Service.		

5.4.6.4 Adverse events costs

The costs associated with the management of AEs are applied in the first cycle of the model as one-off costs. The estimated costs per episode are summarised in Table 50.

Table 50. Costs of managing adverse events (CS, page 217-218, Table 71)

Adverse event	Cost	NHS Reference Cost[131]
Febrile neutropenia	£6,697.31	PA45Z (NHS 2011/2012) Febrile Neutropenia with Malignancy
Neutropenia	£1,096.05	Weighted average of the codes: SA08G, SA08H, SA08J for Other Haematological or Splenic Disorders
Anaemia	£788.00	Weighted average of the codes: SA04G, SA04H, SA04I, SA04J, SA04K, SA04L for Iron Deficiency Anaemia
Thrombocytopenia	£617.55	Weighted average of the code: SA12G, SA12H, SA12J, SA12J, SA12K for Thrombocytopenia
Lymphopenia	£1,096.05	Weighted average of the codes: SA08G, SA08H, SA08J for Other Haematological or Splenic Disorders
Leukopenia	£1,096.05	Weighted average of the codes: SA08G, SA08H, SA08J for Other Haematological or Splenic Disorders
Upper respiratory infection (all grades)	£759.21	Weighted average of the codes: DZ19D, DZ19E, DZ19F, DZ19G for Other Respiratory Disorders
Pneumonia	£1,965.45	Weighted average of the codes: DZ11D, DZ11E, DZ11F, DZ11G, DZ11H, DZ11J for Lobar, Atypical or Viral

		Pneumonia and DZ23D, DZ23E, DZ23F, DZ23G for Bronchopneumonia
Hypophosphatemia	£1,249	Weighted average of the codes: KC05G, KC05H, KC05J, KC05K, KC05L, KC05M, KC05N for Fluid or Electrolyte Disorders, without Interventions
Diarrhoea	£1,165	Weighted average of the codes: FZ91J, FZ91K, FZ91L, FZ91M for Non-Malignant Gastrointestinal Tract Disorders without Interventions
Nausea (all grades)	£727.55	WA21Z: Other Procedures or Health Care Problems
Vomiting	£727.55	WA21Z: Other Procedures or Health Care Problems
Fatigue	£727.55	WA21Z: Other Procedures or Health Care Problems
Asthenia	£727.55	WA21Z: Other Procedures or Health Care Problems
Dyspnoea	£216.66	DZ46Z: Respiratory Muscle Strength Studies. Service code 258
Back pain	£863.18	Weighted average of the codes: HC32D, HC32E, HC32F for Low Back Pain
Peripheral neuropathy (all grades)	£643.85	AB10Z: Unspecified Pain Procedures
Flatulence	£0	Assumed
Abdominal Pain	£2,410	FZ90A: Abdominal Pain with intervention
Abdominal distention	£2,410	FZ90A: Abdominal Pain with intervention
Hypokalaemia	£1,249	Weighted average of the codes: KC05G, KC05H, KC05J, KC05K, KC05L, KC05M, KC05N for Fluid or Electrolyte Disorders, without Interventions
Dehydration	£0	Assumed
Hypotension	£1,096	Weighted average of the codes: SA08G, SA08H, SA08J for Other Haematological or Splenic Disorders
Septic Shock	£2,973	WH07D: Infections or Other Complications of Procedures, with Single Intervention, with CC
Syncope	£0	Assumed
Sepsis	£2,973	WH07D: Infections or Other Complications of Procedures, with Single Intervention, with CC
Abbreviations in table: CC, complications and comorbidity; NHS, National Health Service.		

5.4.6.5 Subsequent therapy costs

In order to reflect clinical practice, patients are assumed to receive further treatment lines once they progress in the economic model. The company reports to use data on subsequent therapies received in the GEN501 and MMY2002 trials combined with clinical expert opinion to model post-daratumumab treatments. The proportion of pom+dex patients receiving subsequent treatments in the model was reportedly taken from the MM-003 trial, while clinical expert opinion was used to derive the subsequent treatments received post-pano+bort+dex. It is assumed that the proportion of patients who go on to receive subsequent treatments in the pano+bort+dex and bendamustine arms of the model are the same.

In order to estimate the treatment duration for subsequent therapies in the model, the company reviewed the population cohort data collected by the Haematological Malignancy Research Network (HMRN)

for 2004-2013 which show that the average duration of fifth-line therapy in patients with rrMM is 94 days. Therefore, subsequent therapy costs are applied in the model for a total of 94 days. [136]The distribution of patients receiving subsequent therapies and associated costs are summarised in Table 51 and Table 52, respectively.

A one-off administration cost of £192 (NHS Reference Code, SB11Z Deliver Exclusively Oral Chemotherapy) is applied for dexamethasone, pomalidomide and cyclophosphamide at the beginning of therapy. The administration cost for the remaining subsequent therapies is assumed to be £257 per infusion (SB12Z Deliver simple Parenteral Chemotherapy at first attendance).[131]

The ERG identified an error in the model as the drug acquisition cost for subsequent treatments used by the company was based on the price per pack (and did not consider treatment duration, dose or number of cycles received). This is further explored in Section 5.5.9.

Table 51. Distribution of patients receiving subsequent treatments (CS, page 220, Table 72)

Subsequent treatment	Daratumumab	Pano+bort+dex	Bendamustine-based therapy	Pom+dex
Dexamethasone	44%	25%	25%	25%
Pomalidomide	0%	0%	0%	0%
Cyclophosphamide	24%	17%	17%	17%
Carfilzomib	0%	0%	0%	0%
Bortezomib	0%	15%	15%	15%
Melphalan	17%	0%	0%	0%
Etoposide	11%	0%	0%	0%
Bendamustine	0%	10%	10%	10%

Table 52. Subsequent therapy costs (CS, page 221, Table 73)

Subsequent treatment	Formulation	Dose per administration	Dose per week	Drug Cost per week	Admin cost per week	Source
Dexamethasone	2mg	40mg	3.00	£30.19[132]	£192	eMIT
Pomalidomide	4mg	4mg	5.25	£2,221.00[129]	£192	MIMS
Cyclophosphamide	500mg	450mg/m²	1.00	£8.10[132]	£192	eMIT
Carfilzomib	60mg	20mg/m²	1.50	£528.00[129]	£1,542	MIMS
Bortezomib	4mg	1mg/m²	1.33	£377.56[129]	£1,028	MIMS[c]
Melphalan	2mg	150mg/m²	0.67	£90.76[129]	£192	MIMS
Etoposide	100mg	100mg/m²	1.25	£15.19[129]	£1,285	MIMS[e]
Bendamustine	100 mg	100 mg/m²	0.50	£137.90[129]	£514	MIMS

Abbreviations in table: DoH, Department of Health; eMIT, electronic Market Information Tool; m, metre; mg, milligrammes; MIMS, Monthly Index of Medical Specialities; tabs, tablets.

5.4.6.6 End of life costs

Terminal care is assumed to be distributed across hospital services (20%), hospice services (40%) and home services (40%) in the model. These estimates and the costs associated with each setting were obtained from TA338. [133]The cost of end of life care is estimated to be £854 and is applied when patients enter the death state in the economic model.

5.4.7 Model validation

Upon a brief initial review of the company's model, the ERG identified implementation errors, related with the fact that the model cycles had been changed from daily to seven-day cycles before the company submitted the final analysis. Furthermore, several of the company's scenario analysis (whether using alternative data or methodologies) were also found not to work properly. The ERG was concerned that this reflected a poor level of internal quality assessment of the model by the company before the submission date and invited the company to amend the economic model at the clarification stage. As a result of this, the company provided the ERG with an updated model before the end of the clarification process. Upon the ERG's initial alert to the mistakes in the model, the company advised that since submission the model had undergone further consistency checks and had been reviewed by the vendor who had built the model; a different vendor and Janssen internally.

Despite this, the ERG identified further mistakes in the second model submitted by the company and so the company submitted a third model after the clarification stage, as a reply to the ERG's request for clarification related to new errors identified. After the submission of the third model, the ERG still found a considerable number of serious errors in the economic model (described throughout the report).

Furthermore, the references included in the original CS were incorrectly labelled or missing. Upon a request for revision of the references and respective sources by the ERG, the company submitted new references and an updated CS. The ERG still found mislabelled references after the company's attempt to correct these. This added to the burden of the ERG's review process and increased the likelihood of mistakes as the sources provided for the respective references were not always correct or available to the ERG.

The company also submitted new data (as a response to the ERG's request). The ERG encountered several errors and discrepancies in the data forwarded by the company to the ERG at the clarification stage. For example, all the overall survival Kaplan-Meier curves for subsequent treatments were labelled with the incorrect treatment (for instance, what the company reported as being the subsequent pomalidomide overall survival Kaplan-Meier curve, was actually the subsequent lenalidomide overall survival Kaplan-Meier curve, as the ERG discovered later).

As a consequence, the ERG lacks overall confidence in the Excel model and in the company analysis of data. The specificities of this STA allied with the submission of multiple model versions and the limited time available for the ERG review, make it very likely that some mistakes were not detected by the ERG. The key specificities of this STA are as follows:

- The absence of RCT evidence;
- The possible permutations for the data analysis (three datasets for daratumumab – MMY2002; GEN501 and integrated; two different trials for the two comparator; two subgroups of relevance related with subsequent therapies and pre-treatment received by patients; two possible modelling approaches – dependent or independent fit and finally the variation in the adjustment factors included in the MAIC).

Furthermore, the ERG had to make several data assumptions due to lack of clarity in the model and in the CS. The fact that ERG kept on finding mistakes in data handling and labelling increases the probability that some other similar mistakes were not identified. It is impossible to foresee the impact of such potentially unidentified mistakes. It is the ERG's opinion that the company's model and data analysis need further internal consistency checks and a thorough quality check before a robust ICER can be determined for daratumumab.

5.5 Critique of the company's economic evaluation

5.5.1 NICE reference case checklist

Table 53 and Table 54 summarise the ERG's quality assessment of the company's economic evaluation. Table 53 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE scope outlined in Section 3.[1] Table 54 summarises the ERG's appraisal of the quality of the company's *de novo* economic model using the Philips checklist [137]

Table 53. NICE reference checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by NICE	No. The ERG considers that the evidence put forward by the company is not appropriate to determine the cost effectiveness of daratumumab monotherapy alone. The impressive OS benefit associated with daratumumab works majorly through the OS benefit likely to be due to subsequent therapies. To determine the cost-effectiveness of daratumumab monotherapy alone, we would need to be able to disentangle further the estimate of OS for daratumumab alone vs daratumumab followed by other treatments. If we are to consider the cost-effectiveness of daratumumab treatment followed by other subsequent rrMM therapies, given the company claims that one of the main benefits of daratumumab is to allow more patients to move on to subsequent

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
		treatments, then the estimation of effectiveness for daratumumab needs adjusting for the impact of subsequent therapies received in the daratumumab trials which are not available in the UK.
Comparator(s)	Alternative therapies routinely used in the NHS	Yes. Clinical expert opinion provided to the ERG confirmed that bendamustine is not an appropriate comparator for daratumumab. Furthermore, bendamustine does not have a marketing authorisation in the UK for rrMM although it's currently funded through the CDF. Given this information, the ERG considers that bendamustine is not a relevant comparator for this submission. The ERG's clinical experts anticipate that daratumumab would be used before pano+bort+dex, considering the adverse safety profile of panobinostat. Clinical expert opinion was not in agreement when it came to decide between pom+dex and daratumumab as a first treatment, given that while pom+dex has the advantage of being an oral treatment, daratumumab seems to have a better safety profile. The ERG agrees with the choice of pom+dex and of pano+bort+dex as relevant comparators, although it emphasises the importance of pom+dex and the most likely relevant comparator for this submission.
Perspective costs	NHS and Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-utility analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Systematic review	The ERG disagrees with the company's approach of limiting the cost-effectiveness search to a specific intervention (daratumumab), as this led the company to exclude relevant sources of data. As the cost-effectiveness search was limited by intervention and the ERG is unware of how the company searched for TA submissions, it is difficult to predict why some relevant QoL data (identified by the ERG on the SMC pomalidomide submission) were missed by the company.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes, EQ-5D.
Benefit valuation	Time-trade off or standard gamble	Time trade-off.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes, UK general population values were used in the paper from which the HRQoL data was obtained.[117]
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals	Yes.

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
	receiving the health benefit	
Sensitivity analysis	Probabilistic sensitivity analysis	Unfortunately, the ERG had insufficient time to fully validate the PSA undertaken by the company.
Abbreviations used in the table: EQ-5D, EuroQoL 5-Dimension; HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; TA, technology appraisal.		

Table 54. Philip's checklist[137]

Dimension of quality	Comments
Structure	
S1: Statement of decision problem/objective	Clearly stated.
S2: Statement of scope/perspective	Clearly stated (UK NHS and PSS) and consistent with the scope.
S3: Rationale for structure	The model structure is consistent with previously used models in rrMM and has been validated by clinical experts.
S4: Structural assumptions	The chosen structure is appropriate.
S5: Strategies/ comparators	The company included all the comparators specified in the NICE scope: pano+bort+dex, pom+dex and bendamustine-based therapy. However, both the company and the ERG's clinical experts consider that bendamustine-based therapy is not an appropriate comparator since it is not currently licensed for use in the NHS in this patient population. [1]
S6: Model type	Appropriate but not clearly stated. The model was based on the area under the curve (AUC) approach however the company did not provide details on the approach taken.
S7: Time horizon	A life time horizon of 15 years is used in the base case analysis, by when less than 1% of patients in all treatment arms of the model are alive.
S8: Disease states/pathways	The health states included in the model are generally appropriate.
S9: Cycle length	The cycle length is appropriate. No half-cycle correction was applied due to the short length of cycles.
Data	
D1: Data identification	The ERG disagrees with the company's approach of limiting the cost-effectiveness search to a specific intervention (daratumumab), as this led the company to exclude relevant sources of data. As the cost-effectiveness search was limited by intervention and the ERG is unware of how the company searched for TA submissions, it is difficult to predict why some relevant QoL data (identified by the ERG on the SMC pomalidomide submission) were missed by the company.
D2: Pre-model data analysis	The ERG considers that the curve fitting exercise undertaken by the company lacks transparency and consistency. The ERG disagrees with the company's assessment of PH and therefore the company's modelling approach. To derive the survival curves for pom+dex and pano+bort+dex the weighted HRs derived from the MAIC were applied to the estimated daratumumab unadjusted survival curves derived from the integrated MMY2002/GEN501 data for OS and PFS. The ERG considers that the company's MAIC results should have adjusted for the maximum number of characteristics possible across trials (Section 4). The ERG theoretically preferred modelling approach is not allowed for in the company's model. This consists on the use the independently fitted

Dimension of quality	Comments
	curves, however using fully MAIC-adjusted daratumumab curves for OS and PFS compared with unadjusted pom+dex and pano+bort+dex curves. The ERG is also concerned with the estimation of TTD data in the model (Section 5.5.5.3),
D2a: Baseline data	The baseline characteristics were based on the characteristics of the integrated GEN501 and MMY2002 trials dataset.
D2b: Treatment effects	The ERG has serious concerns with the estimation of treatment effectiveness in the economic analysis. The ERG considers that the analysis undertaken by the company is not robust enough to ascertain the cost-effectiveness of daratumumab compared with pom+dex or with pano+bort+dex. The key issues identified by the ERG relate with uncertainty around the difference between OS and PFS outcomes for daratumumab (and the impact of subsequent treatments in OS), the lack of statistical significance for daratumumab OS and PFS estimates compared with pom+dex and pano+bort+dex and the lack of confidence in the company's internal process of model validation and quality assessment of the economic data.
D2c: Costs	The ERG's clinical experts disagree with the resource use estimated for disease management (i.e. health state costs). The company reports that to estimate costs associated with subsequent therapy, the proportions of patients who received subsequent treatments in trials were adjusted to reflect UK clinical practice. As a result, the company uses clinical expert opinion and assumes that 55% of patients receiving daratumumab and pano+bort+dex will receive subsequent therapies in clinical practice. To note is that 72% of patients across the GEN501/MMY2002 trials received subsequent treatments and that the company refers to this as one of the main advantages of daratumumab throughout the CS. Therefore, there is a deep discrepancy between the company's anticipated clinical benefit of daratumumab and the company's approach to estimating subsequent therapy costs.
D2d: Quality of life weights (utilities)	The ERG disagrees with the company's approach of applying utility decrements to adverse events experienced by patients. This is explored in Section 5.5.8.
D3: Data incorporation	The ERG identified various errors in the incorporation of data in the model, mainly for the implementation of scenario analysis.
Assessment of uncertainty	
D4a: Methodological	The company included options to explore methodological and structural uncertainty in the economic model. Nonetheless the ERG found mistakes in the implementation of some scenario analysis and the ERG theoretically preferred modelling approach is not allowed for in the company's model. This consists on the use the independently fitted curves, however using fully MAIC-adjusted daratumumab curves for OS and PFS compared with unadjusted pom+dex and pano+bort+dex curves.
D4b: Structural	
D4c: Heterogeneity	The ERG considers that heterogeneity across the daratumumab patients was not explored appropriately. Further analysis needs to be undertaken to understand the difference in the cost-effectiveness of daratumumab monotherapy for patients receiving subsequent therapy vs. patients not receiving any further treatment. The same is true for the subgroup of patients pre-treated with pomalidomide.
D4d: Parameter	Unfortunately, the ERG had insufficient time to fully validate the PSA undertaken by the company.
Consistency	
C1: Internal consistency	It is the ERG's opinion that the company's model and data analysis need further internal consistency checks and a thorough quality check before a robust ICER can be determined for daratumumab.
C2: External consistency	The company validates median and PFS and OS for daratumumab against the estimated median PFS and OS in the integrated analysis of the MMY2002 and the GEN501.

Dimension of quality	Comments
Abbreviations used in table: CS, company's submission; ERG, evidence review group; HRQoL, health-related quality of life; NHS, National Health System; NICE, National Institute for Health and Care Excellence; PSA, probabilistic sensitivity analysis; PSS, Personal Social Services; QALYs, quality-adjusted life years; TTD, time to treatment discontinuation.	

5.5.2 Modelling approach and model structure

The company developed a cohort-based partitioned survival model (presented in Figure 11, Section 5.4) which includes four health states: progression-free on treatment (PFT), progression-free off treatment (PFOT), progressed disease (PD) and death. The ERG is generally satisfied with the model structure and the patients' flow through the model. The progression-free (PF) state was disaggregated into PFT and PFOT to reflect the fact that patients can discontinue treatment before disease progression, which is in line with the ERG's clinical expert's opinion. Once patients progress they can receive further treatment lines in the model. After entering the PD state patients cannot enter remission. Patients who receive subsequent therapies are assumed to start treatment as soon as they enter the progression state. To illustrate this with an example, in the same model cycle (7 days) daratumumab patients can fail fourth-line treatment (with daratumumab) and move to a fifth-line treatment option. Clinical opinion sought be the ERG informed that after a patient stops treatment, a 4-weeks' time gap would be expected until new treatments are initiated. The ERG understands this is a modelling simplification of clinical reality. Nonetheless it means that there is no clear separation between second-line treatment outcomes and the beginning of the third-line treatment option and respective outcomes. This is particularly important in this case given the lack of RCT data and the fact that the OS observed for daratumumab is confounded by the OS benefit of subsequent treatments received by patients. While in theory this might also be true for the comparator treatments, the ERG considers this to be true to a smaller extent as explored in Section 5.5.7.2. For this reason, the ERG concludes that it would be extremely important to disentangle the fourth-line ICER of treatment with daratumumab and appropriate comparators, and the ICERs related with further treatment lines. The ERG acknowledges that while this wold be possible to model for daratumumab, as the company has all the necessary data, this would require additional data for the comparator drugs, which might not be publicly available.

The partitioned survival (or area under the curve [AUC]) approach employed by the company is appropriate, however, the company did not report sufficient details on the analysis undertaken. A life time horizon of 15 years is adopted in the model and time is discretised into weekly cycles with a half-cycle correction not applied. The ERG agrees that a half-cycle correction was not necessary given the short cycle duration.

5.5.3 Population

5.5.3.1 Comparison with the NICE final scope

The population considered by the company for this STA comprises people with rrMM who have previously been treated with a PI and an IMiD and who have demonstrated disease progression on the last therapy. The company adds that the anticipated positioning of daratumumab monotherapy is as an alternative treatment for people who have received three or more prior therapies.

The company undertook subgroup analysis to estimate the impact of excluding patients pre-treated with pomalidomide. This analysis is extremely relevant considering that one of the main comparators for daratumumab is pomalidomide and that patients were also subsequently treated with pomalidomide in the daratumumab trials. The company included this subgroup analysis without any description or explanation in the CS. Upon a request for clarification from the ERG, the company explained that the originally ran subgroup analysis, *"applied the HR from the MAIC, where patients who have been pre-treated with POM+DEX have been excluded, to the full daratumumab dataset."* The company also included an additional scenario in their post-clarification model explaining that, *"A further scenario is now available in the model where this HR is applied to a subset of the daratumumab data, where patients pre-treated with POM+DEX have been excluded".*

The ERG disagrees with the approach originally taken by the company of applying the subgroup MAIC-adjusted HR for pom-naïve patients to the overall daratumumab trial population. The second approach taken by the company is more appropriate from a methodological point of view (i.e. applying the pom-naïve HR to the pom-naïve daratumumab population baseline curves) albeit incorrectly applied in the model. The HRs used in this scenario analysis were the HRs for the GEN501 analysis and not the pom-naïve subgroup analysis. Not only were the HRs used the incorrect ones but also the curves used to extrapolate the PFS curves for the pom-naïve population were linked to the model choice used for OS curves. The ERG did not explore this issue further in the model (therefore did not look at curve fitting or corrected the HRs used) considering the uncertainty around the additional KM provided by the company on pom-naïve patients, which is now discussed.

As a reply to the ERG's request for clarification, the company submitted what was meant to be daratumumab adjusted and unadjusted OS, PFS and TTD KM data excluding pomalidomide pre-treated patients for the integrated data and for the MMY2002 and for the GEN501 trials separately. Nonetheless the ERG found inconstancies in the data provided which mean that these data cannot be guaranteed to reflect the pomalidomide naïve OS, PFS and TTD curves. The inconsistencies found by the ERG are linked to the number of patients at risk for each survival outcome which are summarised in Table 55. The ERG would have expected to see the same number of patients at risk for the OS and PFS integrated pom-naïve curves (the KM data sent through by the company show 66 patients at risk for OS and 148

patients for PFS) but also the ERG would expect to see the same numbers of patients at risk as the number of patients who were pom-naïve in the trials, instead of the overall trial population as the company data suggests.

Despite the fact that the pom-naïve population survival curves included the same number of patients as the entire trial population curves, the actual KM curves provided by the company were different from the entire trial population KM curves in the integrated dataset and in the individual trial datasets. This suggests that some sort of adjustment might have been carried by the company to the entire trial population KM curves. Without knowing what this adjustment was, or if these are the correct data for pom-naïve patients, the ERG cannot attest to the validity of the subgroup analysis the company carried for pom-naïve patients.

Table 55. Number of patients at risk in OS and PFS curves for the pom-naïve population

Population	Number of total patients	Number of patients at risk at the beginning of pom-naïve KM OS curves	Number of patients at risk at the beginning of pom-naïve KM PFS curves
MMY2002/GEN501 integrated population	148	n/a	n/a
MMY2002 population	106	n/a	n/a
GEN501 population	42	n/a	n/a
MMY2002/GEN501 integrated pom-naïve population	49	66	148
MMY2002 pom-naïve population	43	106	106
GEN501 pom-naïve population	6	42	42
Abbreviations in table: KM, Kaplan Meier; OS, overall survival; PFS, progression-free survival; pom, pomalidomide.			

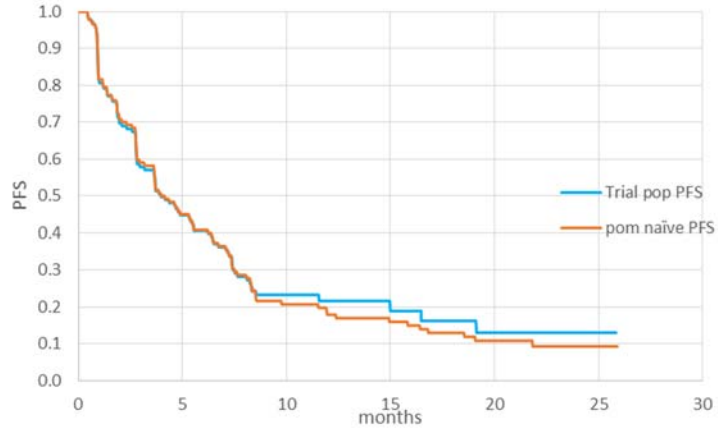
Nonetheless, and for inclusiveness purposes, the ERG notes that the HRs for the pom-naïve subgroup analysis ran by the company (reported in Table 56 below) show that daratumumab compared with pom+dex is less effective in the pom-naïve population than in the overall trial population (albeit not statistically significant for PFS). This is understandable in theory as one could anticipate that pre-treated pomalidomide patients will respond less well to retreatment with pomalidomide compared with a pom-naïve population. The ERG also presents the KM curves forward by the company in Figure 22. Even though the ERG cannot validate the data reported in the figure and table below, it is still worth noting that the data trends observed in the company's data suggest. That is, while there seems to be no difference for PFS across pom-naïve and non-pom-naïve patients, there is a considerable difference in OS between pom-naïve and non-pom-naïve patients, with OS being better for pom-naïve patients than for the overall trial population. The ERG interprets this trend in the data as a possible consequence of the effect of daratumumab as a subsequent therapy. It can be hypothesised that given that pre-treatment with pomalidomide does not seem to influence PFS, the considerable difference in the OS curves across

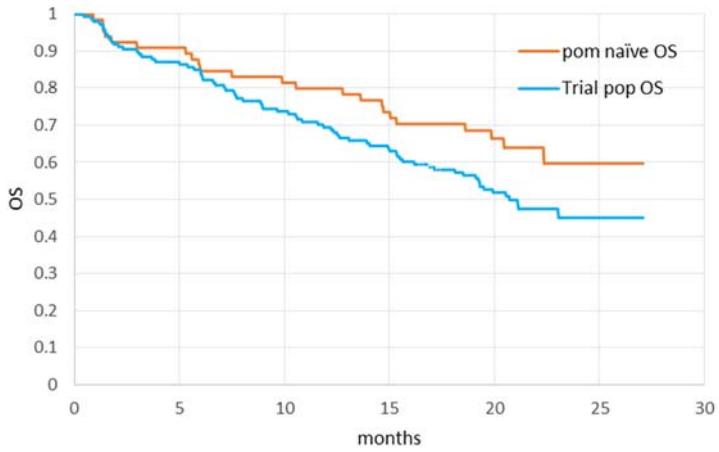
the pom-naïve and the overall trial population is due to the effect that pomalidomide would have as a subsequent treatment in the pom-naïve patients, compared to the effect that pomalidomide would have as a subsequent treatment in patients pre-treated with pomalidomide. Unfortunately, the ERG cannot validate this hypothesis given the uncertainty around the data and the fact that company did not provide the OS KM curve for patients subsequently treated with pomalidomide, despite the ERG's request for such data (Section 5.5.7.2).

Table 56. Pom-naïve MAIC-adjusted HRs for OS and PFS

Daratumumab compared with	Weighted HR from MAIC	95% confidence interval	Number of characteristics matched
Pom+dex OS pom-naïve	1.639	(1.242; 2.165)	11
Pom+dex PFS pom-naïve	1.139	(0.897; 1.447)	11
Pom+dex OS base case	1.742	(1.238; 2.457)	11
Pom+dex PFS base case	1.241	(0.920; 1.675)	11
MAIC, matched adjusted indirect comparisson			

Figure 22. PFS and OS curves for pom-naïve patients





5.5.4 Interventions and comparators

5.5.4.1 Comparison with the NICE final scope

Intervention

In their submission, the company presented the cost-effectiveness of daratumumab monotherapy. Considering that daratumumab is being positioned by the company as a fourth line treatment option, there would not be many options left as subsequent treatments for these patients currently available in the NHS.

Around 72% of the population in the MMY2002/GEN501 trials received further treatment for rrMM after daratumumab, more specifically carfilzomib (28%), lenalidomide (15%), bortezomib (24%) and pomalidomide (31%) among others. Out of these, only pomalidomide is NICE-approved as a potential treatment option for post-daratumumab treatment. As daratumumab patients received several non-NICE approved subsequent treatments which have been shown to be associated with a large improvement in the daratumumab OS estimate (see Section 5.5.7.2), the ERG considers that the true effectiveness of daratumumab monotherapy is greatly overestimated in the economic analysis. On this point, the company claims that one of the benefits of daratumumab is the fact that it allows more patients to move on to subsequent treatments given its advantageous safety profile. However, in direct contradiction to this, the company also considers that the 72% of patients receiving subsequent treatment after daratumumab in the MMY2002/GEN501 trials is an overestimation of clinical reality, bringing this estimate down to 55% in the economic model (this is the same as the proportion of patients receiving subsequent therapy after pano+bort+dex). Nonetheless, if in fact the OS benefit associated with daratumumab appropriately reflects the OS benefit associated with the subsequent treatments which daratumumab allows patients to receive, then the scope of the submission should consider daratumumab monotherapy followed by subsequent therapies as the intervention (instead of daratumumab monotherapy alone). This would also require further analysis of the subsequent treatments which are available for rrMM patients in the UK and not be reliant on treatments that are unavailable as subsequent treatments in the UK.

Comparators

The company considered pom+dex, pano+bort+dex and bendamustine as the relevant comparators for this submission. Clinical expert opinion provided to the ERG confirmed that bendamustine is not an appropriate comparator for daratumumab. Furthermore, bendamustine does not have a marketing authorisation in the UK for rrMM although it's currently funded through the CDF. Given this information, the ERG considers that bendamustine is not a relevant comparator.

The ERG's clinical experts also anticipate that daratumumab would be used before pano+bort+dex, considering the adverse safety profile of panobinostat. Clinical expert opinion was not in agreement when it came to decide between pom+dex and daratumumab as a potentially preferred initial treatment, given that while pom+dex has the advantage of being an oral treatment, daratumumab seems to have a better safety profile. The ERG agrees with the choice of pom+dex and of pano+bort+dex as relevant comparators, although it emphasises the importance of pom+dex as the most likely relevant comparator for this submission.

In conclusion, the ERG considers that the evidence put forward by the company is not robust enough to determine the cost-effectiveness of daratumumab monotherapy alone. To determine this, the estimate of OS for daratumumab alone would need to be estimated without being confounded by highly effective subsequent treatments. If the cost-effectiveness of daratumumab monotherapy followed by subsequent rrMM therapies were to be considered, then this has two implications. The first one is the recognition that the scope of the submission is not daratumumab monotherapy alone. The second, and more important one, is that the effectiveness of daratumumab needs adjusting for the impact of subsequent therapies which are not available in the UK. Finally, there is an important inconsistency in the company's proposed advantage of daratumumab. That is, it allows a higher proportion of patients to receive subsequent therapy. On one hand, the company claims that the novel mode of action of daratumumab increases the likelihood of patients benefiting from subsequent therapy pointing to the fact that, *"…of the 148 patients treated with daratumumab 16mg/kg monotherapy in the MMY2002/GEN501 cohort, 72% went on to receive subsequent therapy compared with 39% of the 302 patients randomised to POM+DEX in MM-003"*. On the other hand, the company also states that *"…clinical opinion suggested that…this figure* [72%] *is high compared to what is seen in clinical practice…* [and that] *the proportion of patients who receive subsequent therapy after daratumumab is 55%*". The company also assumed that the proportion for patients receiving subsequent therapy after pano+bort+dex is 55% in the model, making it equally likely for pano+bort+dex and daratumumab patients to receive subsequent therapy.

5.5.5 Treatment effectiveness

The ERG considers that the crucial issues for discussion regarding treatment effectiveness in the submission are related to the following:

1. The very high estimated survival benefit associated with daratumumab and the relatively short (or non-existent) progression-free survival benefit in the economic analysis;

2. The company's claim that daratumumab allows a higher proportion of patients to receive further active treatments (and retreatment with drugs previously received) when compared to other available rrMM treatments.

The ERG begins by reviewing the statistical approach taken by the company to estimate parametric survival models using OS, PFS and TTD data from MMY2002 and GEN501 with the focus on the two issues aforementioned. Discussion of PFS and TTD data is approached separately in Section 5.5.5.2 and Section 5.5.5.3 respectively. Overall survival data is discussed in Section 5.5.7.

5.5.5.1 Statistical approach

For the base case analysis the company decided to use the integrated patient-level data from MMY2002 and GEN501 (described in Section 4 of the ERG report). In order to extrapolate OS, PFS and TTD data into the model time horizon the company fitted a variety of parametric curves to the integrated data.

The ERG considers that the curve fitting exercise undertaken by the company lacks transparency and consistency. Even though the company reports to have followed guidance from the NICE Technical Support Document (TSD) 14, the CS did not mention Gompertz curves as an alternative modelling option.[97] Despite this, the option to model survival outcomes with a Gompertz distribution was partially included in the company's Excel model, with AIC and BIC statistics and curves provided for some clinical outcomes.

When enquired by the ERG, the company formally provided all the AIC and BIC statistics together with the fitted Gompertz curves for all survival outcomes, for all the modelling approaches (i.e. independent and dependant fit options). When asked to explain why the Gompertz distribution led to such high AIC and BIC statistics compared with a seemingly very good visual fit to the PFS curves, the company replied that, "*there is a discrepancy in the AIC/BIC statistics submitted, due to different SAS procedures being used to derive these estimates. The AIC/BIC statistics for the Gompertz distribution are on the original scale whereas; the AIC/BIC for other distributions tested are on the log scale."* The ERG cannot see a reason why the AIC and BIC statistics would have to be provided in a "different scale" from the AIC and BIC statistics for other distributions. Furthermore, this renders the assessment of goodness-of-fit for the Gompertz curve against the other parametric curves much more difficult, therefore removing transparency from the company's approach. Indeed, the company confirmed that the Gompertz distribution is the best fitting curve to PFS data, albeit not having been chosen due to their clinical expert validation.

To derive the survival curves for pom+dex and pano+bort+dex the weighted HRs derived from the MAIC were applied to the estimated daratumumab unadjusted survival curves derived from the integrated MMY2002/GEN501 data for OS and PFS. Taking the MAIC-adjusted HRs and applying these to the unadjusted daratumumab survival curves to derive the comparator's survival curves has two underlying implications. From a methodological point of view, it implies the existence of PH across the intervention and comparator's OS and PFS data. From a theoretical point of view, given that the MAIC approach adjusted the HRs using a specific group of patients with specific baseline prognostic

factors (11 prognostic factors in the pom+dex comparison and five prognostic factors for pano+bort+dex in the company's base case analysis), then applying these adjusted HRs to the unadjusted overall population implies that the relative difference in efficacy between daratumumab and its comparators is unaffected by baseline prognostic indicators and any unobserved treatment effect modifiers. These two issues are further discussed in turn below.

5.5.5.1.1 Proportional hazards assumption

Appendix 11 of the CS reports the tests undertaken for the validation of the PH assumption for OS data. Assessment of the PH assumption for PFS data were not initially reported by the company. There was no assessment of the PO or accelerated failure time AFT assumptions. Upon a clarification request by the ERG, the company submitted various plots to aid the assessment of PH for PFS and assessment of PO and AFT for PFS and OS. However, the company did not carry out the assessment itself (through an exercise of interpreting the plots) as requested by the ERG.

The OS plots put forward by the company are reported in Figure 23. The company's conclusion from the log-log plot (second plot from the left, first row) and from the Schoenfeld residuals is that PH holds for OS across daratumumab and pom+dex. The ERG interpretation of the plots suggests otherwise. The log-log plot indicates crossing curves which suggests that the PH assumption does not hold. Furthermore, the ERG was concerned with the face validity of the log (h(t)) vs time plot (which the company put forward as a test for the assessment of fit of the Gompertz distribution). The ERG decided to investigate this further and to fit the OS daratumumab and pom+dex data in *R* statistical package.

The ERG used the KM curves reported by the company in the economic model for the daratumumab adjusted to pom+dex integrated OS curves and for the unadjusted pom+dex curves from San Miguel *et al*, 2013.[82] Figure 24 shows the KM curves in the company's model referring to the daratumumab MAIC-adjusted curves to pom+dex and the KM curve for pom+dex. Figure 25 shows the same curves estimated by the ERG using the company's data and the numbers at risk provided in the pivotal trials through the Guyot *et al*. method.[138] This simulates the pseudo-individual patient-level data, using the algorithm in the *survHE R* package. The ERG notes that Figure 24 and Figure 25 are very similar. The ERG proceeded to run PH, PO and AFT tests in *R* statistical package. The ERG obtained a similar log-log plot to that obtained by the company. The ERG fitted a Cox proportional hazards model and performed the Grambsch and Therneau test for the proportionality of the hazards between the treatments via the *cox.zph* function in *R* statistical package. Even though the test results suggest proportionality of the hazards given that p-value>0.05 ($\rho = 0.18, \mathrm{X}_1^2 = 3.05, p = 0.081$), the scaled Schoenfeld residuals against time shown in Figure 27 do not show a straight line, suggesting the violation of the PH assumption.

Considering the evidence presented and the fact that the OS KM curves for daratumumab adjusted and pom+dex curves cross, the ERG concludes that the PH assumption is not fully satisfied for OS data and therefore a constant HR should not be used to model this outcome. During the curve fitting exercise the ERG discovered more worrying issues, such as the fact that some of the OS fitted and extrapolated curves by the company differ very considerably from the ones obtained by the ERG. This is further explored in Section 5.5.7.

Figure 23. Company's diagnostic plots of adjusted integrated daratumumab OS versus POM+DEX, 11 characteristics matched

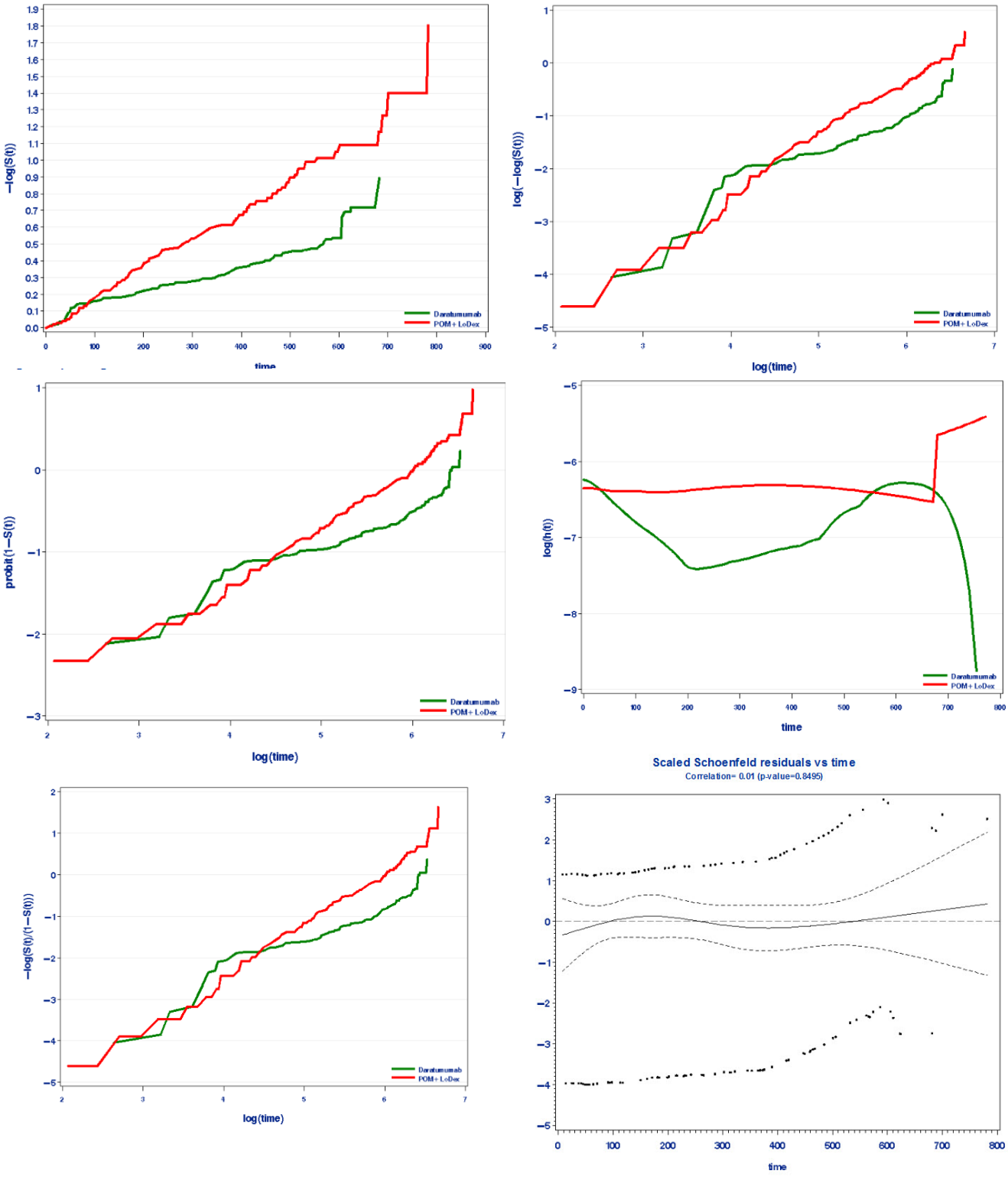


Figure 24. Overall survival KM curves from company's excel model

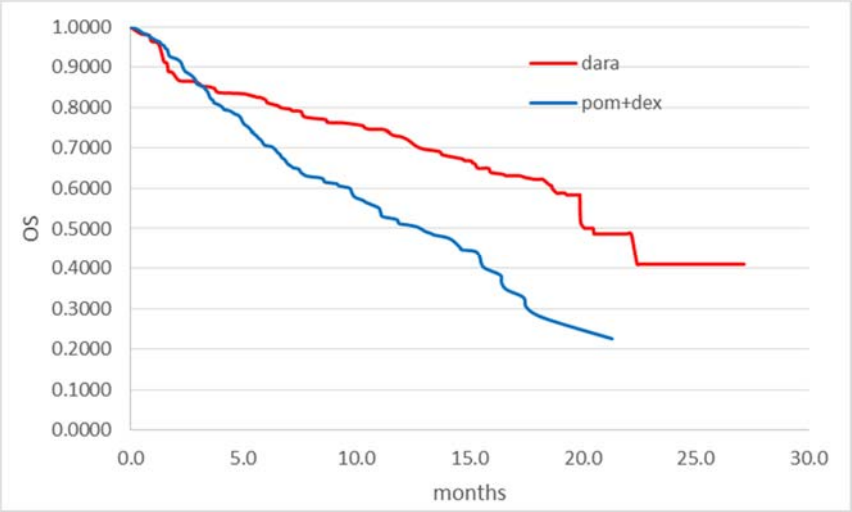


Figure 25. Overall survival KM curves derived by the ERG in *R* statistical package

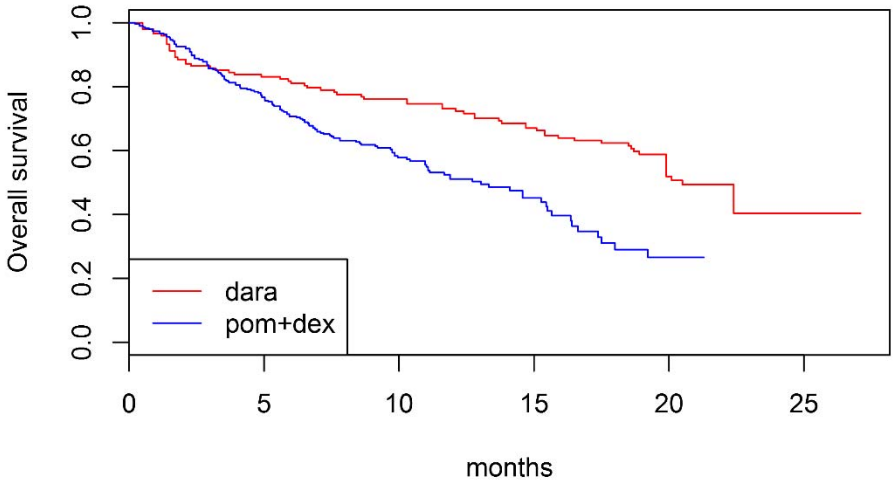


Figure 26. Log cumulative hazard versus log time for OS

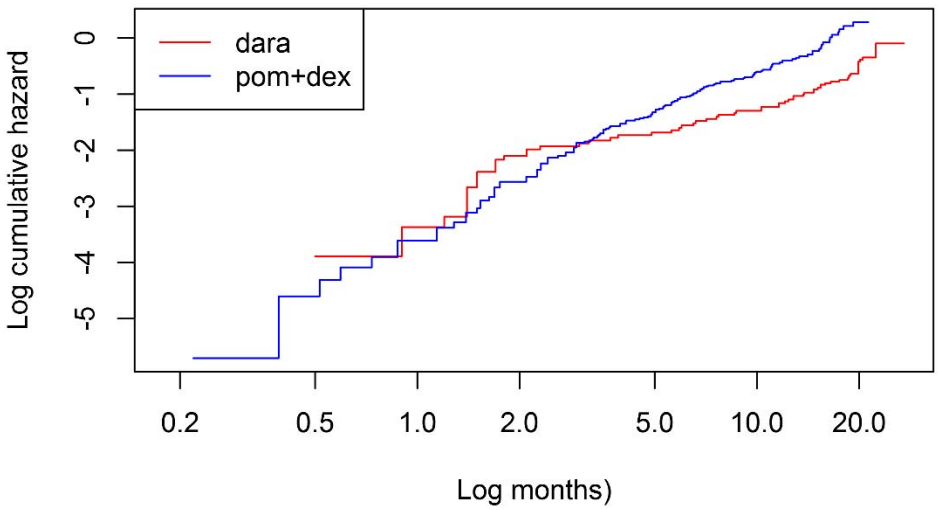
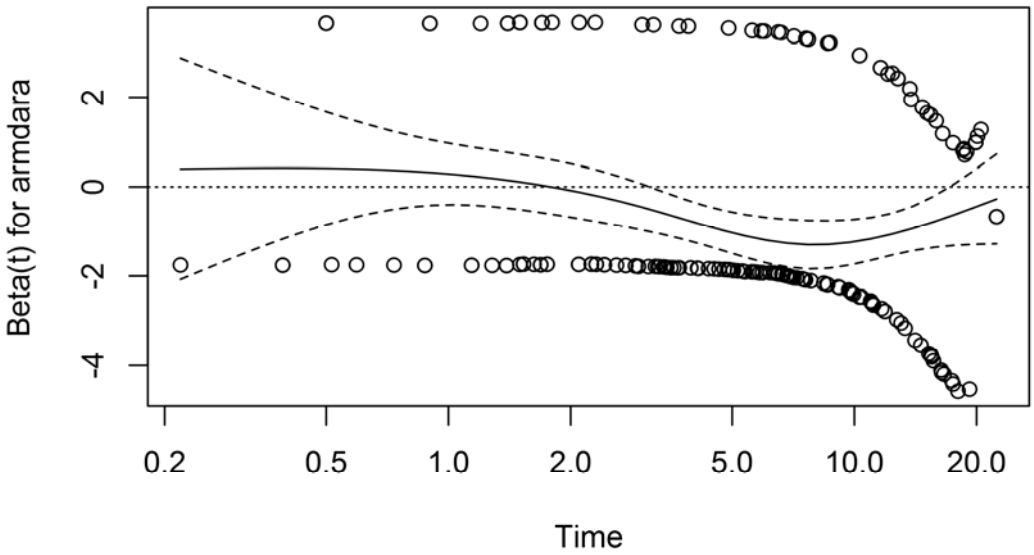


Figure 27. Scaled Schoenfeld residuals versus time for OS



In conclusion, the ERG disagrees with the company's assessment of PH and therefore the company's modelling approach. This has methodological implications given the company's use of an exponential model to fit the daratumumab OS unadjusted curves, and subsequent application of a HR to estimate the OS curves for pom+dex. Not only is this methodologically incorrect (when PH do not hold) but more importantly, the company is assuming a constant hazard for daratumumab and a constant HR

(1.74; 95% CI: 1.24 to 2.26) across daratumumab and pom+dex, when the KM curves for these treatments cross at the beginning of the trial periods.

To note is that the assessment undertaken by the company and the ERG uses the MAIC-adjusted daratumumab KM curves (adjusted for 11 characteristics) against the pom+dex unadjusted curves. It is the ERG opinion that the assessment of the PH assumption could change, had the number of characteristics adjusted for in the MAIC been different. This is because the shape of the MAIC-adjusted KM curve for daratumumab also changes. This issue is also related with the appropriateness of the adjusted HRs used by the company (explored in Section 4), which suggests that OS results are different depending on the number of characteristics adjusted for in the MAIC. These issues are further explored in Section 5.5.5.2 for PFS and in and Section 5.5.7 for OS.

The company's original model included an option to run the cost-effectiveness analysis using independently fitted curves for OS. This could have overcome the PH issue, had the company not decided to model the independently fitted curves with an exponential model (Section 5.5.7). Nonetheless, this would also imply using the 11-characteristic-adjusted daratumumab curves. Given that the ERG considers that the company should be adjusting for the maximum number of characteristics possible across trials (Section 4), the option to fit curves independently in the model is not ideal as it could solve one problem but would create a potentially bigger one. Additionally, using the independently fitted curves also implies using the integrated dataset (as the company did not include an option to fit treatment curves separately for MMY2002 and GEN501 alone). As the ERG explains in the next subsection, this carries additional problems as the fully adjusted HR for OS implies using the MMY2002 trial population, which is the trial that allows the adjustment for the maximum possible number of baseline characteristics.

The ERG did not have time to carry a similar assessment of PH for PFS. The diagnostic curves submitted by the company in the clarification response document are not particularly indicative of PH or AFT. Unfortunately, the ERG also did not have the time to carry the same assessment for pano+bort+dex. Ideally the ERG would have carried these assessments, however considering the relative lower importance of pano+bort+dex as a comparator (when compared with pom+dex) and of PFS as a survival outcome, the ERG decided to prioritise OS for daratumumab vs pom+dex.

5.5.5.1.2 Application of MAIC-adjusted HRs to unadjusted integrated daratumumab survival curves

As explained in Section 4, and based on the recommendations from the DSU, the ERG considers that the most adjusted MAIC analysis set is likely to the least biased but potentially still confounded by unobserved prognostic indicators and/or treatment effect modifiers. This means that the most appropriate analysis set is the one incorporating adjustment for cytogenetics and ISS stage. This, in its

turn, implies that the daratumumab dataset used in the MAIC analysis is MMY2002 (which has information on cytogenetics and ISS staging) and that GEN501 is excluded from the analysis as these prognostic indicators were not collected as baseline characteristics for patients in GEN501. The fully-adjusted HRs (i.e. adjusted to the maximum possible number of prognostic indicators and using MMY2002 instead of the integrated daratumumab dataset) for OS and PFS are considerably different from the ones used by the company in their base case analysis, where 11 characteristics were adjusted for the comparison of daratumumab against pom+dex (for OS and PFS) and five characteristics were adjusted for the comparison of daratumumab with pano+bort+dex.

With this in mind, and the conclusion that the PH assumption is not fully satisfied for OS, the ERG was left with two options within the company's approach to modelling the cost-effectiveness of daratumumab:

1. Using the company's dependently fitted curves, which relies on the assumption that PH holds, but allows the use of the fully adjusted HRs from the MAIC;

2. Using the company's independently fitted curves, which could overcome the PH issue, but would not allow the use of a fully adjusted HR in the model.

The ERG's preferred assumption would be a third one, which is not currently allowed for in the company's model. The ERG preferred approach would have been to use the independently fitted curves, however using the MAIC fully adjusted daratumumab curves for OS and PFS compared with unadjusted pom+dex and pano+bort+dex curves. The company has provided the ERG with these KM data (i.e. the fully MAIC-adjusted OS and PFS KM curves for daratumumab) at clarification. The ERG presents these curves and discusses the potential implications of these data in this section. Nonetheless, due to time constraints, and the remit of the ERG's review, it was not possible to use these KM data to fit and extrapolate survival curves for inclusion in the company's model.

Overall survival

Table 57 summarises the number of characteristics adjusted for in the company's base case MAIC analysis (11 for pom+dex and five for pano+bort+dex) and in the ERG's preferred approach to the company's MAIC (28 for pom+dex and 16 for pano+bort+dex). Figure 28 and Figure 29 report the KM curves for the MAIC-adjusted daratumumab OS data against pom+dex and pano+bort+dex, respectively, when a different number of characteristics is adjusted for. The red KM curves in both graphs show the MAIC-adjusted daratumumab curves used in the company's scenario analysis for fitting independent curves (i.e. adjusting for 11 for pom+dex and five for pano+bort+dex).

Analysis of these KM curves leads to important conclusions. The number of characteristics included in the MAIC adjustment drastically changes the positioning of the daratumumab OS adjusted KM curves in relation to pom+dex and, to a less but also important extent, in relation to pano+bort+dex. This means that adjusting for 28 (or 16) characteristics or for 11 (or 5) characteristics is not indifferent. As explained in Section 4, based on the recommendations from the DSU, the most adjusted MAIC analysis set is likely to be the least biased one in an unanchored comparison, which implies that the number of characteristics adjusted for in the company's base case is not sufficient to capture the relevant prognostic differences across trial populations. Equally important, the 26-characteristc-adjusted OS curve for daratumumab crosses the OS pom+dex curve around month 10, showing a lower survival benefit compared with pom+dex before then and a modest benefit after that point in time. This is a major departure from the 11-characteristic-adjusted OS curve, which crosses the pom+dex curve at month 4, to then show an impressive survival benefit compared with pom+dex. This has crucial implications for the OS estimated survival curves and therefore to the cost-effectiveness of daratumumab when compared with pom+dex.

Conversely, the 5-characteristic-adjusted OS curve for daratumumab vs pano+bort+dex seems to underestimate the survival benefit for daratumumab when compared with the 16-characteristic-adjusted OS curve. Both curves maintain a broadly similar relative position when compared with the unadjusted pano+bort+dex curve. This also has implications for the OS estimated curves for daratumumab vs pano+bort+dex and therefore to the cost-effectiveness analysis.

It is also interesting to note that even though the patients in MMY2002 are thought to have a worse prognosis than patients included in the GEN501 trial, the exclusion of the GEN501 patients (in principle with better survival outcomes) from the pom+dex-adjusted daratumumab KM curves (i.e. the exclusion from the GEN501 patients on the 26-characteristic-adjusted daratumumab OS curve to pom+dex) did not offset the negative impact of adjusting for a higher number of patient characteristics on the OS curve.

Table 57. Number of characteristics adjusted for in different MAIC approaches

	Daratumumab vs pom+dex	**Daratumumab vs pano+bort+Dex**
Number of characteristics adjusted for in company's MAIC-adjusted HRs and KM daratumumab curves (using integrated dataset)	11	5
Maximum number of possible characteristics adjusted for through MAIC (using MMY2002)/ ERG's preferred approach	28	16

Figure 28. Overall survival KM data for daratumumab (adjusted) vs pom+dex (unadjusted)

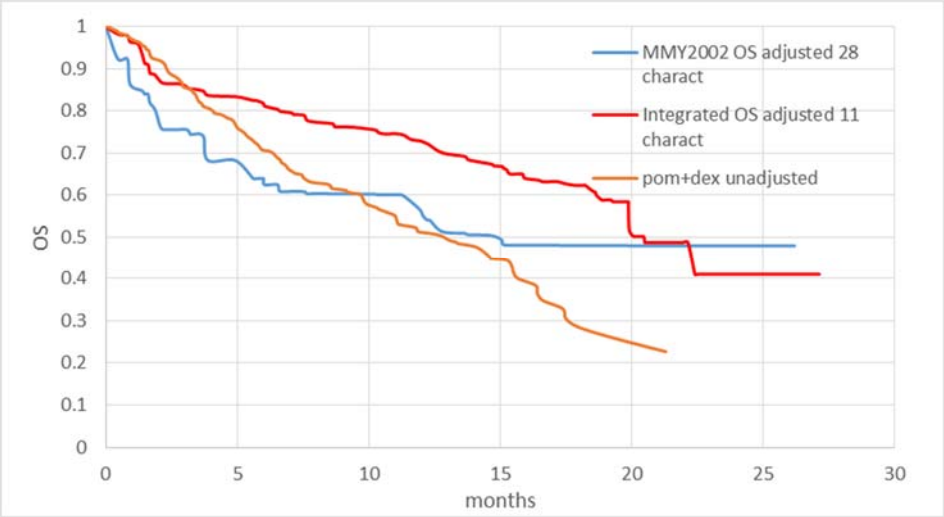
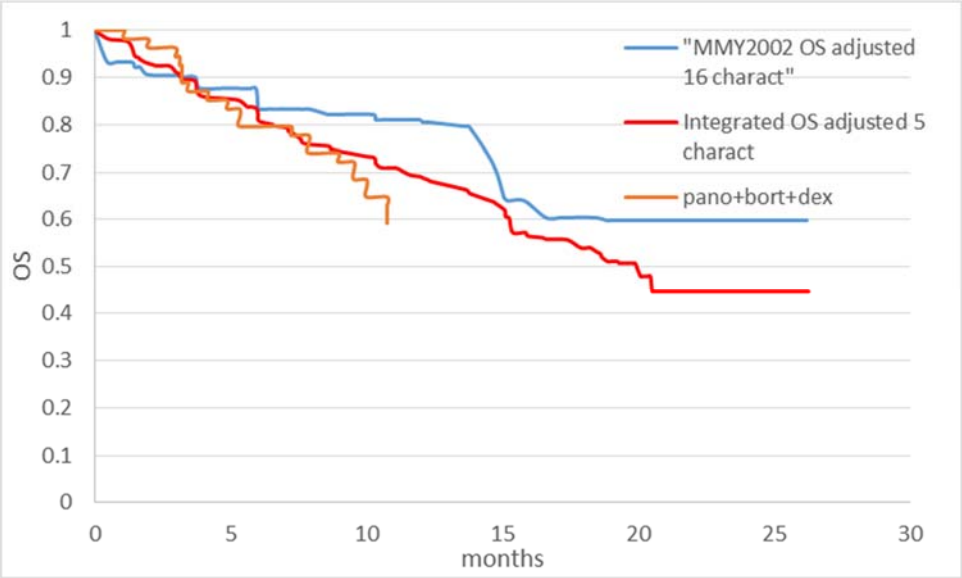


Figure 29. Overall survival KM data for daratumumab (adjusted) vs pano+bort+dex (unadjusted)



Progression-free survival

Table 58 summarises the number of characteristics adjusted for in the company's base case MAIC and in the ERG's preferred approach to the company's MAIC. Figure 30 and Figure 31 report the KM curves for the MAIC-adjusted daratumumab PFS data against pom+dex and pano+bort+dex, respectively, when a different number of characteristics is adjusted for.

Analysis of these KM curves leads to important conclusions. The number of characteristics included in the MAIC adjustment changes the positioning of the daratumumab PFS adjusted KM curves in relation to pom+dex and in relation to pano+bort+dex (although to a less extent than observed for OS data). The

28-characteristic-adjusted PFS curve for daratumumab is consistently lower than the PFS pom+dex curve for the entire trial period, showing a smaller benefit for daratumumab when compared with pom+dex. This is a major departure from the 11-characteristic-adjusted PFS curve, which is consistently above (or overlapping) the pom+dex curve. This has crucial implications for the PFS estimated curves and therefore to the cost-effectiveness of daratumumab when compared with pom+dex.

Conversely, the 5-characteristic-adjusted PFS curve for daratumumab vs pano+bort+dex seems to underestimate the benefit for daratumumab when compared with the 16-characteristic-adjusted PFS curve. Even though the curves could be considered broadly similar, given that PFS curves are a key diver of treatment costs, the slightest shift in the curves is likely to have an impact on the cost-effectiveness analysis' results.

Table 58. Number of characteristics adjusted for in different MAIC approaches

	Daratumumab vs pom+dex	**Daratumumab vs pano+bort+dex**
Number of characteristics adjusted for in company's MAIC-adjusted HRs and KM daratumumab curves (using integrated dataset)	11	5
Maximum number of possible characteristics adjusted for through MAIC (using MMY2002)/ ERG's preferred approach	28	16
Abbreviations in table: bort, bortezomib; dex, dexamethasone; HR, hazard ratio; KM, Kaplan Meier; MAIC, matched adjusted indirect comparison; pano, panobinostat; pom, pomalidomide.		

Figure 30. Progression-free survival KM data for daratumumab (adjusted) vs pom+dex (unadjusted)

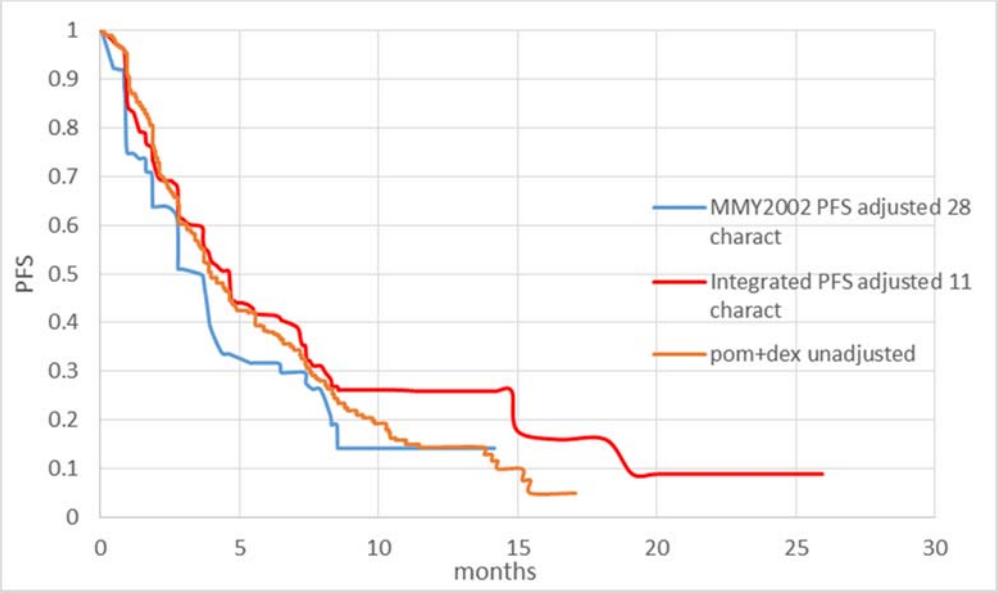
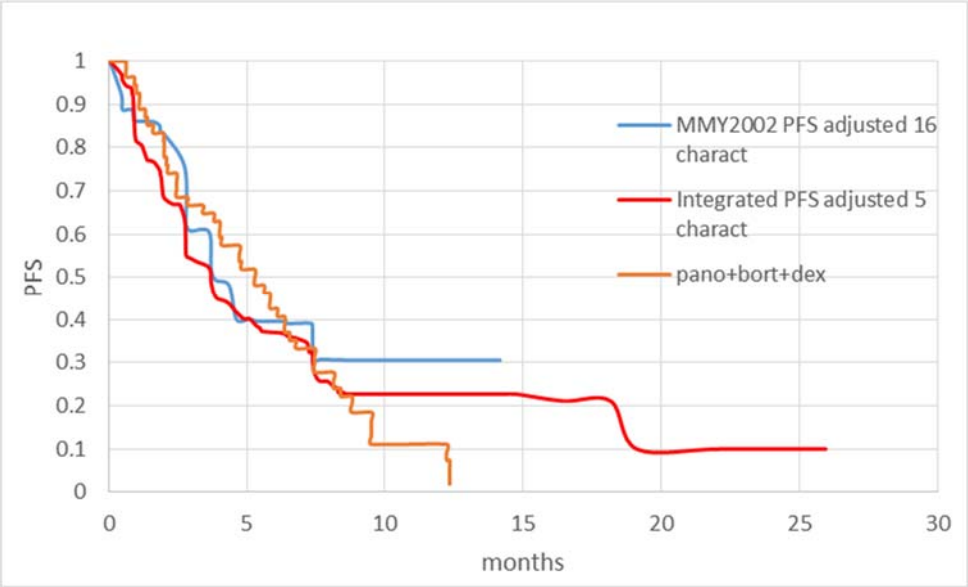


Figure 31. Progression-free survival KM data for daratumumab (adjusted) vs pano+bort+dex (unadjusted)



Finally, it should be considered that the sample sizes used to run the fully adjusted MAIC analyses are different from the ones used in the base case MAIC analysis. While the base case MAIC analysis comparing daratumumab with pom+dex uses a sample size of 148 patients and a net effective sample size of 84 patients, the fully adjusted MAIC analysis uses a sample size of 93 patients and a net effective sample size of 19 patients. This has implications for the uncertainty of the analysis, with higher weights being attributed to patients as the net effective sample size reduces. The ERG is not entire clear how the adjustment of the KM curves was undertaken but the number of patients included in the OS and PFS KM curves for daratumumab adjusted to pom+dex is 93 patients. The same is true for the daratumumab curves adjusted to pano+bort+dex. The base case MAIC-adjusted curves comparing daratumumab with pano+bort+dex rely on a sample size of 125 patients and on a net effective sample size of 80 patients, while the fully adjusted MAIC analysis is based on a sample size of 84 patients and a net effective sample size of 13 patients.

In conclusion, the ERG has several concerns with the company's statistical approach to the economic analysis. The ERG considers that the curve fitting exercise undertaken by the company lacks transparency and consistency. This is related with the approach taken to the modelling of Gompertz curves and the lack of an appropriate assessment of the PH, PO and AFT assumptions consistently across modelled outcomes. The ERG disagrees with the company's assessment of PH for OS data and thus with the company's modelling approach. This has several implications considering the company's use of exponential models to fit the daratumumab unadjusted OS curves and application of a HR to estimate the OS curves for comparator treatments. The ERG is also concerned with the validity of the curve fitting exercise undertaken by the company for OS data as some of the OS extrapolated curves by

the company seem to differ considerably from the ones obtained by the ERG. The company's original model included an option to run the cost-effectiveness analysis using independently fitted curves for OS. This could have overcome the PH issue, nonetheless, this would also imply using the 11-characteristics-adjusted daratumumab curves. Given the ERG's consideration that the company should be adjusting for the maximum number of characteristics possible across trials (Section 4), the option to fit curves independently in the model is not ideal as it solves one problem but creates a potentially bigger one. The ERG preferred statistical approach is therefore not currently allowed for in the company's model. The ERG preferred approach would have been to use the independently fitted curves, however using the MAIC fully adjusted daratumumab curves for OS and PFS compared with unadjusted pom+dex and pano+bort+dex curves. The company has provided the ERG with these data (i.e. the fully MAIC-adjusted OS and PFS KM curves for daratumumab) at clarification. The ERG discusses the potential implications of these data however due to time constraints, and the remit of the ERG's review, does not use these KM data to fit and extrapolate curves for inclusion in the company's model. Analysis of the fully adjusted KM curves led to important conclusions:

1. The number of characteristics included in the MAIC adjustment drastically changes the positioning of the daratumumab OS adjusted KM curves in relation to pom+dex (and to a less but also important extent) in relation to pano+bort+dex. The fully adjusted OS curve for daratumumab crosses the OS pom+dex curve around month 10, showing a lower survival benefit than pom+dex before then, and a modest benefit after that point in time. This is a major departure from the 11-characteristic-adjusted OS curve, which crosses the pom+dex curve at month 4, to then show an impressive survival benefit. Conversely, the 5-characteristic-adjusted OS curve for daratumumab vs pano+bort+dex seems to underestimate the survival benefit for daratumumab when compared with the fully adjusted OS curve. This has crucial implications for the cost-effectiveness of daratumumab when compared with pom+dex and pano+bort+dex;

2. The number of characteristics included in the MAIC adjustment changes the positioning of the daratumumab PFS adjusted KM curves in relation to pom+dex and in relation to pano+bort+dex, although to a less extent than observed for OS data. Regardless of this, given that PFS curves are a key diver of treatment costs, the slightest shift in the curves is likely to have an impact on the cost-effectiveness analysis' results.

Even though the ERG's methodologically preferred approach would be to use the MAIC fully adjusted curves (as advised by the DSU), it also acknowledges the limitations of the underlying clinical data considering that the sample sizes used to run the fully adjusted MAIC analyses are smaller than the ones considered in the base case MAIC analysis. This has implications for the uncertainty of the analysis, with higher weights being attributed to patients as the net effective sample size reduces.

5.5.5.2 Progression-free survival

5.5.5.2.1 Company's base case approach (dependent fit)

In their base case approach, the company applies the 11-characteristics MAIC-adjusted PFS HR to the unadjusted daratumumab PFS curve to derive the PFS curve for pom+dex. To estimate the PFS curve for pano+bort+dex, the company applies the 5-characteristics MAIC-adjusted PFS HR to the unadjusted daratumumab PFS curve. These HRs are reported in Table 59, together with the HRs resulting from carrying the fully adjusted MAIC analysis to derive HRs for daratumumab against its comparators, provided to the ERG by the company upon the clarification stage. To note is that when the HRs are fully adjusted for the maximum number of patients' characteristics the HRs change the direction of the effect (for example, the HR for daratumumab vs pom+dex goes from 1.24 to 0.88). Nonetheless, all of the HRs remain non-statistically significant when comparing daratumumab with the two relevant treatments.

The company fitted the PFS daratumumab curves with a lognormal model. From a methodological point of view, the application of an HR to a lognormal model (i.e. to a non-PHs model) is not appropriate. The company included the option to model the PFS baseline curve for daratumumab with other distributions (Weibull, exponential, log-logistic, gamma and Gompertz-after the ERG request). The ERG found a mistake in the implementation of the option to use different curves, as the gamma curve had not been correctly implemented as an option.

Table 59. Progression-free survival HRs according to the number of characteristics adjusted for in MAIC

Comparison	Hazard ratio	95% confidence interval
11 characteristics adjusted for daratumumab vs pom+dex (company's base case)	1.241	(0.920; 1.675)
5 characteristics adjusted for daratumumab vs pano+bort+dex (company's base case)	0.920	(0.623; 1.357)
28 characteristics adjusted for daratumumab vs pom+dex (ERG's preferred approach)	0.877	(0.493; 1.563)
16 characteristics adjusted for daratumumab vs pano+bort+dex (ERG's preferred approach)	1.176	(0.532; 2.564)
Abbreviations in table: bort, bortezomib; dex, dexamethasone; pano, panobinostat; pom, pomalidomide.		

5.5.5.2.2 Independently fitted PFS curves

The company included an option to fit PFS curves independently in the model. Nonetheless the implementation of this option in the model had several mistakes and unjustified assumptions. The formulae in the model was incorrect and it used the MAIC HR to apply to the daratumumab curve (dependent fit) when an option to independently fit the curves was chosen. The models used to fit the

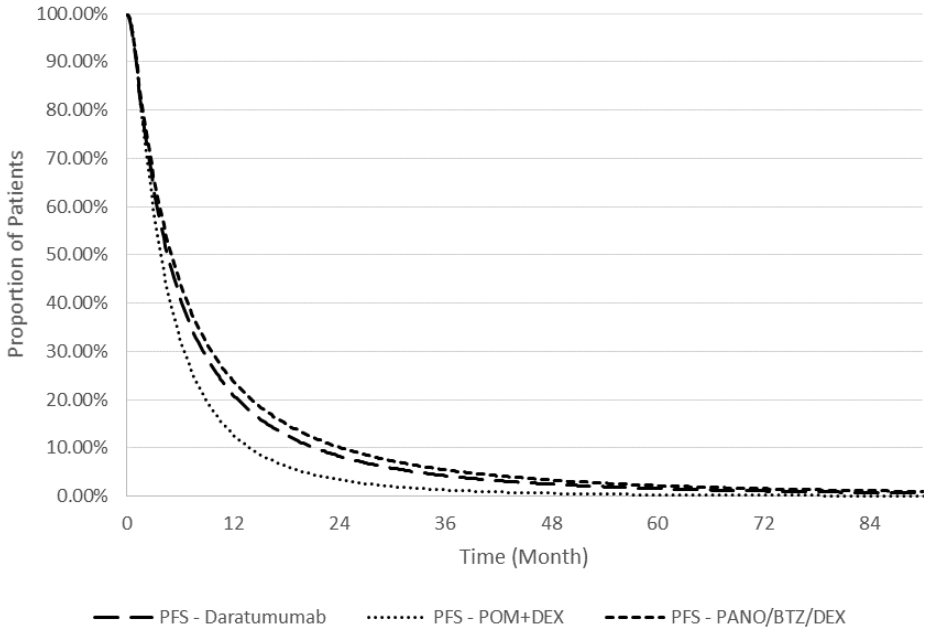
daratumumab MAIC-adjusted PFS curves were also incorrectly applied in the model as the formulae linked these to the models chosen for OS instead of PFS, which resulted in the daratumumab PFS curves being fitted with exponential curves and the pom+dex and pano+bort+dex curves being fitted with lognormal curves. The ERG corrected these mistakes in the economic model. Changing the PFS modelling approach from a dependent to an independent fit approach for the comparison of daratumumab and pom+dex, resulted in a change in ICERs from £55,766 to £57,684 in the ERG corrected model (this changed the ICER to £46,181 in the company's uncorrected model). The ICER changed from £32,593 to £27,256 in the ERG corrected model (and to £726 in the company's uncorrected model) when comparing daratumumab with pano+bort+dex.

The models used to fit the daratumumab MAIC-adjusted curve and the pom+dex and pano+bort+dex curves were lognormal models. There was no justification provided by the company for this, and an assessment of fit should have been undertaken for this curve fitting exercise (instead of replicating the model selection for the dependent fit approach).

As mentioned in Section 5.5.5.1.1, the ERG did not have time to carry a proper assessment of the PH, PO and AFT assumption for PFS. The diagnostic curves submitted by the company in the clarification response document are not particularly indicative of PH or AFT.

As discussed in Section 5.5.5.1.2, the number of characteristics included in the MAIC adjustment changes the positioning of the daratumumab PFS adjusted KM curves in relation to pom+dex and in relation to pano+bort+dex. The 28-characteristc-adjusted PFS curve for daratumumab is consistently lower than the PFS pom+dex curve for the entire trial period, showing a smaller benefit for daratumumab when compared with pom+dex. This is a major departure from the 11-characteristic-adjusted PFS curve, which is consistently above (or overlapping) the pom+dex curve. Conversely, the 5-characteristic-adjusted PFS curve for daratumumab vs pano+bort+dex seems to underestimate the benefit for daratumumab when compared with the 16-characteristic-adjusted OS curve. This has crucial implications for the PFS estimated curves (Figure 32) and therefore the cost-effectiveness of daratumumab when compared with pom+dex. Unfortunately, these KM curves were not used by the company to model daratumumab fully adjusted survival curves. Therefore, the ERG cannot provide results for this approach. The anticipated impact of this shift in the PFS curves is also not easily predicted. While the decrease in the PFS benefit for daratumumab in relation to pom+dex would generate less QALYs than in the base case analysis, it would also decrease the costs associated with daratumumab. The inverse would be verified for the comparison of daratumumab against pano+bort+dex.

Figure 32. Company's indepdendent fit approach to PFS curves



5.5.5.2.3 ERG's exploratory approach

Given that the ERG's preferred methodological approach is not available as a modelling option in the company's Excel model, the ERG proposes some exploratory analysis to assess the impact of using fully adjusted HRs in the company's base case approach. To note is that this approach carries all the flaws previously described. It uses a dependent fit approach, it implies the application of HRs to lognormal models and the use of non-fully assessed (for goodness-of-fit) models. Nonetheless, it is a step in the right direction compared with the company's approach, as it uses the fully adjusted HRs.

As the fully adjusted HRs obtained with the MAIC result from including only the MMY2002 dataset, instead of the integrated population, in the MAIC analysis the ERG used the MMY2002 baseline daratumumab curves to apply the MAIC-adjusted HRs. The PFS KM data for the individual trials (Figure 33) suggests that when changing the pooled population to MMY2002, the expected PFS for daratumumab patients is lower. This makes sense, considering the worse prognosis of patients in MMY2002. What seems counterintuitive and lacking face validity is the fact that the GEN501 curve would be below the MMY2002 and the integrated population curve. The PFS KM curves reported by the company in the CS (and reproduced in the ERG report in Section 4) show that patients in GEN501 had better PFS outcomes than patients in MMY2002. Therefore, the KM data provided by the company to the ERG is likely to be wrong. Depending on which data are correct, this could also have implications for the data integration method undertaken by the company as in theory, the integrated curve should be somewhere between the individual trial curves.

The company included the option to use the MMY2002 trial population instead of the integrated population in the economic model (with a dependent fit approach). The HRs for PFS outcomes are reported in Table 60. It can be noted that both HRs for the comparison of daratumumab vs pom+dex and pano+bort+dex decreased, as would be expected considering the shift in the PFS curves from the integrated population to MMY2002. To also note is that the ERG's preferred HRs (Table 60), also using the MMY2002 population, but adjusting for the maximum possible number of patients' characteristics, lead to a further decrease in the HR for pom+dex but to a considerable increase in the pano+bort+dex HR.

Figure 33. Progression-free survival KM data for daratumamab (integrated data, MMY2002 and GEN501)

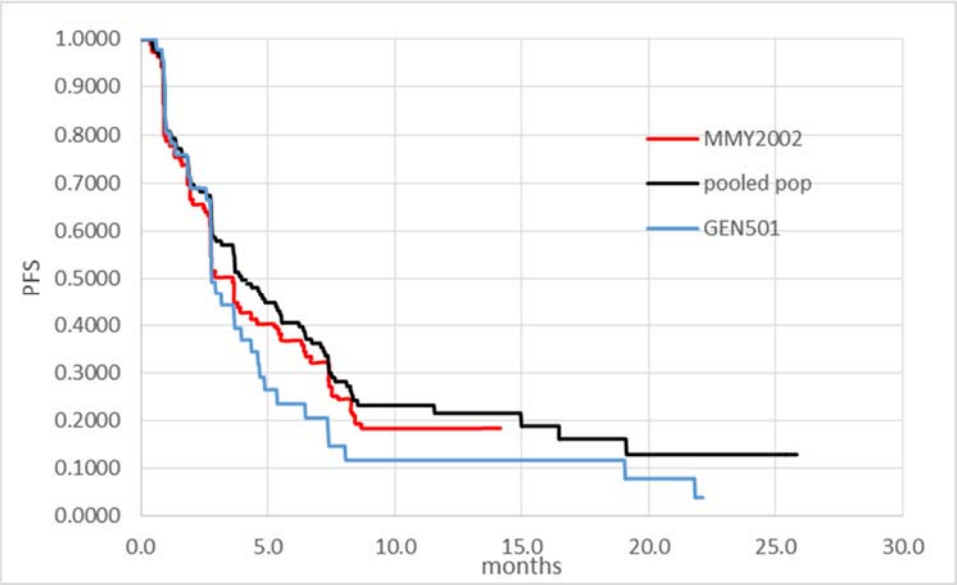


Table 60. Progression-free survival HRs according to different populations

Comparison	Hazard ratios	95% confidence interval
11 characteristics adjusted for daratumumab vs pom+dex (integrated population, company's base case)	1.241	(0.920; 1.675)
5 characteristics adjusted for daratumumab vs pano+bort+dex (integrated population, company's base case)	0.920	(0.623; 1.357)
11 characteristics adjusted for daratumumab vs pom+dex (MMY2002 population, company's scenario analysis)	0.935	(0.651; 1.340)
5 characteristics adjusted for daratumumab vs. pano+bort+dex (MMY2002 population, company's scenario analysis)	0.832	(0.535; 1.294)
28 characteristics adjusted for daratumumab vs pom+dex (ERG's preferred approach)	0.877	(0.493; 1.563)
16 characteristics adjusted for daratumumab vs pano+bort+dex (ERG's preferred approach)	1.176	(0.532; 2.564)

Abbreviations in table: bort, bortezomib; dex, dexamethasone; pano, panobinostat; pom, pomalidomide.

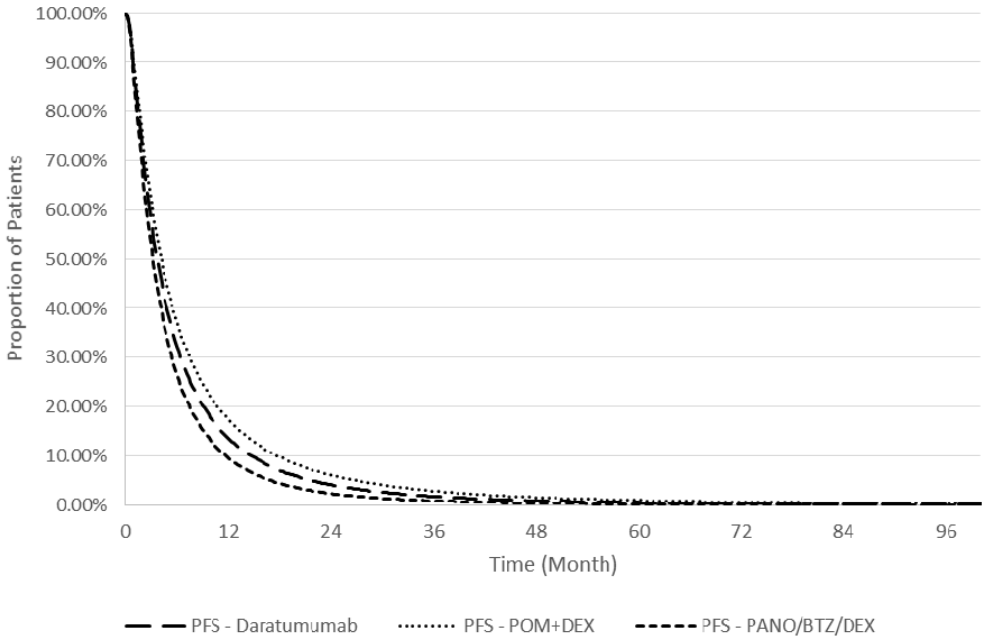
The results of the ERG exploratory analysis are shown in Table 61 below. Figure 34 shows the daratumumab unadjusted, pom+dex and pano+bort+dex estimated curves with the fully adjusted PFS HRs. Results in in Table 61 show a great increase in the daratumumab vs pano+bort+dex ICER (from £32,593 to £101,040) when the MMY2002 and the fully adjusted HR for PFS is used. The ICER for daratumumab vs pom+dex shows a decrease from £55,766 to £54,348. Two forces play in the change of the ICERs. One is related with the change in the trial population (and therefore in the daratumumab baseline curve) and the other is the HR used. Even though the baseline daratumumab PFS curve decreases (with the shift from the integrated to the MMY2002 population), the HRs comparing daratumumab with the different treatments go in different directions. While the HR for pom+dex decreases (reflecting a loss in the relative effectiveness of daratumumab) the HR for pano+bort+dex increases, reflecting a better performing daratumumab. It would also appear that the decrease in the HR for PFS leads to a lower ICER (as was the case with pom+dex) while the increase in the PFS HR for pano+bort+dex leads to a higher ICER. While this might seem counterintuitive, it is likely to be related with the cost estimation in the model, which is highly dependent on the PFS estimates.

Nonetheless considering the lack of statistical significance in the fully adjusted HRs (and the base case adjusted HRs) and the uncertainty around the true relative difference in PFS estimates for daratumumab and its comparators, the ERG also ran an exploratory analysis using a HR of 1 for PFS for both treatments. The results of this analysis are reported in Section 6.

Table 61. ICERs resulting from fully adjusted PFS HRs

Treatment	Total			Incremental			ICER (using ERG's assumptions)	Base case ICERs
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Daratumumab	£71,560	1.12	2.16					
Pom+dex	£49,846	0.72	1.41	£21,715	0.40	0.75	£54,348	£55,766
Pano+bort+dex	£60,067	1.01	1.99	£11,493	0.11	0.17	£101,040	£32,593

Figure 34. Progression-free survival curves for daratumumab, pom+dex and pano+bort+dex with fully adjusted HRs



In conclusion, the ERG has several issues with the estimation of PFS in the company's model and with the uncertainty around the company's PFS data. The ERG discusses three approaches for the estimation of PFS: the company's base case approach (dependent fit); the company's alternative approach (independent fit) and the ERG's exploratory analysis. Regardless of the approach undertaken, the ERG considers that there is too much uncertainty around PFS data and notes the lack of statistical significance in the fully adjusted HRs (and the base case adjusted HRs). With the objective of aiding the Committee's consideration of PFS data, the ERG also summarises the results of the discussion of the three approaches to modelling PFS:

1. The company's base case approach implies the verification of the PH assumption. Even though the ERG did not have time to carry a proper assessment of the PH (and notes the company did not supply it), the diagnostic curves submitted by the company in the clarification response document are not particularly indicative of PH or AFT. Nonetheless the company fitted the PFS daratumumab curves with a lognormal model. From a methodological point of view, the application of an HR to a lognormal model (i.e. to a non-PHs model) is not appropriate. The company included the option to model the PFS baseline curve for daratumumab with other distributions. The ERG found a mistake in the implementation of the option to use different curves, as the gamma curve had not been correctly implemented as an option;

2. The company also included an option to fit PFS curves independently in the model. Nonetheless the implementation of this option in the model had several mistakes and unjustified

assumptions. The formulae in the model were incorrect and the models used to fit the daratumumab MAIC-adjusted curve and the pom+dex and pano+bort+dex curves were lognormal models. There was no justification provided by the company for this, and an assessment of fit should have been undertaken for this curve fitting exercise. Changing the PFS modelling approach from a dependent to an independent fit approach for the comparison of daratumumab and pom+dex, resulted in a change in ICERs from £55,766 to £57,684 in the ERG corrected model (this changed the ICER to £46,181 in the company's uncorrected model). The ICER changed from £32,593 to £27,256 in the ERG corrected model (and to £726 in the company's uncorrected model) when comparing daratumumab with pano+bort+dex;

3. Given that the ERG's preferred methodological approach is not available as a modelling option in the company's Excel model, the ERG undertook some exploratory analysis to assess the impact of using fully adjusted HRs in the company's base case approach. To note is that this approach carries all the flaws described before. It uses a dependent fit approach, it implies the application of HRs to lognormal models and the use of non-fully assessed (for goodness-of-fit) models. Nonetheless, it is a step in the right direction compared with the company's approach, as it uses the fully adjusted HRs. As the fully adjusted HRs obtained with the MAIC resulted from including only the MMY2002 dataset instead of the integrated one in the MAIC analysis, the ERG used the MMY2002 baseline unadjusted daratumumab curves to apply the MAIC-adjusted HRs. The PFS KM data for the individual trials suggests that when changing the pooled population to the MMY2002 one, the PFS outcomes for daratumumab patients are worse. This is expected, considering the worse prognosis of patients in MMY2002. What seems counterintuitive and lacking face validity is the fact that the GEN501 KM curves is below the MMY2002 and the integrated population KM curves. The ERG concludes that the KM data provided by the company to the ERG are likely to be wrong. Depending on which data are correct, this could also have implications for the data integration method undertaken by the company as in theory, the integrated curve should be somewhere between the individual trial curves. The ERG's preferred HRs, also using the MMY2002 population, but adjusting for the maximum possible number of patients' characteristics lead to a decrease in the HR for pom+dex (reflecting a loss in the relative effectiveness of daratumumab) but to a considerable increase in the pano+bort+dex HR. The ICERs resulting from the ERG exploratory analysis show a great increase in the ICER for daratumumab vs pano+bort+dex (from £32,593 to £101,040) and a decrease in the daratumumab vs pom+dex ICER (from £55,766 to £54,348). Two forces play in the change of the ICERs. One is related with the change in the trial population (and therefore in the daratumumab baseline curve) and the other is the HR used. Even though the baseline daratumumab PFS curve shifts down (with the change from the integrated to the MMY2002 population), the HRs comparing daratumumab with the different treatments go in different

directions. While the HR for pom+dex decreases (reflecting a loss in the relative effectiveness of daratumumab) the HR for pano+bort+dex increases, reflecting a better performing daratumumab.

5.5.5.3 Time to treatment discontinuation

Time to treatment discontinuation is used by the company to model treatment costs for daratumumab and pom+dex. This is done by subtracting the PFS from the TTD curves for each treatment, to obtain time on treatment for daratumumab and pom+dex patients (TOT = P(PFS)-P(TTD)). The company estimated TTD curves for daratumumab using the integrated data from MMY2002 and GEN501. For pom+dex, only mean and median TTD could be obtained from the literature, therefore the TTD curves for daratumumab were calibrated to match the observed mean and median from MM-003.

The estimation of TTD curves in the company's analysis is another example of the lack of transparency and clarity throughout this STA. Firstly, the ERG could not find TTD as a specified outcome in the MMY2002 CSR or in GEN501 CSR. After a request for clarification, the company explained that TTD was not a pre-specified outcome in the MMY2002 and GEN501 trials but instead resulted from a *post-hoc* analysis of the patient level data. Therefore, the ERG has little to no information on this clinical outcome. Secondly, the estimation of adjusted TTD curves for daratumumab through the, "calibration approach" is a black box in the company's analysis. No further details were provided by the company other than the fact that, *"the TTD curves for daratumumab were calibrated to match the observed mean and median from MM-003".* A mean and median TTD of 4.7 months and 2.9 months was observed for pom+dex in the MM-003 trial, respectively. [43]

The daratumumab TTD and PFS curves are compared in Figure 35, which shows that the extrapolated curves separate with a higher rate of discontinuation than progression. The ERG notes that different functions were used to fit PFS and TTD (i.e. lognormal and log-logistic), and that may also lead to a more accentuated difference in the curves. The PFS and TTD curves for pom+dex indicate that patients are more likely to discontinue treatment for reasons other than progression compared to daratumumab. This would make sense considering the advantageous safety profile of daratumumab compared with pom+dex.

Considering the uncertainty around the TTD data and estimation, the ERG considers that using these data in the economic analysis carries a potentially high risk. While the PFS curves and data are also not without problems, PFS curves could be used as an exploratory approach to derive treatment costs, implying that patients receive treatment until progression.

Figure 36 shows the time on treatment (TOT = P(PFS)-P(TTD)) for daratumumab and pom+dex patients compared with the respective PFS curves. Analysis of the curves in Figure 36 shows that when

time on treatment in the economic model is replaced by PFS (instead of the difference between PFS and TTD data), not only there is an absolute shift in the curves but also a considerable relative shift in time on treatment. The relative difference between time on treatment for daratumumab and pom+dex patients decreases, and so daratumumab patients spend more time (but relatively less) on treatment than pom+dex patients when compared with the TTD approach. This drives the costs of daratumumab up (from £81,422 to £86,234) but relatively more so the pom+dex costs (from £49,921 to £66,886). Table 62 and Table 63 show the company's base case ICERs when time on treatment is estimated through the difference between PFS and TTD or PFS alone, respectively. There is no difference in QALYs resulting from this change, as the same proportion of patients accrues the PFS-related utility values in both approaches. Therefore, the ICER for daratumumab vs pom+dex decreases, while the ICER for daratumumab vs pano+bort+dex decreases.

Figure 35. Comparison of TTD and PFS curves for daratumumab and pom+dex

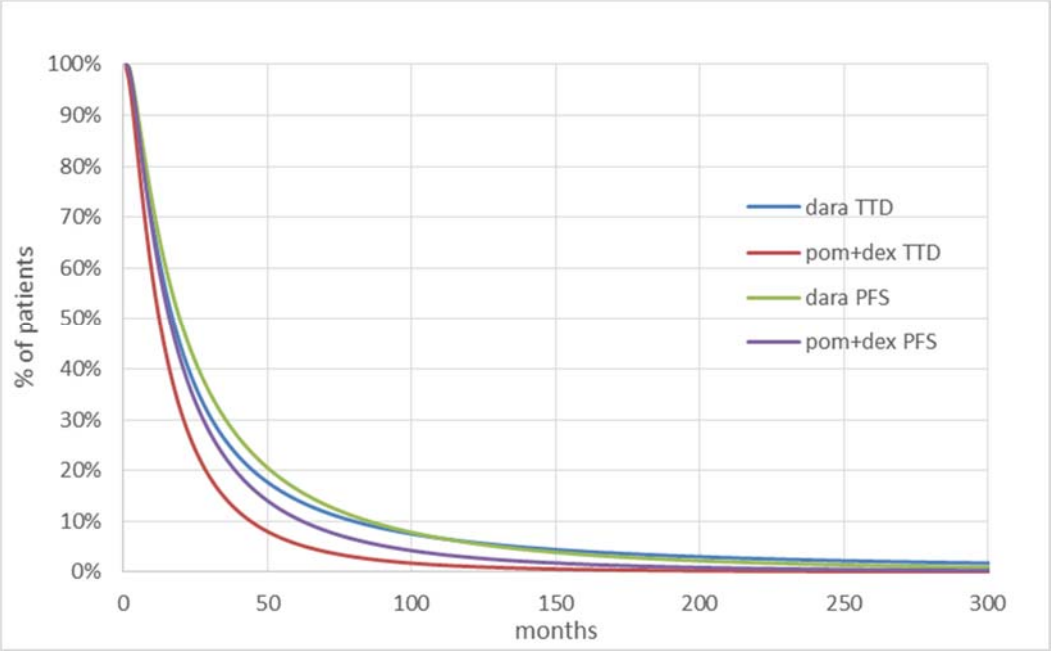


Figure 36. Time on treatment for daratumumab and pom+dex

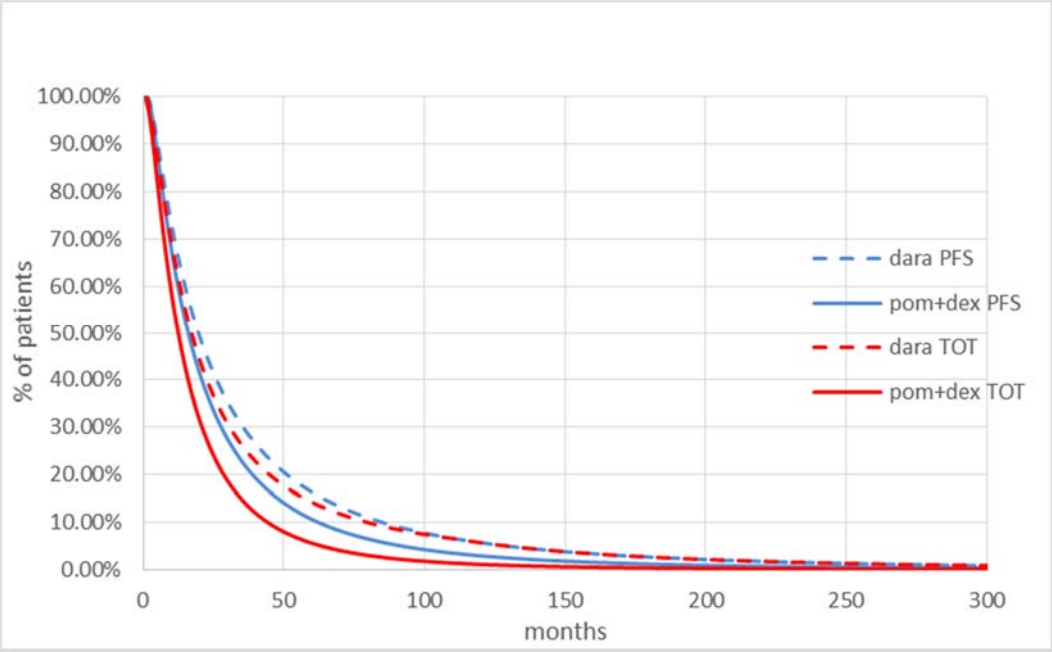


Table 62. Company's base case results

Treatment	Total			Incremental			ICER (Dara vs comparator) at list prices
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Daratumumab	£81,422	1.31	2.54				
Pom+dex	£49,921	0.75	1.46	£31,501	0.56	1.07	£55,766
Pano+bort+dex	£74,530	1.10	2.14	£6,892	0.21	0.39	£32,593

Table 63. Company's base case results when TOT=PFS

Treatment	Total			Incremental			ICER (Dara vs comparator) at list prices
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Daratumumab	£86,234	1.31	2.54				
Pom+dex	£66,886	0.75	1.46	£19,347	0.56	1.07	£34,250
Pano+bort+dex	£74,530	1.10	2.14	£11,704	0.21	0.39	£55,348

5.5.6 Adverse events

The company uses the daratumumab rates of TEAEs observed in the MMY2002 and GEN501 trials, and not treatment-related adverse events to estimate AEs in the model. Upon request for clarification the company reported that TEAEs provide a broader range of adverse events than treatment-related AEs.

The company's approach of including AEs of particular clinical importance (nausea, peripheral neuropathy and upper respiratory tract infections) regardless of grade is reasonable. Nonetheless the ERG notes that the CSRs for MMY2002 and GEN501 do not report peripheral neuropathy for daratumumab patients, which seems slightly contradictory considering the clinical experts' view on the importance of peripheral neuropathy for rrMM treatments and the company's decision of including this event based on its importance. Furthermore, the ERG identified two discrepancies in the estimates of peripheral neuropathy (all grades) used in the model. The company states that the rate of peripheral neuropathy is not reported for pano+bort+dex patients in the PANORAMA2 trial publication [81] and that a 1.7% rate was observed for pom+dex patients in the MM-003 trial.[82] However, according to the publications cited, 27% of patients in the PANORAMA2 trial experienced all-grade peripheral neuropathy (with only 1.8% of patients experiencing Grade 3/4 peripheral neuropathy) while the corresponding number in the MM-003 trial is 15% and not 1.7%. [81, 82] The ERG corrected these values in the model which led to a decrease in the ICER for daratumumab vs pom+dex of £354 and to a decrease of £1,130 per QALY gain in the ICER comparing daratumumab with pano+bort+dex.

The company also assumed that bendamustine patients experience the same AEs as pom+dex patients. It is unclear why the company did not search for data on AEs in any of the bendamustine trials or retrospective studies that were identified in the systematic literature review reported in Section 4.10.1 of the CS. The ERG's clinical experts advised that this assumption is unreasonable as bendamustine-related AEs are expected to be similar to those of chemotherapy. Given the low relevance of bendamustine as a comparator, the impact of the company's decision is likely to be unimportant. The ERG's clinical experts confirmed that all relevant AEs a have been considered in the model.

5.5.7 Mortality

5.5.7.1.1 Company's base case approach (dependent fit)

In their base case approach, the company applies the 11-characteristic MAIC-adjusted OS HR to the unadjusted daratumumab OS curve to derive the OS curve for pom+dex. To estimate the OS curve for pano+bort+dex, the company applies the 5-characteristic MAIC-adjusted OS HR to the unadjusted daratumumab OS curve. These HRs are reported in Table 64 and Table 59, together with the HRs resulting from carrying the fully adjusted MAIC analysis to derive HRs for daratumumab against its comparators, provided to the ERG by the company upon the clarification stage. To note is that when the HRs are fully adjusted for the maximum number of patients' characteristics across trials, the OS HR for daratumumab vs pom+dex decreases (suggesting a lower relative effectiveness for daratumumab) but equally importantly becomes non-statistically significant. The HR for daratumumab vs pano+bort+dex remains non-statistically significant, however the 95% confidence interval increases its range reflecting the higher uncertainty of the point estimate. To note is that the OS HR for daratumumab

vs pano+bort+dex increases, while the OS HR against pom+dex decreases when the fully adjusted MAIC analysis is used.

The company fitted the OS daratumumab curves with an exponential model. From a methodological point of view, the application of an HR to an exponential model is appropriate, as long as the PH assumption holds. As reported in Section 5.5.5.1.1, the ERG considers that the PH assumption is not fully satisfied for OS data and therefore a constant HR should not be used to model this outcome. This problem is only emphasised by the fact that the company uses an exponential model (opposed to any other PH model) given the exponential model assumes that the baseline hazard is constant over time. This is a much stronger assumption than the PH assumption on its own as it assumes that the effect of daratumumab is constant over time. The ERG asked the company to justify the use of the exponential model, considering its strong underlying assumptions. The company replied that, *"the exponential curve was shown to have the best statistical fit and was deemed the most clinical plausible by a practicing haematologist, Kwee Yong, and was selected on this basis."* Clinical expert opinion sought by the ERG advised that the assumption of a constant treatment effect for daratumumab (and a constant relative treatment effect against the comparators) is not clinically plausible for rrMM. Considering the likely violation of PH in OS data and clinical expert opinion provided to the ERG, it follows that the use of an exponential model is not appropriate and likely to overestimate treatment effectiveness with daratumumab.

After assessing the PH assumption in OS data, the ERG undertook a curve fitting exercise with the digitised data in *R* statistical package. The ERG is extremely concerned with the fact that some of the OS fitted and extrapolated curves by the company differ considerably from the ones obtained by the ERG. In Table 65 the ERG reports the AIC and BIC statistics obtained by the ERG compared with the ones reported by the company. The ERG also reproduces the curves fitted by the company (Figure 39 and Figure 40) to aid the visual comparison of the curves fitted by the ERG (Figure 37 and Figure 38). While the lognormal and log-logistic curves seem to have a relatively similar positioning across the ERG estimated and company estimated curves, other curves, in particular the Gompertz and the gamma seem to be radically different. The AIC and BIC statistics estimated by the ERG suggest that the gamma, Gompertz and Weibull distributions would all be possible model candidates. All of these functions would be more flexible than the exponential distribution as they do not assume a constant baseline hazard. As the ERG's curve fitting exercise was carried as exploratory analysis, and there was insufficient time to fully validate the analysis undertaken, and the ERG did not use these curves in the company's model. The ERG would recommend an additional validation exercise of the curves, to be performed by the company, to explain the difference between the company and the ERG estimated survival curves.

Table 64. Overall survival HRs according to the number of characteristics adjusted for in MAIC

Comparison	Hazard ratios	95% confidence interval
11 characteristics adjusted for daratumumab vs pom+dex (company's base case)	1.742	(1.238; 2.457)
5 characteristics adjusted for daratumumab vs pano+bort+dex (company's base case)	1.186	(0.733; 1.919)
28 characteristics adjusted for daratumumab vs pom+dex (ERG's preferred approach)	1.136	(0.565; 2.273)
16 characteristics adjusted for daratumumab vs pom+dex 28 characteristics adjusted for daratumumab vs. pano+bort+dex (ERG's preferred approach)	1.639	(0.690; 4.000)

Table 65. Goodness-of-fit statistics for daratumumab integrated OS data (ERG estimation)

	Exponential	Weibull	Log-normal	Log-logistic	Generalised Gamma	Gompertz
AIC (company's estimates)	361.69	363.33	363.78	363.67	364.89	647.68*
BIC (company's estimates)	364.32	369.32	369.77	369.66	373.89	653.67*
AIC (ERG's estimates)	617.41	619.25	622.21	622.23	618.90	619.09
BIC (ERG's estimates)	620.41	625.25	628.21	628.23	627.90	625.09

AIC, Akaike information criterion; BIC, Bayesian information criterion;
*The company provided the AIC and BIC statistics on a different scale for the Gompertz distribution.

Figure 37. Survival curves derived by the ERG in *R* statistical package (180 months)

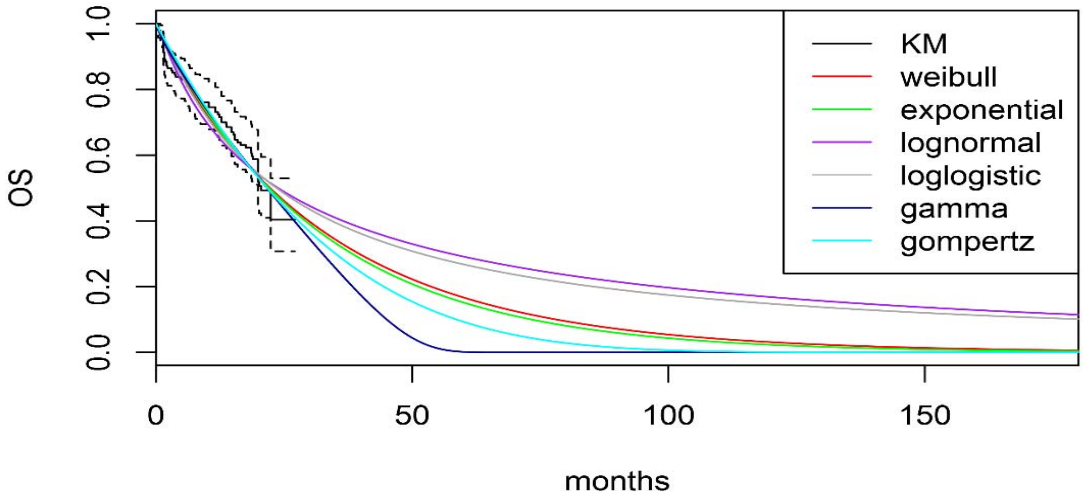


Figure 38. Survival curves derived by the ERG in *R* statistical package (30 months)

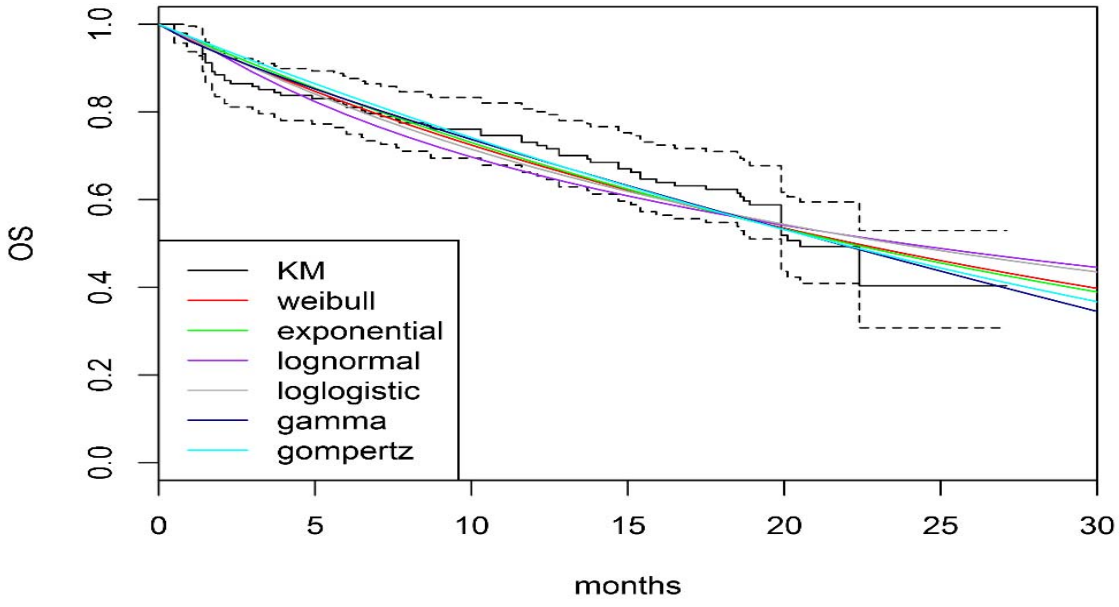


Figure 39. Parametric curves fit to OS data of the integrated MMY2002/GEN501 cohort (15 years time horizon)

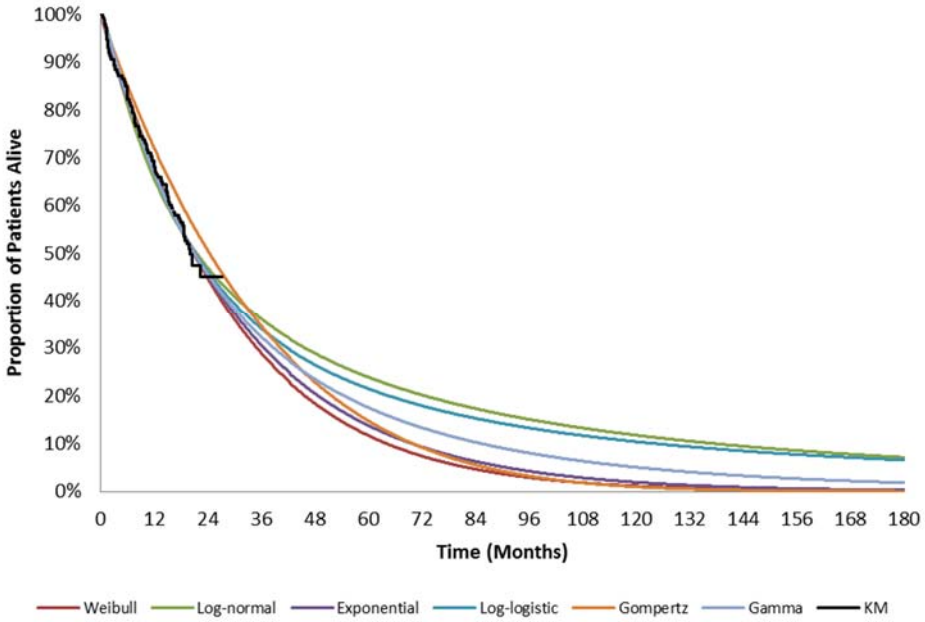
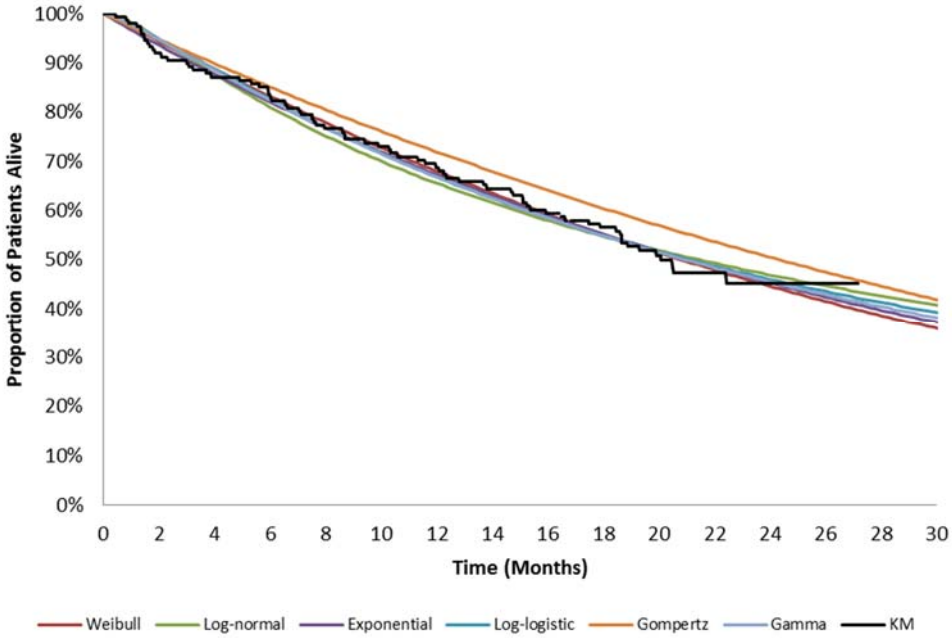


Figure 40. Parametric curves fit to OS data of the integrated MMY2002/ GEN501 cohort (30 months time horizon)



5.5.7.1.2 Independently fitted OS curves

The company included an option to fit OS curves independently in the model. The company used exponential models to fit the daratumumab MAIC-adjusted curve and the pom+dex and pano+bort+dex curves. Using an exponential distribution carries the same issues as the ones described in the previous

section. Even though the company fitted exponential curves for intervention and comparators separately this does not overcome the issue with the PH assumption. By fitting an exponential model to intervention and comparator, even if independently, there is still an underlying assumption of PH, given that the baseline hazard in an exponential model is constant thus making the ratio of the hazards constant as well.

As discussed in Section 5.5.5.1.2, the number of characteristics included in the MAIC adjustment drastically changes the positioning of the daratumumab OS adjusted KM curves in relation to pom+dex and to a smaller extent in relation to pano+bort+dex. In fact, the 28-characteristic adjusted OS curve for daratumumab shows a lower survival benefit with daratumumab compared with pom+dex before month 10, and a modest benefit after that point in time. This is a major departure from the 11-characteristic-adjusted OS curve, which crosses the pom+dex curve at month 4, to then show an impressive survival benefit compared with pom+dex. This represents an even bigger departure from the dependent fit approach where the daratumumab OS curve is consistently above the pom+dex OS curve. Conversely, the 5-characteristic-adjusted OS curve for daratumumab vs pano+bort+dex seems to underestimate the survival benefit for daratumumab when compared with the 16-characteristic-adjusted OS curve. This has crucial implications for the OS estimated curves and therefore the cost-effectiveness of daratumumab when compared with pom+dex.

Unfortunately, the fully adjusted KM curves were not used by the company to model daratumumab in the economic model. Therefore, the ERG cannot provide results for this approach. The anticipated impact of this shift in the OS curves is that by decreasing the survival benefit of daratumumab in comparison with pom+dex, the final ICER would increase, while the inverse would occur for the comparison of daratumumab against pano+bort+dex.

5.5.7.1.3 ERG's exploratory approach

Given that the ERG's preferred methodological approach is not available as a modelling option in the company's Excel model, the ERG proposes some exploratory analysis to assess the impact of using fully adjusted HRs in the company's base case approach. To note is that this approach carries all the flaws described before as it uses a dependent fit approach and fitted curves which may not be reliable. Nonetheless, it is a step in the right direction compared with the company's approach, as it uses the fully adjusted HRs. The ERG also changed the baseline curve used to model survival with daratumumab. Even though the ERG lacks confidence in the estimated curves, using the Weibull curve to model survival with daratumumab at baseline helps alleviate the strong assumption of constant hazard specific to the exponential curve and it is amongst the "best fitting curves" according to AIC and BIC statistics.

As the fully adjusted HRs obtained with the MAIC result from including only the MMY2002 dataset instead of the integrated one in the MAIC analysis, the ERG used the MMY2002 baseline daratumumab curves to apply the MAIC-adjusted HRs. The OS KM data for the individual trials (Figure 41) suggests that when changing the pooled population to the MMY2002 one, the OS outcomes for daratumumab patients are worse. This is expected, considering the worse prognosis of patients in MMY2002. The company also included the option to use the MMY2002 trial population instead of the integrated population in the economic model (with a dependent fit approach). The HRs for OS outcomes are reported in Table 66. It can be noted that both HRs for the comparison of daratumumab vs pom+dex and pano+bort+dex decreased, as would be expected considering the shift in the OS curves from the integrated population to MMY2002. To also note is that the ERG's preferred HRs (Table 66), also using the MMY2002 population, but adjusting for the maximum possible number of patients' characteristics lead to a further decrease in the HR for pom+dex but to a considerable increase in the pano+bort+dex HR. Equally noticeable, all the HRs for the company's analysis using the MMY2002 data and the using the ERG's preferred approach produce non-statically significant HRs against both comparators.

Figure 41. Overall survival KM data for daratumamab (integrated data, MMY2002 and GEN501)

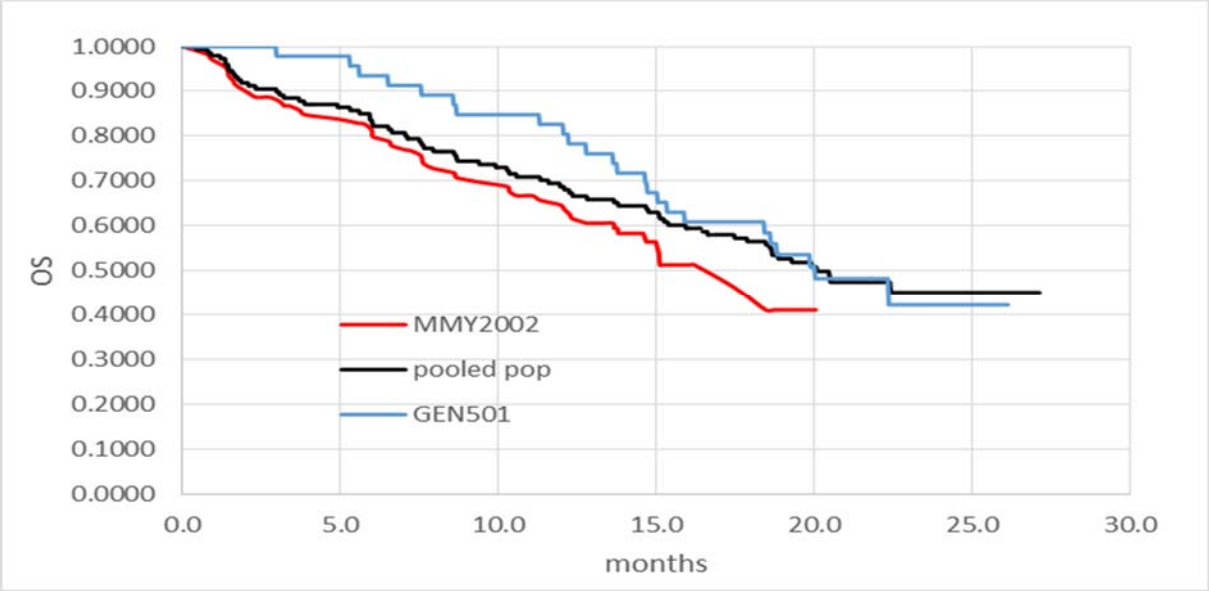


Table 66. Overall survival HRs according to different populations

Comparison	Hazard ratios	95% confidence interval
11 characteristics adjusted for daratumumab vs pom+dex (integrated population, company's base case)	1.742	(1.238; 2.457)
5 characteristics adjusted for daratumumab vs pano+bort+dex (integrated population, company's base case)	1.186	(0.733; 1.919)
11 characteristics adjusted for daratumumab vs pom+dex (MMY2002 population,	1.540	(0.964; 2.463)

company's scenario analysis)		
5 characteristics adjusted for daratumumab vs pano+bort+dex (MMY2002 population, company's scenario analysis)	1.089	(0.863; 1.802)
28 characteristics adjusted for daratumumab vs pom+dex (ERG's preferred approach)	1.136	(0.565; 2.273)
16 characteristics adjusted for daratumumab vs pano+bort+dex (ERG's preferred approach)	1.639	(0.690; 4.000)

The results of the ERG exploratory analysis are shown in Table 67 below. Figure 42 shows the impact of changing the daratumumab population from the integrated to the MMY2002 in the OS curves extrapolated with the exponential (company's base case) and the Weibull (ERG's exploratory analysis) curves. Figure 43 shows the daratumumab unadjusted, pom+dex and pano+bort+dex estimates curves with the fully adjusted PFS HR. Results in Table 61 show a great increase in the daratumumab vs pom+dex ICER (from £55,766 to £154,901) when the MMY2002 fully adjusted HR for OS is applied to the Weibull baseline daratumumab OS model. The ICER for daratumumab vs pano+bort+dex becomes dominant. Three forces play in the change of the ICERs. One is related with the change in the trial population (and therefore in the daratumumab baseline curve), the other is the use of the Weibull curve instead of the exponential for the baseline daratumumab OS curve, and finally the change in the HR used. The change in the trial population and in the type of survival mode used, cause a downwards shift in the OS daratumumab baseline curve (indicating a smaller survival benefit with daratumumab). The HRs for daratumumab vs pom+dex also decrease with the change in population and with the increase in the adjustment factors used to run the MAIC. Altogether, this combination leads to an increase in the final ICER comparing daratumumab with pom+dex. The HRs for daratumumab vs pano+bort+dex increase when the ERG's preferred approach is used, reflecting a gain in the survival benefit for daratumumab compared with pano+bort+dex. The ICER becomes dominant for daratumumab vs pano+bort+dex +dex with daratumumab generating more QALYs at a lower cost. This is related with the shift from the pooled population to MMY2002, as the HR for PFS in MMY2002 in the company's analysis shows that PFS for pano+bort+dex is higher than PFS for daratumumab, which leads to higher treatments costs for pano+bort+dex. This, in association with a loss of effectiveness in OS for the comparator treatment, leads to a dominant ICER for daratumumab.

Nonetheless considering the lack of statistical significance in the fully adjusted HRs (and in the MMY2002 company-adjusted HRs) the ERG also ran an exploratory analysis using a HR of 1 for OS for both treatments. The results of this analysis are reported in Section 6.

Table 67. ICERs resulting from fully adjusted OS HRs

Treatment	Total			Incremental			ICER (Dara vs comparator) at list prices	Base case ICERs
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Daratumumab	£71,506	1.08	2.06					
Pom+dex	£50,181	0.94	1.83	£21,325	0.14	0.23	£154,901	£55,766
Pano+bort+dex	£71,596	0.67	1.30	-£90	0.41	0.76	Daratumumab Dominates	£32,593

Figure 42. Overall survival curves for daratumumab (integrated and MMY2002 populations)

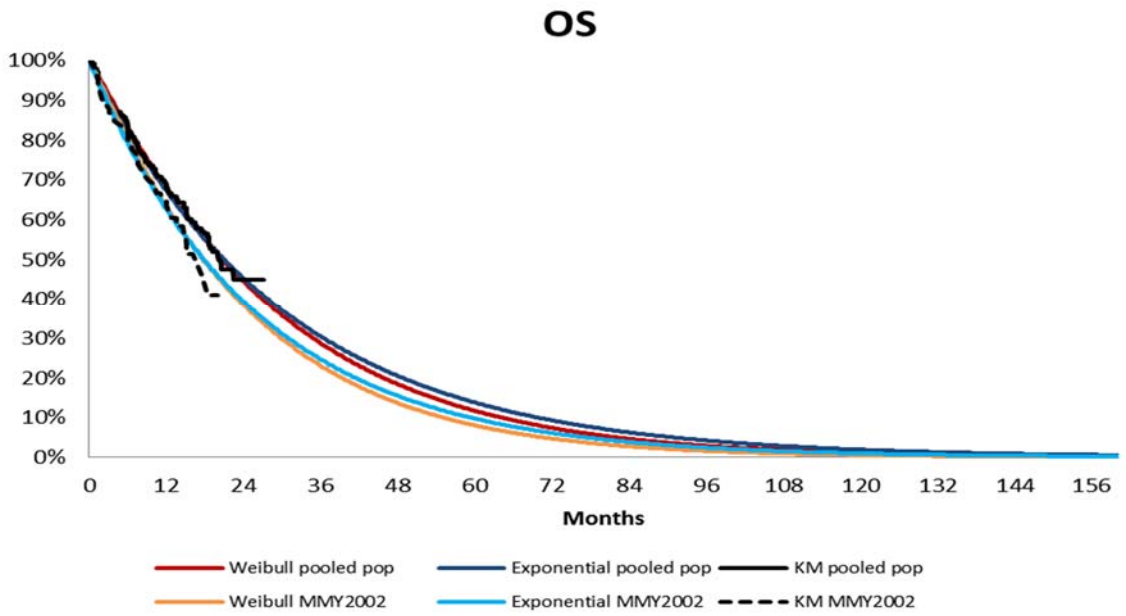
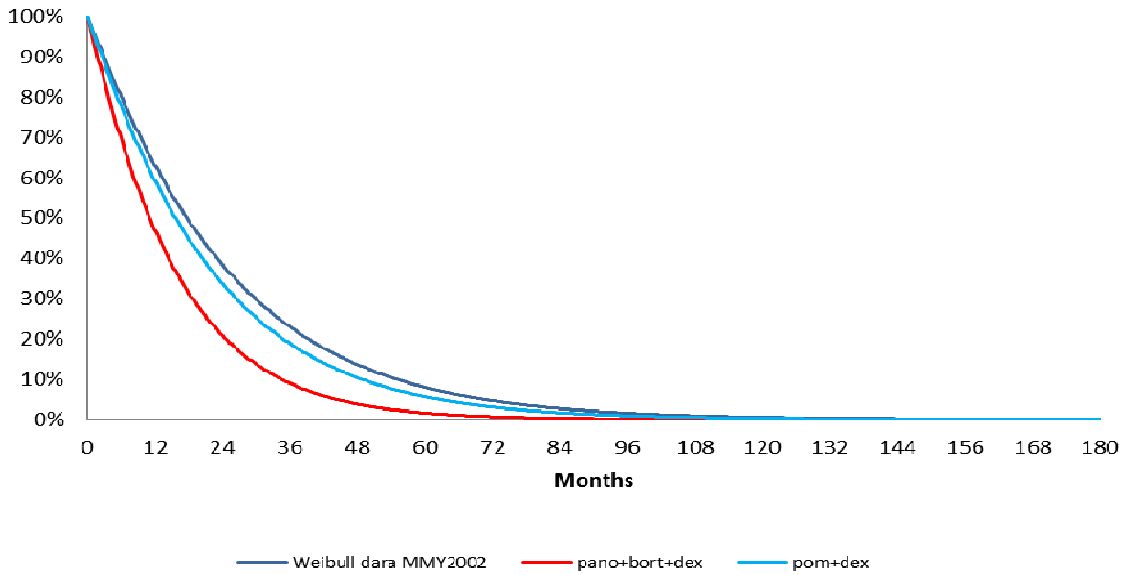


Figure 43. Overal survival curves for daratumumab, pom+dex and pano+bort+dex with fully adjusted HRs



In conclusion, the ERG has several issues with the estimation of OS in the company's model and with the uncertainty around the company's OS data. The ERG discusses three approaches for the estimation of OS: the company's base case approach (dependent fit); the company's alternative approach (independent fit) and the ERG's exploratory analysis. Regardless of the approach undertaken, the ERG considers that there is too much uncertainty around OS data and notes the lack of statistical significance in the fully adjusted HRs. With the objective of aiding the Committee's considerations of OS data, the ERG summarises the discussion around the three approaches to modelling OS in the model:

1. As reported in Section 5.5.5.1.1, the ERG considers that the PH assumption is not fully satisfied for OS data and therefore the company's modelling approach is flawed. This problem is only exacerbated by the fact that the company uses an exponential model as this implies that the daratumumab baseline hazard is constant over time. This is a much stronger assumption than the PH assumption as it assumes that the effect of daratumumab is constant over time. Clinical expert opinion sought by the ERG advised that the assumption of a constant treatment effect for daratumumab (and a constant relative treatment effect against the comparators) is not clinically plausible for rrMM. Considering the likely violation of PH in OS data and clinical expert opinion provided to the ERG, it follows that the use of an exponential model is not appropriate and likely to overestimate treatment effectiveness with daratumumab;

2. The ERG undertook a curve fitting exercise with the digitised data in *R* statistical package. The ERG is extremely concerned with the fact that some of the OS fitted extrapolated curves by the company differ very considerably from the ones obtained by the ERG, in particular the Gompertz and the gamma seem to be radically different. As the ERG's curve fitting exercise was carried as an exploratory analysis, and there was insufficient time to fully validate the curves, the ERG did not use these curves in the company's model. The ERG would recommend an additional validation exercise of the curves, to be performed by the company, to explain the difference between the company and the ERG estimated survival curves;

3. The company included an option to fit OS curves independently in the model. The models used to fit the daratumumab MAIC-adjusted curve and the pom+dex and pano+bort+dex curves were exponential models. Using an exponential distribution carries the same issues as the ones described for the company's base case approach. Even though the company fitted exponential curves for intervention and comparators separately this does not overcome the PH assumption issue. The number of characteristics included in the MAIC adjustment drastically changes the positioning of the daratumumab OS adjusted KM curves in relation to pom+dex and to a smaller extent in relation to pano+bort+dex. In fact, the 28-characteristc adjusted OS curve for

daratumumab shows a lower survival benefit with daratumumab compared with pom+dex before month 10, and a modest benefit after that point in time. This is a major departure from the 11-characteristic-adjusted OS curve, which crosses the pom+dex curve at month 4, to then show an impressive survival benefit compared with pom+dex. This represents an even bigger departure from the dependent fit approach where the daratumumab OS curve is consistently above the pom+dex OS curve. Conversely, the 5-characteristic-adjusted OS curve for daratumumab vs. pano+bort+dex seems to underestimate the survival benefit for daratumumab when compared with the 16-characteristic-adjusted OS curve. This has crucial implications for the OS estimated curves and therefore the cost-effectiveness of daratumumab when compared with pom+dex.

4. Given that the ERG's preferred methodological approach is not available as a modelling option in the company's Excel model, the ERG undertook some exploratory analysis to assess the impact of using fully adjusted HRs in the company's base case approach. To note is that this approach carries the majority of the flaws in the company's base case analysis. It uses a dependent fit approach and fitted curves which may not be reliable. Nonetheless, it is a step in the right direction compared with the company's approach, as it uses the fully adjusted HRs. The ERG also changed the baseline curve used to model survival with daratumumab. Even though the ERG lacks confidence in the estimated curves, using the Weibull curve to model survival with daratumumab at baseline helps alleviating the strong assumption of a constant hazard specific to the exponential curve. As the fully adjusted HRs obtained with the MAIC result from including only the MMY2002 dataset instead of the integrated one in the MAIC analysis, the ERG used the MMY2002 baseline daratumumab curves to apply the MAIC-adjusted HRs. The HRs for OS outcomes in the ERG's preferred HRs lead to a decrease in the HR for pom+dex but to a considerable increase in the pano+bort+dex HR. Equally noticeable, all the HRs using the ERG's preferred approach produce non-statically significant HRs against both comparators.

5. The results of the ERG exploratory analysis show a great increase in the daratumumab vs pom+dex ICER (from £55,766 to £154,901) when the MMY2002 fully adjusted HR for OS is applied to the Weibull baseline daratumumab OS model. The ICER for daratumumab vs pom+dex becomes dominant. Three forces play in the change of the ICERs. One is related with the change in the trial population (and therefore in the daratumumab baseline curve), the other is the use of the Weibull curve instead of the exponential for the baseline daratumumab OS curve, and finally the change in the HR used. The change in the trial population and in the type of survival model used cause a downwards shift in the OS daratumumab baseline curve (indicating a smaller survival benefit with daratumumab). The HRs for daratumumab vs

pom+dex also decrease with the change in population and with the increase in the adjustment factors used to run the MAIC. Altogether, this combination leads to an increase in the final ICER comparing daratumumab with pom+dex. The HRs for daratumumab vs pano+bort+dex increase when the ERG's preferred approach is used, reflecting a gain in the survival benefit for daratumumab compared with pano+bort+dex. The ICER becomes dominant for daratumumab vs pano+bort+dex with daratumumab generating more QALYs at a lower cost. Nonetheless considering the lack of statistical significance in the fully adjusted HRs (and in the MMY2002 company-adjusted HRs) the ERG ran an exploratory analysis using a HR of 1 for OS for both treatments. The results of this analysis are reported in Section 6.

5.5.7.2 Subsequent treatments received

Patients in MMY2002 and GEN501 could receive subsequent treatments after daratumumab. The company provided different sources with different data for the number of patients receiving subsequent therapies, which the ERG summarises below in Table 68. While the difference between the values reported in the CSRs and the CS/reply to ERG questions can be justified by more mature data, the ERG is not clear why the CS and the reply to the ERG's clarification questions report different values. The same is true for the values reported in Table 69, where the values reported in the CS and in the company's reply to the ERG clarification questions are different. The values reported in Table 69 reflect the total number of patients who received any of the subsequent treatments at any point after daratumumab, so these reflect fifth and further treatment lines. Table 70 reports the number of patients receiving treatment as the first subsequent therapy after daratumumab (first row of Table 70) and for further treatment lines, individually.

Table 68. Number of patients reported as receiving subsequent therapy in the daratumumab trials

	Clinical study report	**Company submission (Usmani *et al.* 2016)**	**Reply to ERG clarification question A6 and A9**
Data cut-off point	9 January 2015	31 December 2015	Not reported
MMY2002 daratumumab 16 mg/kg (n=106)	58 (55%)	75 (71%)	73 (69%)
GEN501 daratumumab 16 mg/kg (n=42)	22 (52%)	32 (76%)	31(74%)
Integrated daratumumab 16 mg/kg (n=148)	80 (54%)	107 (72%)	104 (70%)
MMY2002 daratumumab 8 mg/kg (n=18)	14 (78%)	Not reported	Not reported
GEN501 daratumumab 8 mg/kg (n=30)	25 (83%)	Not reported	Not reported
Integrated daratumumab 8 mg/kg (n=48)	39 (81%)	Not reported	Not reported
MMY2002 total (n=124)	72 (58.1%)	Not reported	Not reported
GEN501 total (n=72)	47 (65%)	Not reported	Not reported

Integrated total (n=196)	119 (61%)	Not reported	Not reported

Table 69. Type of susbsequent treatment reported by the company

Subsequent treatment	MMY2002 patients (n=106) (CS)	GEN501 patients (n=42) (CS)	Integrated (n=148) (CS)	Integrated (n=148) (Reply to ERG clarification question A6)
Patients undergoing subsequent treatment	75 (71%)	32 (76%)	107 (72%)	104 (70%)
Dexamethasone	60 (57%)	26 (62%)	86 (58%)	Not reported
Pomalidomide	34 (32%)	16 (38%)	50 (34%)	46 (31%)
Carfilzomib	31 (29%)	11 (26%)	42 (28%)	41 (28%)
Bortezomib	27 (26%)	9 (21%)	36 (24%)	36 (24%)
Lenalidomide	8 (8%)	15 (36%)	23 (16%)	22 (15%)

Table 70. Company reply to ERG clarification question A9, integrated data (time in months)

Subsequent treatment		Bort	Carf	Thal/len	Pom	Chemo	ASCT	Corticosteroids	Other	Total
1	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7	n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	min	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ASCT, Autologous stem cell transplant; BORT, bortezomib; CARF, carfilzomib; POM, pomalidomide.										

Even though the discrepancy in values between the CS and the company's reply to the ERG clarification questions is not large, this adds to the uncertainty around the company's data. The ERG decided to use the values provided by the company in their answer to the ERG's clarification questions.

The considerable difference between the estimated large survival benefit associated with daratumumab and the small (if any) gain in progression-free survival of daratumumab is likely to be related to the impact of subsequent treatments received on patients' survival. In fact, the company explains that one of the key advantages of daratumumab is that it provides patients with time to recover from the cumulative toxicity of previous treatments (through its favourable safety profile) thus allowing a higher proportion of patients to receive subsequent therapy. The company also adds that the novel mode of action of daratumumab, including immune-mediated mechanisms, increases the likelihood of patients' benefiting from subsequent therapy.

Clinical expert opinion sought by the ERG indicates that while it seems plausible that daratumumab's favourable safety profile allows patients to be able to tolerate further treatment lines, thus resulting in more patients being able to receive subsequent treatments, there is no data proving or indicating that daratumumab, "*increases the likelihood of patients benefiting from subsequent therapy"*. This means that while it would be plausible that daratumumab allows more patients to benefit from subsequent therapy (which in itself is a benefit) there is no evidence that it increases the effectiveness of the subsequent therapies given.

Interestingly, there is an inconsistency in the company's message with regards to daratumumab's advantage of allowing higher proportions of patients to receive subsequent therapy. On one hand, the company claims that the novel mode of action of daratumumab increases the likelihood of patients benefiting from subsequent therapy pointing to the fact that, *"of the 148 patients treated with daratumumab 16mg/kg monotherapy in the MMY2002/GEN501 cohort, 72% went on to receive subsequent therapy compared with 39% of the 302 patients randomised to POM+DEX in MM-003"*. On the other hand, the company also states that, *"clinical opinion suggested that…this figure* [72%] *is high compared to what is seen in clinical practice…* [and that] *the proportion of patients who receive subsequent therapy after daratumumab is 55%*". The company also assumed that the proportion for patients receiving subsequent therapy after pano+bort+dex is 55% in the model, making it equally likely for pano+bort+dex and daratumumab patients to receive subsequent therapy.

The ERG asked the company to provide OS estimates, together with KM data, for the different subgroups of patients receiving the following subsequent treatments:

- Bortezomib;
- Carfilzomib;
- Lenalidomide;
- Pomalidomide;
- No subsequent treatment at all.

The company replied with the OS estimates reported in Table 71 These compare with a median integrated OS for daratumumab of 20.1 months (CI; 16.6; not reached). To note is that the median OS for daratumumab includes the effect of patients receiving further treatment lines. It can also be noted that the median OS for patients receiving no subsequent treatment and patients receiving any subsequent treatment in MMY2002 is [redacted] (with the caveat that there is no HR provided or analysis of statistical significance). An important fact is that subsequent treatment could include other treatments such as autologous stem cell transplant (see Table 70). Figure 44 shows the KM curves produced by the ERG with the data provided by the company on OS for patients receiving subsequent treatments for rrMM after daratumumab. The KM data sent by the company were mislabelled for every treatment, with each KM dataset corresponding to the wrong treatment. The ERG noticed the problem as the estimates in Table 71 did not match the KM plot. It would also appear that the company failed to provide the KM data for patients subsequently treated with pomalidomide as requested by the ERG. Again, this adds to the uncertainty around the data provided by the company and thus to the ERG's analysis, as there is a general lack of confidence that the data used is indeed the correct data.

Figure 44 suggests that patients receiving subsequent treatments do considerably better in terms of survival than patients receiving no subsequent treatments after daratumumab. This seems to be true, despite the fact that patients moving on to subsequent therapies will be in a more advanced stage of their disease, with the KM curves for subsequent therapies including up to seven lines of subsequent therapy (see Table 70). The only exception to this seems to be the bortezomib KM curve which shows the deterioration of patients' survival with the passing of time. It is difficult to predict where the pomalidomide curve would appear in the graph, but it is known that the median survival is [redacted] (showing all patients who received any subsequent treatment, which could include treatments beyond the ones portrayed here). Patients receiving carfilzomib and lenalidomide seem to do extremely well compared with other patients. These data (assuming they accurately reflect the studies) warrant further discussion of the

availability of the subsequent treatments received in MMY2002 and GEN501 in the NHS. This is explored in the next subsection of the report.

Table 71. Estimates of OS from post-hoc subgroup analysis

Dataset	Subgroup	Median OS (95% CI)	Sample size
Integrated	Bortezomib as a subsequent treatment	[redacted]	[redacted]
	Carfilzomib as a subsequent treatment	[redacted]	[redacted]
	Lenalidomide as a subsequent treatment	[redacted]	[redacted]
	Pomalidomide as a subsequent treatment.	[redacted]	[redacted]
MMY2002	No subsequent treatment	[redacted]	[redacted]
	Any subsequent treatment.	[redacted]	[redacted]
GEN501	No subsequent treatment	[redacted]	[redacted]
	Any subsequent treatment.	[redacted]	[redacted]

Key: CI, confidence interval; NE, not evaluable; OS, overall survival.

[redacted]

[redacted]

5.5.7.2.1 Availability of the subsequent treatments received in MMY2002 and GEN501 in the NHS

Around 72% of the population in MMY2002/GEN501 received further treatment after daratumumab for rrMM. Considering that daratumumab is being positioned by the company as a fourth line treatment option, there would not be many options for subsequent treatments available for these patients in the NHS. Daratumumab patients received subsequent carfilzomib (28%), lenalidomide (15%), bortezomib (24%) and pomalidomide (31%), among other treatments. As demonstrated above, these treatments are likely to have a great impact on daratumumab's OS, despite being received at a later point in time. Therefore, the possibility of patients receiving this combination of subsequent treatments in the UK needs to be considered.

At its first Committee meeting carfilzomib did not get recommended by NICE. However a final appraisal determination has not been issued yet therefore it is unknown whether it will be made available in the NHS as an rrMM treatment.[139] Lenalidomide is not recommended by NICE as a retreatment option, and given that patients in the UK receive lenalidomide as a third line treatment, they could not be retreated with lenalidomide after daratumumab (note that nearly 100% of patients in the daratumumab trials had been pre-treated with lenalidomide).[71] The same is true for bortezomib, where retreatment with bortezomib alone is not recommended by NICE. In fact, the ERG's clinical experts explained that the main reason for patients being treated with pano+bort+dex is to expose patients to bortezomib for the second time (given that monotherapy is not recommended as a retreatment option).

Therefore, pomalidomide is the only treatment used in the MMY2002/GEN501 trials that is recommended by NICE as a possible subsequent treatment post-daratumumab.[85] Unfortunately the OS KM curve for pomalidomide subsequent treatment was not sent by the company to the ERG. The only information available from Table 71 is that [redacted] Considering that 72% of daratumumab patients received several non-NICE approved subsequent treatments with potentially a large impact on the daratumumab estimate of OS, the ERG considers that the true effectiveness of daratumumab monotherapy alone is likely to be greatly overestimated in the economic analysis.

In conclusion, the ERG is concerned with the highly confounded OS estimates in the company analysis. The ERG considers that the evidence put forward by the company is not robust enough to determine the cost-effectiveness of daratumumab monotherapy alone. To determine this, we would need to be able to disentangle further (if not completely) the estimate of OS for daratumumab alone vs daratumumab followed by other treatments. Similarly, if we are to consider the cost-effectiveness of daratumumab monotherapy followed by subsequent rrMM therapies, then the effectiveness of daratumumab needs adjusting for the impact of subsequent therapies which are not available in the UK. This is particularly important in this case given the lack of RCT data for daratumumab. While in theory this might also be true for the comparator treatments, as pom+dex and pano+bort+dex patients could receive subsequent therapies in MM-003 and PANORAMA2, respectively, the ERG's investigation shows that the risk of OS confounding for pom+dex patients is likely to be considerably smaller than for daratumumab patients. This is because 72% of patients in MMY2002/GEN501 received subsequent therapies, while the corresponding estimate for MM-003 is 44%. However more importantly, in MM-003 patients received carfilzomib, lenalidomide and bortezomib in much smaller numbers than in MMY2002/GEN501 (2% vs 28% for carfilzomib; 5% vs 15% for lenalidomide and 18% vs 24% for bortezomib). Daratumumab patients also received pomalidomide (31%) while pom+dex patients did

not receive any pomalidomide (or daratumumab) after the main treatment in MM-003. [85, 140]As discussed in this section treatment with carfilzomib and retreatment with lenalidomide and bortezomib are not only not available in the UK but also likely to increase overall survival considerably as subsequent therapies for rrMM patients.

5.5.8 Health-related quality of life

The HSUVs used in the model are based on EQ-5D data collected in the MM-003 trial which assesses the effectiveness of pomalidomide in patients with rrMM.[82, 117] The trial population in MM-003 was restricted to patients who had received at least two previous lines of therapy, including lenalidomide and bortezomib. The baseline characteristics of patients in the MM-003 trial are similar to those in the MMY2002 trial in terms of prognostic factors as described in Section 4 (i.e. number of previous treatments received, proportion of patients refractory to lenalidomide and bortezomib, ISS and ECOG scores).The two trials are also well matched in age, median time since diagnosis. [53, 82]

The methods used to analyse the EQ-5D data from MM-003 trial reported in Palumbo *et al.* seem appropriate, however the details of the analysis are insufficiently reported as the source is a poster presentation.[117] Patients in the model are assumed to experience a HSUV of 0.61 prior to progression and 0.57 after progression.

The ERG identified a more recent full publication by Song *et al.* reporting details of the longitudinal analysis of EQ-5D data from MM-003 using a mixed-effects model. According to Song *et al.* the quality of life of patients in the pom+loDEX arm of the MM-003 trial was statistically significantly better (p=0.05) compared to patients in the HiDEX arm in the first 10 treatment cycles. The analysis did not cover the period beyond 10 cycles due to a small sample size.[141] The ERG notes that the utility values of 0.61 prior to progression and 0.57 after progression reported in Palumbo *et al.* are for the whole dataset and not analysed separately by treatment arm, and are therefore confounded by the poorer quality of life experienced by patients receiving high doses of dexamethasone without pomalidomide. Thus, the utility estimates used in the base case analysis are likely to be an underestimate of patients' quality of life. However, the company applies the utility values from TA338 in a scenario analysis reported in Section 5.6.2.1.

The company also reports utility values based on EQ-5D data collected as part of an Early Access Programme (EAP) for daratumumab, and valued using the UK EQ-5D-5L dataset. The company reports that these values are based on EQ-5D data collected from 140 patients with similar characteristics to the GEN501 and MMY2002 trials in the European component of the EAP. The mean utility values at baseline and last assessment are 0.63 and 0.58, respectively which are similar to the values used in the base case analysis.

The utility decrements applied for different AEs are not based on the same population across treatment arms, therefore differences in population baseline characteristics across the different sources may bias the results. More importantly, the HSUVs used by the company to estimate the utility values associated with the PFS and PD sates, implicitly incorporate the impact of the AEs associated with pom+dex on patients' QoL in MM-003. Therefore, the company's approach double-counts the impact of chronic AEs related with pom+dex in the model.

This approach also partly double-counts the impact of chronic AEs related with other treatments. Given that the pom+dex population can be seen as the baseline population for the estimation of AE-related disutilities (as the utility experienced in the PFS and PD states is derived from the MM-003 population), the impact of AEs related with daratumumab and pano+bort+dex will be under or overestimated depending on how much higher or lower the incidence of the specific AE is, for both treatments in each trial, respectively. For example, the incidence of nausea in MM-003 is 15% while the equivalent estimate for daratumumab is 6% and 60% for pano+bort+dex (Table 33). Given that the utility value associated with the PFS and PD sates is taken from MM-003, these values implicitly assume that 15% of patients experience nausea. The consequences of this approach are then two-fold: when the company applies an additional disutility value associated with nausea for pom+dex, the impact of this AE is being double-counted for this treatment; this approach also overestimates the incidence of nausea related with daratumumab (which is lower than that observed with pom+dex) and overestimates the incidence of nausea for pano+bort+dex given that the incidence of this AE is only higher by 45% compared with pom+dex (60%-15%=45%) and not by 60%. The correction of this double-counting effect is not an easy one as regression analysis would have to be undertaken to isolate the impact of disease progression in patients QoL from specific AEs. Furthermore, the company did not collect QoL data for daratumumab and so different utility values for all the different treatments are not available. Therefore, the ERG took a conservative approach and removed the disutility estimates from the company analysis. This implicitly assumes that all drugs have a similar safety profile, which is likely to underestimate the benefit of daratumumab given its advantageous safety profile. Despite its limitations, this approach is less flawed than double-counting and overestimating the impact of AEs on patients' QoL. The results of this analysis are reported in Table 72.

The ERG has also found mistakes in the implementation of the disutility values related with AEs in the economic model as the aggregated disutility value for the safety profile of pano+bort+dex was being applied to bendamustine and pom+dex. The ERG corrected this error and presents the results in Section 6.1. Furthermore, when estimating the aggregated disutility attributed to adverse events, the values associated with some of the adverse events (septic shock, syncope, peripheral neuropathy, and sepsis) were incorrectly applied as positive values (i.e. utilities and not disutilities) in the model. The company corrected this error at clarification stage.

Table 72. ICERs resulting when disutilities associated with adverse events are removed

Treatment	Total			Incremental			ICER (Dara vs comparator) at list prices	Base case ICERs
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Daratumumab	£81,422	1.36	2.54					
Pom+dex	£49,921	0.81	1.46	£31,501	0.54	1.07	£58,144	£55,766
Pano+bort+dex	£74,530	1.17	2.14	£6,892	0.19	0.39	£36,590	£32,593

5.5.9 Resources and costs

Resource use in the model is estimated based on values reported in TA338.[133] Unit costs are based on NHS Reference costs and PSSRU costs, in line with the NICE reference case. [96]

5.5.9.1 Pharmacological costs

The company has considered the following pharmacological costs which are reported in Section 5.4.6.2 of the ERG report:

- Treatment acquisition costs, summarised in Table 43, together with dosage assumptions and specific treatment duration, summarised in Table 42;
- Treatment administration costs as summarised in Table 44;
- Concomitant medication costs (Table 47) and dosage assumptions as reported in Table 45.

The company incorrectly describes the dosage schedule for bortezomib used in the model in the CS, stating that bortezomib (with panobinostat) is administered on days 1 and 8 in the first eight cycles and on days 1,2,8 and 9 for cycles 8 to 16. However, in the model the dosage schedule assumed is days 1, 4, 8 and 11 in the first eight cycles and on days 1 and 8 in the second eight cycles which is in line with the recommended dosage by European Medicines Agency. [127]

The ERG's clinical experts explained that assuming all patients receive 40mg of dexamethasone when taken with pomalidomide is unlikely to reflect clinical practice as patients usually range between 10mg to 40mg doses. The ERG notes that the dose assumed by the company is in line with the recommended dose in the EMA EPAR for pomalidomide but explores the impact of assuming 22.3mg as per the mean weekly dose of dexamethasone received in the MM-003 trial, and assumed in TA338. The ICER of daratumumab compared to pom+dex increases by £238 per QALY compared to the company's base case.

The company assumed that panobinostat could be received for a maximum of 16 cycles or until progression. Clinical expert opinion sought by the ERG indicates that patients can rarely tolerate 16 cycles of panobinostat, so the cost of the treatment is likely to be overestimated in the economic model.

The concomitant treatments included by the company are generally appropriate according to the ERG's clinical experts. However, one expert stated that the proportion of pom+dex patients who require red blood cell and platelet transfusions should be the same as the proportion of daratumumab patients receiving these treatments. The ERG explored the impact of changing the proportions of RBC and platelet transfusions in the pom+dex arm to 30% and 10% respectively and found the ICER for daratumumab compared to pom+dex increased by £290 per QALY gained compared to the company's base case.

5.5.9.2 Disease management costs

The company estimated resource use in the model based on the estimates reported in TA338.[133]According to the ERG's clinical experts' opinion blood tests and biochemistry frequency should overlap with physician visits. Therefore, it would be more appropriate to consider monthly physician visits, blood tests and biochemistry for progression-free patients on treatment. Progression-free patients off treatments should have physician visits, blood tests and biochemistry every three months.

Clinical expert opinion sought by the ERG also indicated that patients receiving subsequent treatment after progression should have monthly physician visits and blood tests (and not every 3 months and every 3 weeks, respectively, as assumed by the company). The ERG's clinical experts also stated that patients who progress and receive BSC also have monthly blood tests and physician visits. The ERG carried out an exploratory analysis to assess the impact of changing resource use to reflect feedback from clinical experts (Table 73) and the results are presented in Table 74. The ICERs for daratumumab compared to pom+dex and pano+bort+dex increase by £1,950 and £2,409 per QALY gained, respectively.

Table 73. Resource use assumption based on ERG's clinical experts

Health state	Resource	Frequency per week	Source
PFS (on treatment)	Physician visit	0.23	NICE TA338[133], clinical expert opinion given to the ERG
	Complete blood count test	0.23	
	Biochemistry	0.23	
PFS (off treatment)	Physician visit	0.08	
	Complete blood count test	0.08	
	Biochemistry	0.08	
PPS, subsequent active treatment	Physician visit	0.23	
	Complete blood count test	0.23	
	Biochemistry	0.23	
PPS, BSC	Physician visit	0.23	
	Complete blood count test	0.23	
	Biochemistry	0.23	

Abbreviations in table: BSC, best supportive care; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; PPS; post-progression survival; TA, Technology Appraisal.

Table 74. ICERs reflecting feedback from ERG's clinical experts

Treatment	Total			Incremental			ICER (Dara vs comparator) at list prices	Base case ICERs
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Daratumumab	£83,445	1.31	2.54					
Pom+dex	£50,997	0.75	1.46	£32,448	0.56	1.07	£57,442	£55,766
Pano+bort+dex	£76,034	1.10	2.14	£7,411	0.21	0.39	£35,045	£32,593

5.5.9.3 Subsequent therapy costs

As explained in Section 5.4.6.5, the company adjusted the distribution of subsequent therapies received by patients in the pivotal trials in order to reflect the currently available treatment options in the UK. Therefore, the costing exercise does not reflect the clinical effectiveness associated with the treatments modelled in the economic analysis.

While the ERG acknowledges the value in portraying the treatment pathway currently available in the UK, the assumptions made by the company (Table 76) were not justified in a transparent way and were considered clinically implausible by the ERG's clinical experts. The company assumes that 10% of patients in the bendamustine-based therapy arm receive bendamustine as a subsequent therapy. This is implausible as patients are unlikely to be retreated with the same treatment received in the previous line of therapy. Also a proportion of patients go on to receive bortezomib after pano+bort+dex which is a bortezomib containing treatment combination, while no patients receive bortezomib after daratumumab.

Furthermore, despite not all patients in the trials went on to receive active treatments after discontinuing treatment this is not reflected in the model as there is no option to proceed to BSC directly after stopping treatment. The company also assumed that 55% of patients (instead of 72%) receive subsequent therapy after daratumumab as clinical expert opinion provided to the company considered that 55% of patients would be a better reflection of clinical reality. In order to reflect this the company multiplied 55% by the proportion of patients receiving the specific subsequent treatment in the overall trial (reported in Table 51 in the ERG report). This is incorrect as the proportion of patients receiving each specific subsequent therapy reported in Table 51 takes the overall trial population as the base. To exemplify this issue, the company took the 44% of patients receiving dexamethasone in the overall trial population as a subsequent treatment (Table 51) and multiplied it by 55%, thus obtaining 24% (Table 76). However, the correct approach would have been to use the proportion of patients receiving dexamethasone within the group of patients receiving subsequent treatments and then multiply this value by 55%. The ERG

corrected this (and the equivalent issue for pom+dex and pano+bort+dex) in the model and presents the results in Section 6.

Furthermore, the CS states that the integrated MMY2002/GEN501 data were used to derive the proportion of patients receiving each type of subsequent therapy. However, this is not the case, as only the MMY2002 values were considered (CS, page 220, Table 72). The ERG corrected this to reflect the values reported in the integrated dataset and reports the results in Section 6. The proportion of patients assumed to receive subsequent therapy after pano+bort+dex was considered to be the same as the proportion of patients receiving subsequent therapy after daratumumab (55%) by the company's clinical experts. This is surprising, considering the company's rationale for daratumumab being able to bridge more patients to further treatments than other rrMM treatments.

The ERG also found a mistake in the estimation of drug acquisition costs in the model. The acquisition cost for subsequent treatments used by the company was based on the price per pack (and did not consider treatment duration, dose or number of cycles received). This means that for example, the drug acquisition cost for dexamethasone was considered to be £50 (which is the price per pack) instead of £450, the company estimated acquisition cost for dexamethasone, when treatment duration, dose and number of cycles are considered. The ERG corrected this in the model and reports the results in Section 6.

In order to link the treatments costs to the corresponding measures of effectiveness for the different treatments, the ERG has conducted exploratory analysis to reflect the distribution of subsequent therapies received in the daratumumab trials (Table 75) and in the pom+dex trial as far as evidence allowed. According to the updated TA for pom+dex, the proportion of patients receiving subsequent treatment after pom+dex in MM-003 was 44% (cut-off point September 2013). To note is that at the time of this submission, the only publicly available data was the cut-off point March 2013, which reported a percentage of 39% receiving subsequent treatment after pom+dex. The ERG also investigated which treatments were received by patients in MM-003 after pom+dex. These are reported in Table 75. [85, 140] The ERG could not find any data from PANORAMA2 on subsequent therapies received after treatment with pano+bort+dex. Results of the ERG's analyses are reported in Table 78. To note is that the company's model did not consider subsequent treatment costs with lenalidomide or thalidomide. Therefore, the ERG could not use the proportions indicated in Table 75 for these drugs as to do so would also imply undertaking a costing exercise, for which the ERG did not have sufficient time.

The ERG consulted with clinical experts to try to understand what would be the expected distribution of subsequent therapies received in the UK. The results are reported in Table 77. The company's model did not include pomalidomide and cyclophosphamide in combination with dexamethasone as a subsequent treatment, neither did it include pano+bort+dex. Therefore, in order to utilise the available

options for modelling subsequent treatments in the model the ERG had to make some assumptions. Pomalidomide and cyclophosphamide were costed as monotherapy regimens instead of combined with dexamethasone and patients receiving pano+bort+dex were assumed to receive bortezomib monotherapy. The dosage assumptions in the model for pomalidomide, bortezomib and dexamethasone are the same regardless treatment line (i.e. fourth line or subsequent therapy) with the dose of dexamethasone assumed to be 40 mg. This approach is underestimates the costs of subsequent therapies, as it assumes that combination regimens are costed as monotherapy regimens to facilitate the implementation of the scenario analysis in the model. Best supportive care was assumed to be associated with no treatment costs. Results of the ERG's analyses are reported in Table 79.

Table 75. Subsequent therapies received in the different trials

Subsequent treatment	Proportion of MMY2002/GEN501 patients	Proportion of MM-003 patients[85, 140]
Dexamethasone	58%	29%
Pomalidomide	31%	0%
Cyclophosphamide	32%	21%
Carfilzomib	28%	**2%**
Bortezomib	24%	18%
Lenalidomide	15%	**5%**
Melphalan	16%	**8%**
Etoposide	10%	**3%**
Bendamustine	14%	11%
Thalidomide	7%	**7%**

Values in bold are from a cut-off date of March 2013 while the other values are from a more up to date cut-off point of September 2013

Table 76. Subsequent therapies modelled by the company

Subsequent treatment	Daratumumab	Pano+bort+dex	Bendamustine-based therapy	Pom+dex
Dexamethasone	24%	14%	10%	10%
Pomalidomide	0%	0%	0%	0%
Cyclophosphamide	13%	9%	7%	7%
Carfilzomib	0%	0%	0%	0%
Bortezomib	0%	8%	6%	6%
Melphalan	9%	0%	0%	0%
Etoposide	6%	0%	0%	0%
Bendamustine	0%	6%	4%	4%

Abbreviations in table: bort, bortezomib; dex, dexamethasone; pano, panobinostat; pom, pomalidomide

Table 77. Subsequent therapies modelled by the ERG to reflect UK clinical practice

Subsequent treatment	Daratumumab	Pano+bort+dex	Bendamustine-based therapy	Pom+dex
Pom+dex	45%	48%	38%	0%
Pano+bort+dex	25%	0%	19%	21%

BSC	10%	32%	19%	42%
Dexamethasone	15%	16%	19%	21%
Cyclo+dex	5%	8%	10%	11%
Abbreviations in table: bort, bortezomib; dex, dexamethasone; pano, panobinostat; pom, pomalidomide				

Table 78. ICERs reflecting subsequent treapies received in daratumumab and pom+dex trials

Treatment	Total			Incremental			ICER (Dara vs comparator) at list prices	Base case ICERs
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Daratumumab	£84,590	1.31	2.54					
Pom+dex	£50,416	0.75	1.46	£34,175	0.56	1.07	£60,498	£55,766
Pano+bort+dex	£74,949	1.10	2.14	£9,641	0.21	0.39	£45,592	£32,593

Table 79. ICERs reflecting feedback from ERG's clinical experts on subsequent therapies.

Treatment	Total			Incremental			ICER (Dara vs comparator) at list prices	Base case ICERs
	Costs	QALYs	LYs	Costs	QALYs	LYs		
Daratumumab	£83,878	1.31	2.54					
Pom+dex	£50,215	0.75	1.46	£33,663	0.56	1.07	£59,592	£55,766
Pano+bort+dex	£76,059	1.10	2.14	£7,819	0.21	0.39	£36,975	£32,593

5.6 Results included in company's submission

Due to mistakes or discrepancies identified before and during the clarification process, the company provided two versions of the written submissions of the economic evidence along with three electronic versions of the Microsoft Excel based economic model. The results presented in this section are based on the addendum to the updated CS (which reported the updated cost-effectiveness results) and the third version of the economic model.

5.6.1 Base case results

The results of the pair-wise comparison of daratumumab with pom+dex, pano+bort+dex and bendamustine-based therapy are presented in Table 80. According to the company's base case analysis daratumumab is expected to increase patients' life expectancy by approximately 17 months, 13 months and 5 months compared to bendamustine-based therapy, pom+dex and pano+bort+dex, respectively. The ICER comparing daratumumab with pom+dex, pano+bort+dex and bendamustine is £55,766, £32,593 and £56,574 per QALY gained, respectively.

Table 80. Pairwise base case results from the company's updated model (CS, Addendum to company evidence submission, Table 2)

Treatment	Total			Incremental			ICER (Dara vs comparator) at list prices
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Daratumumab	£81,422	1.31	2.54				
Pom+dex	£49,921	0.75	1.46	£31,501	0.56	1.07	£55,766
Pano+bort+dex	£74,530	1.10	2.14	£6,892	0.21	0.39	£32,593
Bendamustine-based therapy	£38,327	0.55	1.10	£43,095	0.76	1.44	£56,574

Abbreviations in table: bort, bortezomib; dex, dexamethasone; dara, daratumumab; year; ICER, incremental cost-effectiveness ratio; LY, life year; pano, panobinostat; pom, pomalidomide; QALY, quality-adjusted life year.

The breakdown of life-years and QALYs accumulated in the model according to health state are presented in Table 81 and Table 82, respectively. A summary of costs disaggregated by cost category is presented in Table 83 which shows that more than 85% of the total costs are attributed to treatment-related costs (i.e. treatment acquisition and administration). A summary of costs according to health states is presented in Table 84 .

Table 81. Disaggregated LYs by health state, from company's updated model (CS, Addendum to company evidence submission, Table 6)

Health state	Daratumumab (1)	Pom+dex (2)	Pano+bort+dex (3)	Bendamustine-based therapy (4)	Increment (% increment)		
					1 vs 2	1 vs 3	1 vs 4
Pre-progression On treatment	0.67	0.38	0.78	0.36	0.29 (23%)	-0.11 (18%)	0.31 (22%)
Pre-progression Off treatment	0.05	0.15	0.03	0.00	-0.10 (8%)	0.02 (3%)	0.05 (4%)
Post-progression	1.82	0.93	1.33	0.74	0.88 (69%)	0.49 (79%)	1.08 (75%)
Total LYs	**2.54**	**1.46**	**2.14**	**1.10**	**1.07 (100%)**	**0.39 (100%)**	**1.44 (100%)**

Abbreviations in table: bort, bortezomib; dex, dexamethasone; dara, daratumumab; ICER, incremental cost-effectiveness ratio; LY, life year; pano, panobinostat; pom, pomalidomide.

Table 82. Disaggregated QALYs by health state, from company's updated model (CS, Addendum to company evidence submission, Table 5)

Health state	Daratumumab (1)	Pom+dex (2)	Pano+bort+dex (3)	Bendamustine-based therapy (4)	Absolute increment (% increment)		
					1 vs 2	1 vs 3	1 vs 4
Pre-progression On treatment	0.39	0.23	0.46	0.22	0.16 (24%)	-0.07 (20%)	0.18 (23%)
Pre-progression Off treatment	0.03	0.09	0.02	0.00	-0.06 (8 %)	0.01 (4%)	0.03 (4%)
Post-progression	0.93	0.50	0.69	0.40	0.44 (64 %)	0.24 (71%)	0.53 (70 %)
AE	-0.04	-0.07	-0.07	-0.07	0.02 (3 %)	0.02 (4%)	0.02 (3 %)
Total QALYs	**1.31**	**0.75**	**1.10**	**0.55**	**0.56 (100%)**	**0.21 (100%)**	**0.76 (100%)**

Abbreviations in table: bort, bortezomib; dex, dexamethasone; dara, daratumumab; ICER, incremental cost-effectiveness ratio; pano, panobinostat; pom, pomalidomide; QALY, quality-adjusted life year.

Table 83. Disaggregated costs by cost category, from company's updated model (CS, Addendum to company evidence submission, Table 3)

Cost component	Daratumumab (1)	Pom+dex (2)	Pano+bort+dex (3)	Bendamustine-based therapy (4)	Increment (% absolute increment)		
					1 vs 2	1 vs 3	1 vs 4
Drug costs	£70,905	£44,590	£60,532	£30,853	£26,315 (76%)	£10,373 (71%)	£40,052 (87%)
Admin Costs	£5,836	£191	£7,398	£2,742	£5,645 (16%)	-£1,561 (11%)	£3,094 (7%)
Co-medication costs	£239	£392	£272	£223	-£153 (0%)	-£33 (0%)	£16 (0%)
Adverse Events	£941	£2,236	£2,835	£2,248	-£1,294 (4%)	-£1,894 (13%)	-£1,307 (3%)
Pre-progression Monitoring costs on treatment	£1,272	£741	£1,490	£704	£531 (2%)	-£218 (1%)	£569 (1%)
Pre-progression Monitoring costs off treatment	£35	£104	£18	£0	-£68 (0%)	£18 (0%)	£35 (0%)
Subsequent treatment costs	£9	£43	£60	£45	-£34 (0%)	-£52 (0%)	-£37 (0%)
Subsequent treatment Admin costs	£162	£151	£211	£159	£12 (0%)	-£48 (0%)	£4 (0%)
Post-progression Monitoring	£1,239	£661	£920	£532	£578 (2%)	£319 (2%)	£707 (2%)
Terminal Care	£782	£812	£793	£822	-£30 (0%)	-£11 (0%)	-£40 (0%)
Total	**£81,422**	**£49,921**	**£74,530**	**£38,327**	**£31,501 (100%)**	**£6,892 (100%)**	**£43,095 (100%)**

Abbreviations in table: bort, bortezomib; dex, dexamethasone; dara, daratumumab; pano, panobinostat; pom, pomalidomide.

Table 84. Disaggregated costs by health state, from company's updated model (CS, Addendum to company evidence submission, Table 4)

Health state	Daratumumab (1)	Pom+dex (2)	Pano+bort+dex (3)	Bendamustine-based therapy (4)	Increment (% increment)		
					1 vs 2	1 vs 3	1 vs 4
Pre-progression On treatment	£79,194	£48,151	£72,527	£36,769	£31,044 (98%)	£6,667 (96%)	£42,425 (98%)
Pre-progression Off treatment	£35	£104	£18	£0	-£68 (0%)	£18 (0%)	£35 (0%)
Post-progression	£1,410	£855	£1,191	£736	£555 (2%)	£219 (3%)	£674 (2%)
Terminal costs	£782	£812	£793	£822	-£30 (0%)	-£11 (0%)	-£40 (0%)
Total costs	**£81,422**	**£49,921**	**£61,438**	**£38,327**	**£31,697 (100%)**	**£19,983 (100%)**	**£43,174 (100%)**
Abbreviations in table: bort, bortezomib; dex, dexamethasone; dara, daratumumab; pano, panobinostat; pom, pomalidomide.							

5.6.2 Sensitivity analysis

5.6.2.1 Scenario analysis

The company carried out scenario analyses testing assumptions surrounding the following:

- Time horizon;
- Discount rates;
- Utilities;
- Overall survival (curve fit);
- Progression-free survival (curve fit and type of assessment);
- Time on treatment (curve fit);
- MAIC analysis (source of efficacy data for daratumumab, number of matched criteria, inclusion of patients pre-treated with pomalidomide, proportional hazards assumption);
- Method used to estimate comparative efficacy of pom+dex.

Due to the number of issues identified within the company's model related with running scenario analyses the ERG does not report the results of the analyses. These can be found in Table 8 of the addendum to the submission received on 21/12/2016. Some of the results reported in Table 8 could not be validated by the ERG.

5.6.2.2 One-way sensitivity analysis

The one-way sensitivity analysis was carried out using the net monetary benefit (NMB) estimation approach. Net benefit in the model is calculated based on an assumed willingness-to-pay (WTP) threshold of £50,000 per QALY gained. The base case NMB is estimated to be -£3,257, £3,681, and -£5,008 for daratumumab compared to pom+dex, pano+bort+dex, and bendamustine-based therapy respectively. The results of the OWSAs of daratumumab compared to bendamustine-based therapy, pano+bort+dex, and pom+dex are presented in Figure 45, Figure 46, and Figure 47 respectively.

For the analysis of daratumumab compared to pom+dex, varying the HR for OS from the pooled MAIC analysis had a great impact on the results causing a change of £ £25,272 in NMB compared to the base case, while varying the HR for PFS from the same analysis had a relatively minor impact on the results. Varying the scale parameters for the daratumumab TTD and OS curves also affected the results leading to a change of around £12,000 and £10,000 compared with the base case.

In the pair-wise analysis of daratumumab compared to pano+bort+dex, the most influential parameter seems to be the HR for OS from the pooled MAIC analysis leading to a change of around £50,000 in the NMB compared to the base case when varied. Varying the HR for PFS leads to a change of approximately £25,000 in the NMB relative to base case. Varying the scale parameter for daratumumab TTD leads to a change of around £12,000 compared to the base case.

Figure 45. OWSA for daratumumab compared to bendamustine-based therapy, from company's updated model (CS, addendum to company's evidence submssion, Figure 7)

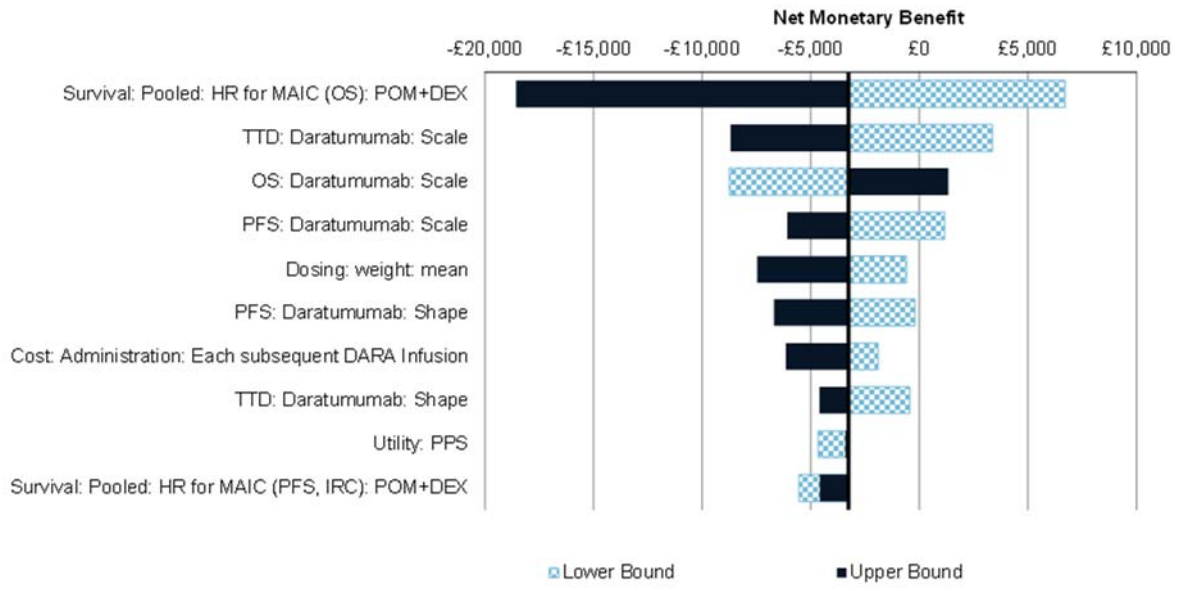


Figure 46. OWSA for daratumumab compared to pano+bort+dex, from company's updated model (CS, addendum to company's evidence submssion, Figure 8)

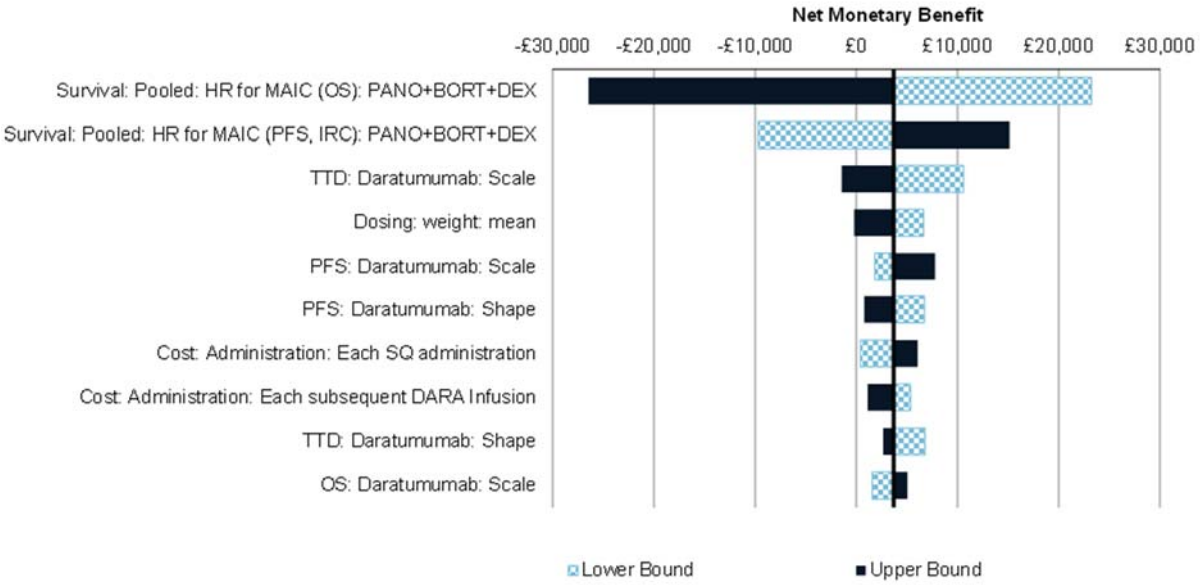
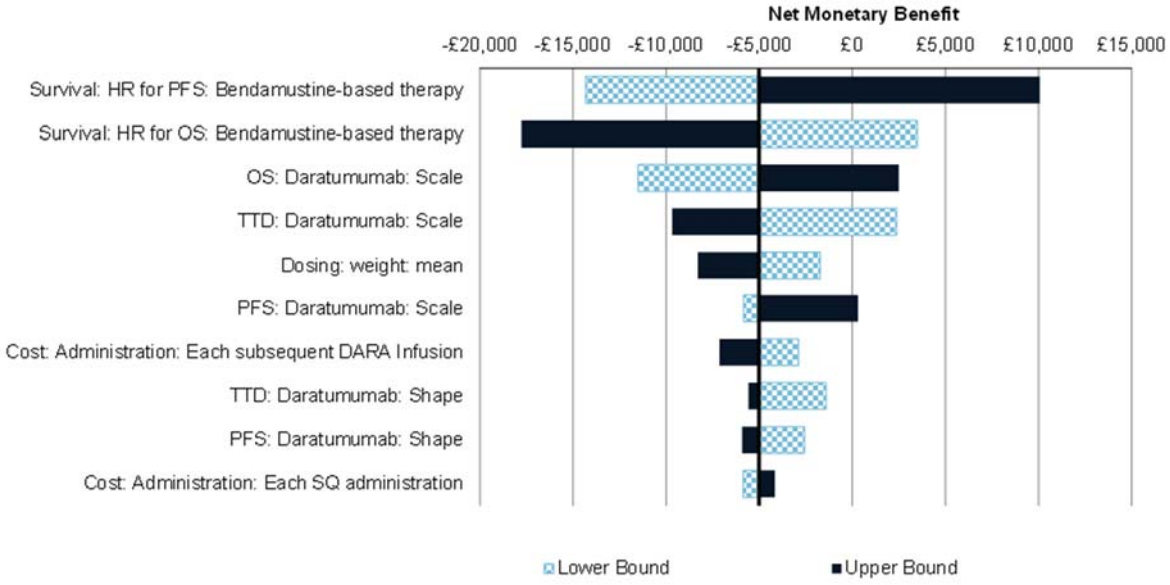


Figure 47. OWSA for daratumumab compared to bendamustine-based therapy, from company's updated model (CS, addendum to company's evidence submssion, Figure 9)



5.6.2.3 Probabilistic sensitivity analysis

The company carried out probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around the base case results. The mean results of the simulations across 8,000 iterations are presented in Table 85. The probabilistic ICERs for daratumumab compared to pom+dex, pano+bort+dex, and bendamustine-based therapy are £54,987, £31,079, and £54,149 per QALY gained, respectively. Unfortunately, the ERG had insufficient time to fully validate the PSA undertaken by the company.

Table 85. Mean PSA from company's updated model (CS, addendum to company's evidence submssion, Table 7)

Treatment	Total			Incremental			ICER (Dara vs Comparator)
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Daratumumab	£80,197	1.32	2.55				
Pom+dex	£49,653	0.76	1.50	£30,544	0.56	1.06	£54,987
Pano+bort+dex	£74,516	1.14	2.22	£5,681	0.18	0.33	£31,079
Bendamustine-based therapy	£39,313	0.56	1.13	£40,884	0.76	1.43	£54,149

Abbreviations in table: dex, dexamethasone; pano, panobinostat; bort, bortezomib; LY, life years; pom, pomalidomide; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; dara, daratumumab

The scatterplots for daratumumab compared to pom+dex, pano+bort+dex and bendamustine are presented in Figure 48, Figure 49 and Figure 50, respectively. The cost-effectiveness acceptability curves (CEACs) for daratumumab compared to pom+dex, pano+bort+dex and bendamustine-based therapy are presented in Figure 51, Figure 52, and Figure 53, respectively. The probability of daratumumab being cost-effective at a WTP threshold of £30,000 is 1%, 4% and 50% when compared to pom+dex, pano+bort+dex and bendamustine, respectively. When the WTP threshold is increased to 50,000 per QALY, the probability of daratumumab being cost-effective compared to pom+dex, pano+bort+dex, and bendamustine-based therapy is 37%, 60%, and 35% respectively.

Figure 48. Scatterplot of daratumumab compared to pom+dex from company's updated model (CS, addendum to company's evidence submission, Figure 1)

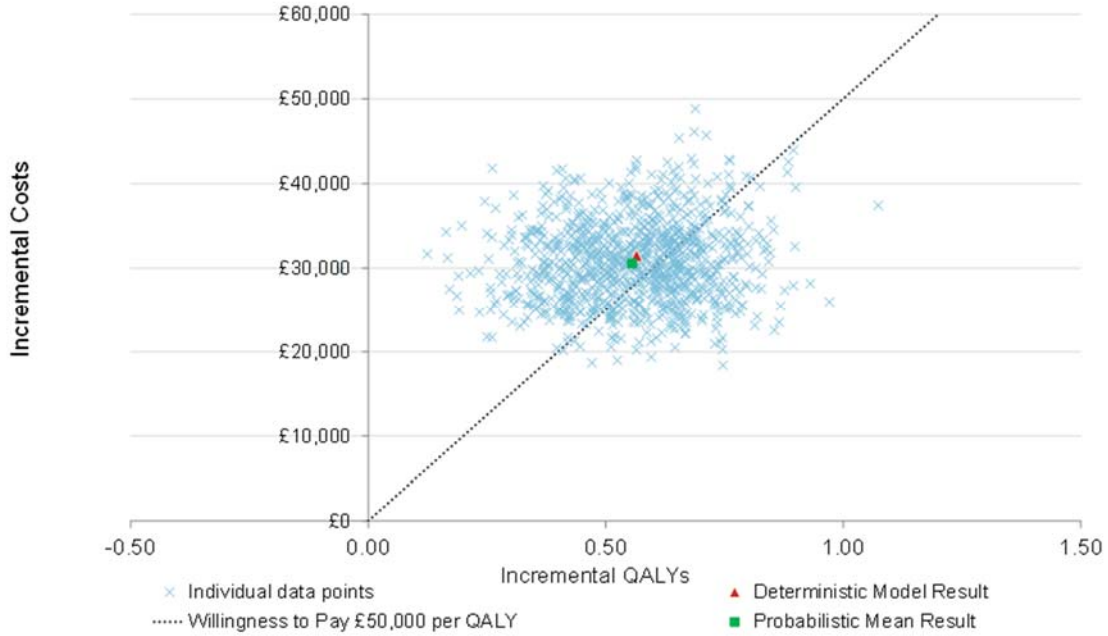


Figure 49. Scatterplot of daratumumab compared to pano+bort+dex from company's updated model (CS, addendum to company's evidence submission, Figure 3)

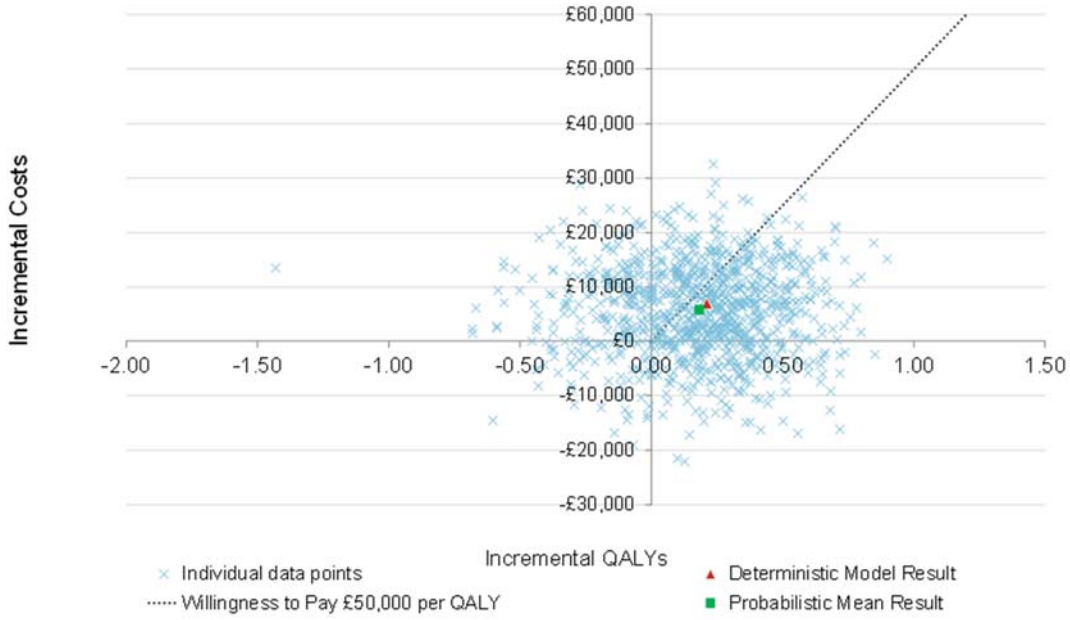


Figure 50. Scatterplot of daratumumab compared to bendamustine-based therapy from company's updated model (CS, addendum to company's evidence submission, Figure 5)

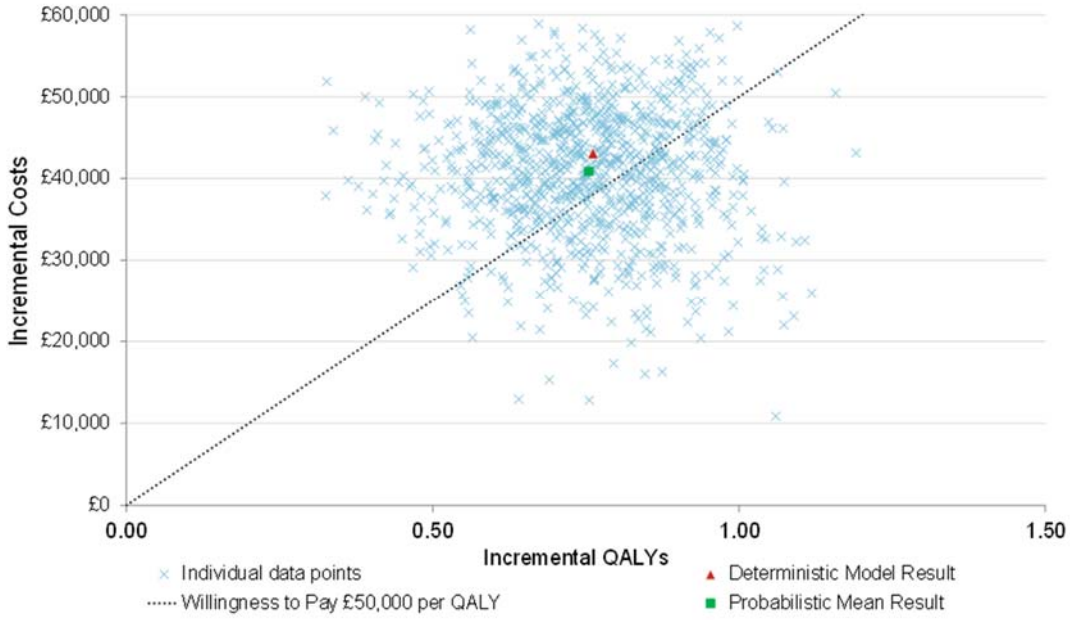


Figure 51. CEAC of daratumumab compared to pom+dex (CS, addendum to company's evidence submission, Figure 2)

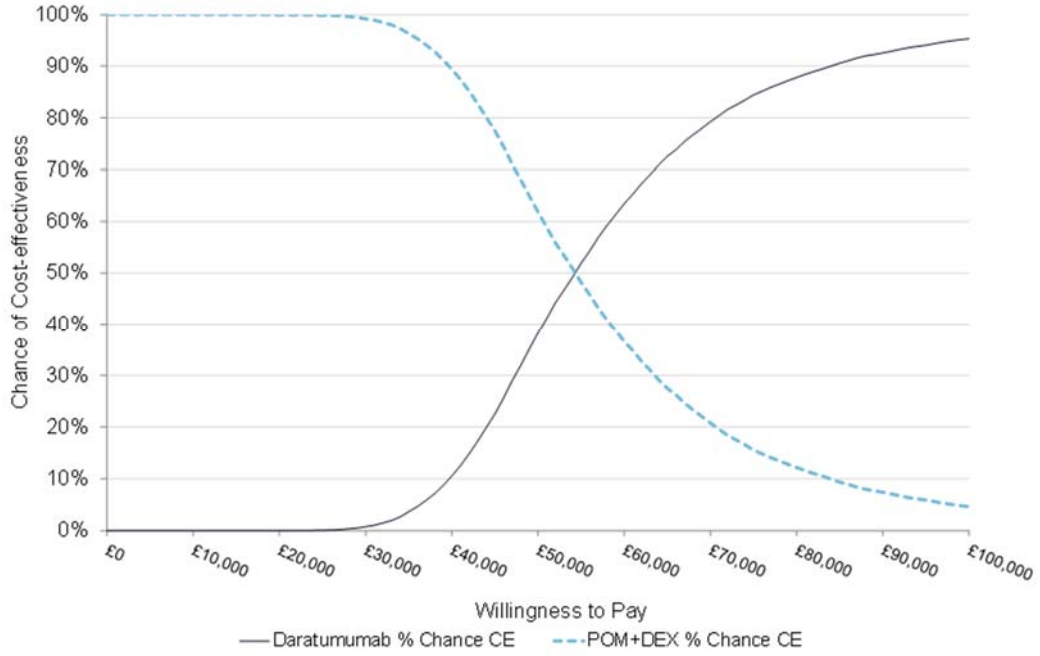


Figure 52. CEAC of daratumumab compared to pano+bort+dex from company's updated model (CS, addendum to company's evidence submission, Figure 4)

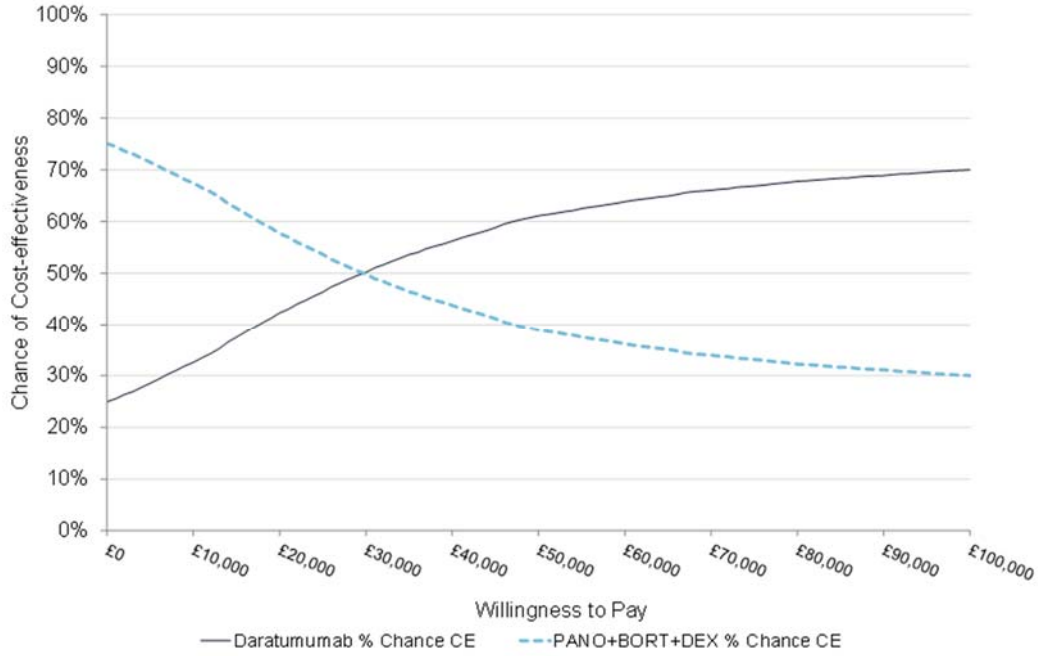
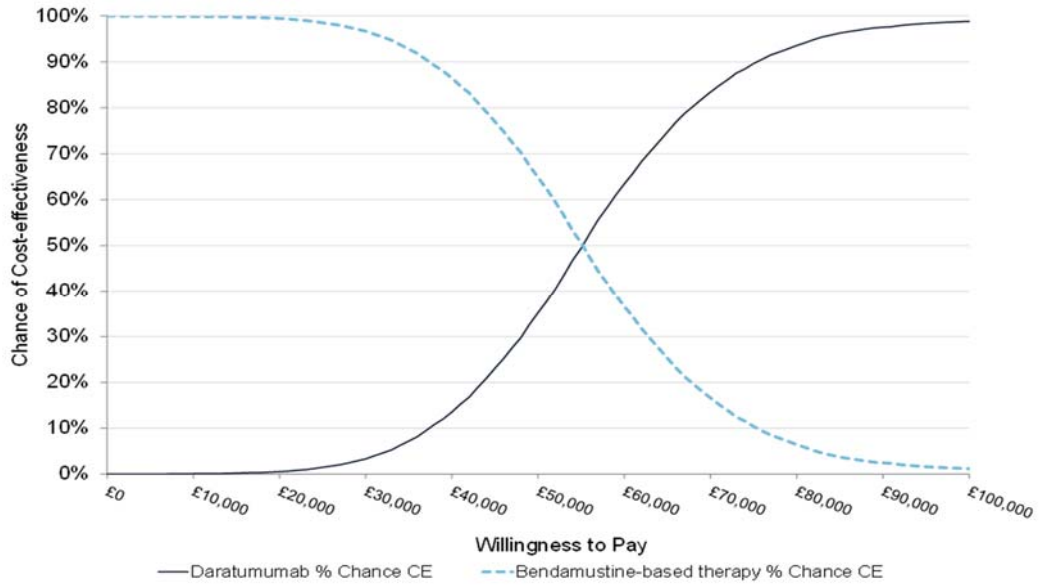


Figure 53. CEAC of daratumumab compared to bendamustine-based therapy (CS, addendum to company's evidence submssion, Figure 6)



6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

Most of the discrepancies or errors identified by the ERG cannot be easily corrected considering these are related with data inputs (i.e. not knowing if the correct data from the correct sources are being used or not in the company's analysis). Other potential mistakes are related with the uncertainty in the company's analysis of curve extrapolation, which also cannot be easily corrected. Finally, a considerable portion of the mistakes found by the ERG are related with scenario analyses in the company's model. The ERG corrected these as needed (i.e. if the specific analysis was deemed relevant) and reported the results throughout the report. In this section the ERG presents the company's base case results corrected for errors in formulae found in the economic model. The ERG corrected four mistakes:

1. The company states that the rate of peripheral neuropathy is not reported for pano+bort+dex patients in the PANORAMA2 trial publication [81]and that a 1.7% rate was observed for pom+dex patients in the MM-003 trial.[82] However, according to the publications cited, 27% of patients in the PANORAMA2 trial experienced all-grade peripheral neuropathy (with only 1.8% of patients experiencing Grade 3/4 peripheral neuropathy) while the corresponding number in the MM-003 trial is 15% and not 1.7%; [81, 82]

2. The implementation of the disutility values related with AEs in the economic model was incorrect as the aggregated disutility value for the safety profile of pano+bort+dex was being applied to bendamustine and pom+dex;

3. The company assumed that 55% of patients receive subsequent therapy after daratumumab (instead of the 72% observed in the trials). In order to reflect this the company multiplied 55% by the proportion of patients receiving the specific subsequent treatment in the overall trial population. The correct approach would have been to use the proportion of patients receiving a specific treatment within the group of patients receiving subsequent treatments and then multiply this value by 55%. The equivalent problem was encountered for pom+dex and pano+bort+dex. Furthermore, the CS states that the integrated MMY2002/GEN501 data were used to derive the proportion of patients receiving each type of subsequent therapy. However, this is not the case, as only the MMY2002 values were considered. The ERG replaced these data by the integrated data;

4. The acquisition cost for subsequent treatments used by the company was based on the price per pack (and did not consider treatment duration, dose or number of cycles received). The ERG corrected this in the model (by replacing the costs being taken from tab "Costs" cells J133:J140 and replacing it by cells L133:L140 in the economic model).

The results are presented in Table 86 for daratumumab at list price.

Table 86. Pairwise base case results from the company's updated model (CS, Addendum to company evidence submission, Table 2)

Treatment	Total			Incremental			ICER (Dara vs comparator) at list prices
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Daratumumab	£81,663	1.31	2.54				
Pom+dex	£50,665	0.73	1.46	£30,998	0.58	1.07	£53,471
Pano+bort+dex	£75,631	1.10	2.14	£6,032	0.21	0.39	£28,249
Bendamustine-based therapy	£39,022	0.54	1.10	£42,641	0.78	1.44	£54,982

Abbreviations in table: bort, bortezomib; dex, dexamethasone; dara, daratumumab; year; ICER, incremental cost-effectiveness ratio; LY, life year; pano, panobinostat; pom, pomalidomide; QALY, quality-adjusted life year.

6.2 ERG exploratory analysis

The scenario analyses undertaken by the ERG are explained throughout Section 5 of the report, with the respective impact on the final ICER. Some of the exploratory analyses (such as the ones relating to PFS and OS) are still based on some flawed assumptions or methods, however they are provided as a step in the right direction compared with the company base case approach. The ERG notes that all exploratory analyses are an academic exercise to explore the possible direction of the change in the final ICER and the overall impact of changes when considered together. Nonetheless the ERG stresses its opinion that the company's model and data analysis need further internal consistency checks and a

thorough quality check before a reliable ICER can be determined for daratumumab. Results of the exploratory analyses are reported in Table 87.

The exploratory analyses undertaken by the ERG uses the MMY2002 population instead of the daratumumab integrated dataset as this is the cohort which allows the use of fully-adjusted HRs. The analyses consist on the following:

1. Given that the ERG's preferred methodological approach is not available as a modelling option in the company's Excel model, the ERG explored the impact of using fully adjusted HRs for PFS. This means using PFS HRs of 0.88 for pom+dex and of 1.18 for pano+bort+dex (instead of 0.935 and 0.83, respectively, in the company's scenario analysis for MMY2002);

2. Considering the uncertainty around the TTD data and estimation, the ERG used the PFS curves to derive treatment costs, implying that patients receive treatment until progression;

3. The ERG explored the impact of using fully adjusted HRs for OS. This means using OS HRs of 1.14 for pom+dex and of 1.64 for pano+bort+dex (instead of 1.54 and 1.09, respectively, in the company's scenario analysis for MMY2002). Even though the ERG lacks confidence in the estimated curves, the ERG used the Weibull curve to model survival with daratumumab at baseline to help alleviate the strong assumption of constant hazard specific to the exponential curve used by the company;

4. The ERG carried out an exploratory analysis to assess the impact of changing health states resource use to reflect feedback from clinical experts (Table 73, Section 5.5.9.2);

5. In order to link the treatments costs to the corresponding measures of effectiveness for the different treatments, the ERG has conducted exploratory analysis to reflect the distribution of subsequent therapies received in the daratumumab trials (Table 50, Section 5.5.9.3) and in the pom+dex trial as far as evidence allowed;

6. The ERG consulted with clinical experts to try to understand what would be the expected distribution of subsequent therapies received in the UK (Table 52, Section 5.5.9.3);

7. Considering the lack of statistical significance in the fully adjusted (and in the MMY2002 company-adjusted) OS and PFS HRs, the ERG ran an exploratory analysis using a HR of 1 for OS and PFS for daratumumab compared with pom+dex and with pano+bort+dex.

8. The ERG took a conservative approach and removed the AE-related disutility estimates from the company analysis. This implicitly assumes that all drugs have a similar safety profile, which is likely to underestimate the benefit of daratumumab given its advantageous safety profile.

Despite its limitations, this approach is less flawed than double-counting and overestimating the impact of AEs on patients' QoL.

Using PFS curves to derive treatment costs in the model (instead of TTD curves) is one of the model's key drivers, shifting the ICER for daratumumab vs pom+dex from £51,120 to dominant. This is because in the company's scenario analysis using the MMY2002 population and in the ERG's exploratory analysis, the HR for PFS shows a benefit for pom+dex. Considering that PFS for pom+dex is higher than PFS for daratumumab (and that costs are determined by the time spent on the progression-free state), the beneficial effect of pom+dex penalises the treatment in terms of treatment costs. Nonetheless the total costs for pom+dex are similar to daratumumab's costs as can be observed in Table 66: £75,554 total costs for daratumumab compared with £76,031 for pom+dex (when PFS is used instead of TTD to model treatment cost). Therefore using PFS curves to model treatment costs penalises the relatively better effect of pom+dex in terms of progression-free survival (the total costs for daratumumab increase from £71,811 to £75,554, while the total costs for pom+dex increase from £50,525 to £76,031).

The other key drivers of the economic results are the HRs for PFS and OS. Changing the HR for PFS for daratumumab vs pom+dex does not have a big impact on the final ICER, while the change in the PFS HR for pano+bort+dex changes the ICER from dominant to £89,539. This is due to the fact that the company's HRs for PFS in the MMY2002 population are 0.94 for pom+dex and 0.83 for pano+bort+dex. Therefore, when the ERG replaces these for the fully-adjusted HRs (0.88 for pom+dex and of 1.18 for pano+bort+dex) there is not a major shift in the relative effectiveness of pom+dex (which continues to show a benefit compared with daratumumab) but there is a considerable change on the pano+bort+dex ICER as daratumumab becomes more effective than pano+bort+dex in delaying progression. This is counterintuitive as it shows that a beneficial change in the relative effectiveness of daratumumab's PFS increases the final ICER, while a detrimental change in the relative effectiveness of daratumumab's PFS decreases the final ICER.

When the HRs for OS are changed from the company's analysis of MMY2002 (1.54 for pom+dex and of 1.09 for pano+bort+dex) to the fully-adjusted HRs (1.14 for pom+dex and of 1.64 for pano+bort+dex), the ICER for pom+dex increased to £136,128 while the ICER for pano+bort+dex remained dominant. This is not surprising as the fully-adjusted HR for pano+bort+dex shows a higher survival benefit for daratumumab against pano+bort+dex than the one obtained in the company's analysis. For pom+dex, the fully adjusted HR shows a loss of about 40% in the effectiveness of daratumumab when compared with the company's analysis.

These analyses need to be considered with extreme caution as all the HRs for PFS and OS are non-statistically significant and they rely on the company's model and data analysis, which need further

internal consistency checks and a thorough quality check before a reliable final ICER can be determined for daratumumab.

Table 87. Results of the ERG's scenario analysis

	Results per patient	Daratumumab (1)	Pom+dex (2)	Pano+bort+dex (3)	Incremental value	
					(1-2)	(1-3)
0	**Corrected base case (MMY2002 population)**					
	Total costs (£)	£71,811	£50,525	£73,234	£21,286	-£1,423
	QALYs	1.12	0.71	1.02	0.42	0.11
	ICER				**£51,120**	**Daratumumab dominates**
1	**Using fully adjusted HRs for PFS (HRs of 0.88 for pom+dex and of 1.18 for pano+bort+dex)**					
	Total costs (£)	£71,811	£50,477	£61,440	£21,334	£10,371
	QALYs	1.12	0.71	1.01	0.41	0.12
	ICER (compared with base case)				**£51,485**	**£89,539**
2	**Using PFS (instead of TTD) curves to derive treatment costs**					
	Total costs (£)	£75,554	£76,031	£73,234	-£476	£2,321
	QALYs	1.12	0.71	1.02	0.42	0.11
	ICER (compared with base case)				**Daratumumab dominates**	**£21,913**
3	**Using fully adjusted HRs for OS (HRs of 1.14 for pom+dex and of 1.64 for pano+bort+dex) + using a Weibull curve to model OS for daratumumab**					
	Total costs (£)	£71,761	£51,002	£72,482	£20,759	-£722
	QALYs	1.08	0.92	0.67	0.15	0.41
	ICER (compared with base case)				**£136,128**	**Daratumumab dominates**
4	**Changing health states resource use to reflect feedback from clinical experts**					
	Total costs (£)	£73,620	£51,447	£74,673	£22,173	-£1,053
	QALYs	1.12	0.71	1.02	0.42	0.11
	ICER (compared with base case)				**£53,251**	**Daratumumab dominates**
5	**Linking treatments costs to the corresponding measures of effectiveness for the different treatments using the distribution of subsequent therapies observed in the daratumumab and pom+dex trials**					
	Total costs (£)	£79,768	£50,838	£73,234	£28,930	£6,534
	QALYs	1.12	0.71	1.02	0.42	0.11
	ICER (compared with base case)				**£69,478**	**£61,697**
6	**Using clinical expert opinion to reflect the distribution of subsequent therapies received in the UK**					
	Total costs (£)	£79,378	£50,559	£78,052	£28,819	£1,325
	QALYs	1.12	0.71	1.02	0.42	0.11
	ICER				**£69,212**	**£12,514**

	(compared with base case)					
7	**Using a HR of 1 for OS and PFS for daratumumab compared with pom+dex and with pano+bort+dex**					
	Total costs (£)	£71,761	£51,264	£67,087	£20,497	£4,674
	QALYs	1.08	1.04	1.05	0.04	0.03
	ICER (compared with base case)				**£540,389**	**£185,698**
8	**Removing the AE-related disutility estimates from the company analysis**					
	Total costs (£)	£71,811	£50,525	£73,234	£21,286	-£1,423
	QALYs	1.17	0.79	1.09	0.38	0.08
	ICER (compared with base case)				**£56,243**	**Daratumumab dominates**

Abbreviations in table: AE, adverse event; bort; bortezomib; dex, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LY, life year; OS, overall survival; pano, panobinostat; PFS, progression-free survival; pom, pomalidomide; QALY, quality-adjusted life year; TTD, time to treatment discontinuation.

6.3 ERG alternative exploratory analysis

In this section the ERG presents the same analyses as the ones reported in the previous section, with all changes combined and incorporated into the final ICER. Even though the ERG does not have a preferred base case due to the lack of robustness of the final ICER, some alternative approaches are more conservative (or methodologically preferred) than others. Each scenario analysis numbered in Table 88 corresponds to the scenarios reported in Section 6.2

The ERG arrives at two possible sets of ICERs, both of which need careful interpretation. The first set of ICERs show a dominated daratumumab against pom+dex and pano+bort+dex. This is because the analysis uses HRs of 1 for both PFS and OS, leaving the economic analysis reduced to a cost-minimisation exercise. The use of HRs of 1 reflects the lack of statistical significance of HRs for OS and PFS throughout the ERG analyses. In this scenario, the total costs for daratumumab are £85,327, while the total costs for pom+dex are £73,260 and £68,798 for pano+bort+dex.

The alternative set of ICER, using the fully-adjusted, albeit non-statistically significant, HRs for OS and PFS produce a final ICER of £8,559 per QALY gained for daratumumab compared with pom+dex and of £59,960 for the comparison of pano+bort+dex. However these results are extremely volatile. Firstly, these results depend on the synergy between PFS curves determining treatment costs and the fact that pom+dex shows a relative benefit compared with daratumumab for PFS outcomes, with a HR of 0.88 (95% CI: 0.49 to 1.56). The very wide range and the lack of statistical significance of the PFS HRs imprint a great amount of uncertainty in the analysis. The ERG ran an additional exploratory analysis replacing the PFS HR for pom+dex with the value of 1.01 (so reflecting a 1% gain in

effectiveness for daratumumab against pom+dex). The final ICER went from £8,559 to **£114,278 per QALY gained**. This shows the fragility of the ICER for daratumumab against pom+dex, depending on the HR used for PFS (when treatment costs are determined by PFS curves). Secondly, these results are also highly dependent on the HRs for OS which are not only non-statistically significant, but show an incredible wide range of possible HRs. with 95% confidence intervals going from values such as 0.69 to 4.00. The OS HR for pom+dex is 1.14 (95% CI: 0.57 to 2.27) while the HR for pano+bort+dex is 1.64 (95% CI: 0.69 to 4.00). Equally important is the fact that the OS estimates for daratumumab are likely to be highly confounded by the subsequent treatments received in MMY2002 and GEN501. Therefore the ERG considers that the "true" ICERs comparing daratumumab with pom+dex and pano+bort+dex can lie anywhere between dominant to dominated in the company's analysis.

Table 88. Results of the ERG's alternative scenario analysis

	Results per patient	**Daratumumab (1)**	**Pom+dex (2)**	**Pano+bort+dex (3)**	**Incremental value**	
					(1-2)	**(1-3)**
0	**Corrected base case (MMY2002 population)**					
	Total costs (£)	£71,811	£50,525	£73,234	£21,286	-£1,423
	QALYs	1.12	0.71	1.02	0.42	0.11
	ICER				**£51,120**	**Daratumumab dominates**
2	**Using PFS (instead of TTD) curves to derive treatment costs**					
	Total costs (£)	£75,554	£76,031	£73,234	-£476	£2,321
	QALYs	1.12	0.71	1.02	0.42	0.11
	ICER (compared with base case)				**Daratumumab dominates**	**£21,913**
4	**Changing health states resource use to reflect feedback from clinical experts**					
	Total costs (£)	£73,620	£51,447	£74,673	£22,173	-£1,053
	QALYs	1.12	0.71	1.02	0.42	0.11
	ICER (compared with base case)				£53,251	Daratumumab dominates
	ICER with all changes incorporated				**£974**	**£25,416**
5	**Linking treatments costs to the corresponding measures of effectiveness for the different treatments using the distribution of subsequent therapies observed in the daratumumab and pom+dex trials**					
	Total costs (£)	£79,768	£50,838	£73,234	£28,930	£6,534
	QALYs	1.12	0.71	1.02	0.42	0.11
	ICER (compared with base case)				£69,478	£61,697
	ICER with all changes incorporated				**£19,332**	**£100,545**
8	**Removing the AE-related disutility estimates from the company analysis**					
	Total costs (£)	£71,811	£50,525	£73,234	£21,286	-£1,423
	QALYs	1.17	0.79	1.09	0.38	0.08
	ICER (compared				£56,243	Daratumumab dominates

	with base case)					
	ICER with all changes incorporated				**£21,269**	**£131,891**
7	**Using a HR of 1 for OS and PFS for daratumumab compared with pom+dex and with pano+bort+dex**					
	Total costs (£)	£71,761	£51,264	£67,087	£20,497	£4,674
	QALYs	1.08	1.04	1.05	0.04	0.03
	ICER (compared with base case)				£540,389	£185,698
	ICER with all changes incorporated				**Daratumumab dominated**	**Daratumumab dominated**
1+3	**Using fully adjusted HRs for PFS (HRs of 0.88 for pom+dex and of 1.18 for pano+bort+dex) + Using fully adjusted HRs for (HRs of 1.14 for pom+dex and of 1.64 for pano+bort+dex) + using a Weibull curve to model OS for daratumumab**					
	Total costs (£)	£71,811	£50,978	£60,672	£20,833	£11,139
	QALYs	1.12	0.96	0.67	0.16	0.45
	ICER (compared with base case)				£129,127	£24,579
	ICER with all changes incorporated				**£8,559**	**£59,960**

Abbreviations in table: AE, adverse event; bort; bortezomib; dex, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LY, life year; OS, overall survival; pano, panobinostat; PFS, progression-free survival; pom, pomalidomide; QALY, quality-adjusted life year; TTD, time to treatment discontinuation.

7 END OF LIFE

The company concludes that daratumumab monotherapy should be considered in the end of life setting, as per the assessment reported in Table 89. The ERG assessment of end of life criteria shows that even though comparator treatments offer a life extension of less than 24 months, this is a close call for pom+dex, offering an additional 22 months of survival. The same is true for the difference between life-years gained with the two treatments with daratumumab offering just 3 months over and above pom+dex. Considering the uncertainty surrounding OS estimates in the company's model and the fact that the OS estimates for daratumumab are likely to be highly confounded by the subsequent treatments received in MMY2002 and GEN501, the ERG does not consider that a robust assessment can be made on life years gained, especially for the comparison with pom+dex.

In MMY2002, the median OS was 18.6 months (95% CI 13.7 months to not reached) and, in GEN501 Part 2, median OS had not been reached at the time of analysis (95% CI 18.7 months to not reached). The company also presents results from an integrated analysis of data from MMY2002 and GEN501 Part 2. Median OS in the integrated analysis was 20.1 months (95% CI 16.6 months to not reached).

Table 89. End of life considerations

NICE criterion	Company assessment	ERG assessment
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median life expectancy: less than 24 months, and is in fact closer to 12 months.	The corrected model for the company's analysis of the MMY2002 population shows the following undiscounted total life-years for each treatment: Daratumumab: 26 months Pom+dex: 17 months Pano+bort+dex: 24 months Bendamustine: 11 months The ERG's exploratory analysis using the fully adjusted HRs shows the following undiscounted total life-years for each treatment: Daratumumab: 25 months Pom+dex: 22 months Pano+bort+dex: 16 months Bendamustine: 11 months
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Mean OS estimates: Daratumumab monotherapy: 2.54 life years (30.4 months) Pano+bort+dex: 2.14 life years (25.7 months) Pom+dex: 1.46 life years (17.5 months) Bendamustine: 1.10 life years (13.2 months) Source: MMY2002/GEN501, PANORAMA 2, MM-003, IMF cohort	
The treatment is licensed or otherwise indicated, for small patient populations	In 2013, the Committee for Orphan Medicinal Products (COMP) granted daratumumab orphan drug status due to the classification of MM as a rare disease: COMP defines a rare disease as one that affects fewer than 5 in 10,000 people across the European Union	n/a

8 OVERALL CONCLUSIONS

Clinical

In support of the submission to NICE, the company presented data on the clinical effectiveness of daratumumab from two studies, MMY2002 and GEN501 Part 2, together with an integrated analysis that pooled data from the two studies. Daratumumab has a European marketing authorisation for the treatment of people with rrMM, whose prior therapy included a PI and an IMiD and who demonstrated disease progression on the last therapy.[50]

The population of interest to the decision problem as set out in the final scope issued by NICE is those with rrMM previously been treated with a PI and an IMiD and who have demonstrated disease progression on the last therapy. In the CS, the company positions daratumumab as a fourth-line treatment in the rrMM setting, which is narrower than the final scope issued by NICE. The ERG's clinical experts support, to an extent, the positioning of daratumumab as a fourth-line treatment, feeding back that their likely preference would be to use daratumumab after len+dex but before pano+bort+dex, with the caveat that treatment choice at this stage of rrMM is tailored to the patient based on available options and is determined on a case-by-case basis.

MMY2002 and GEN501 are a Phase II and Phase I/II study, respectively, that were carried out in parallel. Neither study had a site in the UK. Both studies were carried out in two stages, with the first stage in each study involving investigation of different doses of daratumumab. In MMY2002, people were initially randomised to daratumumab 8.0 mg/kg or 16.0 mg/kg. In GEN501, people were allocated sequentially to daratumumab, starting at 0.05 mg/kg dose, escalating to 16.0 mg/kg. Subsequent to identification of the optimum dose of 16.0mg/kg, the final stage in each study involved following a single cohort to evaluate clinical effectiveness and safety of daratumumab at the licensed dose (16.0 mg/kg). Thus, the second stage of GEN501 and both stages of MMY2002 from which data are presented in support of the submission is observational in nature, not having a randomised component. It is noted that guidance from the FDA reports that single-arm studies are not appropriate for capturing time-to-event data such as PFS and OS.

With a primary outcome of ORR, MMY2002 was designed to evaluate the clinical efficacy of daratumumab in people with rrMM previously treated with at least three therapies (including PIs and IMiDs) or who were refractory to both a PI and an IMiD. By contrast, the primary goal of GEN501 was to assess safety and tolerability of daratumumab. The population enrolled in GEN501 Part 2 were those with MM whose disease was relapsed or relapsed and refractory to two prior lines of therapy and who did not have further established treatment options.

Outcomes were captured at three time points in both MMY2002 and GEN501 Part 2. However, the same outcomes were not recorded at the same time points, with longer follow-up for ORR in GEN501 Part 2 compared with MMY2002.

Comparison of baseline characteristics across MMY2002 and GEN501 Part 2 identified differences in characteristics associated with prognosis and outcome. Based on the median number of prior therapies (five in MMY2002 vs four in GEN501 Part 2), and the proportion of people who were refractory to their last treatment (97.2% in MMY2002 and 76.2%), the ERG notes that people in MMY2002 are more heavily pre-treated and are more refractory to treatment than those in GEN501 Part 2. In addition, information on ISS stage and cytogenetics, characteristics that are also associated with prognosis, were not recorded for GEN501 Part 2.

The ERG recognises that MMY2002 and GEN501 Part 2 represent the best available evidence on daratumumab but considers that the trials are associated with a high risk of bias that is inherent in observational studies. In addition, given the identified differences in baseline characteristics and lack of information on ISS stage and cytogenetics in GEN501 Part 2, the ERG considers it inappropriate to combine the data sets in an integrated analysis for estimation of non-comparative outcomes relating to daratumumab.

The ERG has concerns around the generalisability of the studies to the UK population most likely to be eligible for treatment with daratumumab. In MMY2002 and GEN501 Part 2, some of the therapies people had received prior to trial entry are not available treatment options within the UK (carfilzomib, and, until January 2017, pomalidomide). Moreover, some of the subsequent treatments given on disease progression are not available treatment options in this setting in UK clinical practice.

To address the lack of evidence from RCTs on comparative effectiveness of daratumumab, the company carried out a MAIC comparing daratumumab versus the identified relevant comparators of pom+dex and pano+bort+dex for PFS and OS. The company followed reported methods. The ERG's preferred dataset from the MAIC differs from that of the company. Based on guidance from the DSU, the ERG considers that the most adjusted dataset to be the most appropriate, which included adjustment for ISS and cytogenetics (therefore based on MMY2002 alone).

The ERG advises that the results of the MAIC are interpreted with caution. The most adjusted sets had small effective sample sizes, which indicates poor overlap between studies and that the estimates are likely to be unstable. In addition, there is considerable uncertainty around the results, as illustrated by the change in direction of effect within some MAIC and the wide 95% CIs.

The company proposes that daratumumab is associated with an unprecedented survival benefit, attributable to "...the novel and unique multifactorial MoA [mechanism of action] of daratumumab

which appears to change the natural course of disease, such that the disease is effectively reset". Additionally, the company proposes that the novel mode of action of daratumumab increases the likelihood of patients benefiting from subsequent therapy. Given that no study comparing daratumumab with another active comparator is available, together with the differences across the studies that form the evidence base for the MAIC, the ERG considers that it is unclear whether the survival benefit associated with daratumumab is unprecedented. As the company acknowledges, across trial simple comparison (with no analysis) of effect estimates is inappropriate

Economic

The ERG has serious concerns with the robustness of the economic analysis undertaken by the company. The ERG encountered several errors and discrepancies in the different versions of the economic model, CS and data provided by the company to the ERG after the clarification stage. The specificities of this STA allied with the submission of multiple model versions and the limited time available for the ERG review, make it very likely that some mistakes were not detected by the ERG. The key aspects of this STA are as follows:

- The absence of RCT evidence;
- The possible permutations for the data analysis (three datasets for daratumumab – MMY2002; GEN501 and integrated; two different trials for the two comparator; two subgroups of relevance related with subsequent therapies and pre-treatment received by patients; two possible modelling approaches – dependent or independent fit and finally the variation in the adjustment factors included in the MAIC).

The fact that ERG kept on finding mistakes in data handling and labelling increases the probability that some other similar mistakes were not identified. It is impossible to foresee the impact of such potentially unidentified mistakes. It is the ERG's opinion that the company's model and data analysis need further internal consistency checks and a thorough quality check before a robust ICER can be determined for daratumumab.

The ERG summarises the key issues surrounding the cost-effectiveness of daratumumab below. These are related with:

- **Pre-treatment with pomalidomide**: The ERG is concerned about the validity of the data sent through by the company at the clarification stage. However, the data suggest that there is no difference in PFS across pom-naïve and non-pom-naïve patients and that OS outcomes are better for pom-naïve patients than for the overall trial population. The ERG interprets this trend in the data as a possible consequence of the effect of daratumumab as a subsequent therapy. It

can be hypothesised that given that pre-treatment with pomalidomide does not seem to influence PFS, the considerable difference in the OS curves across the pom-naïve and the overall trial population is due to the effect that pomalidomide would have as a subsequent treatment in the pom-naïve patients, compared to the effect that pomalidomide would have as a subsequent treatment in patients pre-treated with pomalidomide. Unfortunately the ERG cannot validate this hypothesis given the uncertainty around the data and the fact that company did not provide the OS KM curve for patients subsequently treated with pomalidomide, despite the ERG's request for such data;

- **Subsequent treatments received in MMY2002/GEN501**: The ERG is concerned with the highly confounded OS estimates in the company analysis. The ERG considers that the evidence put forward by the company is not robust enough to determine the cost-effectiveness of daratumumab monotherapy alone. To determine this, we would need to be able to disentangle further the estimate of OS for daratumumab alone vs daratumumab followed by other treatments. Similarly, if we are to consider the cost-effectiveness of daratumumab monotherapy followed by subsequent rrMM therapies, then the effectiveness of daratumumab would need adjusting for the impact of subsequent therapies currently not available in the UK. This is particularly important in this case given the lack of RCT data for daratumumab. While in theory this confounding effect might also apply to the comparator treatments, as pom+dex and pano+bort+dex patients could receive subsequent therapies in MM-003 and PANORAMA2, respectively, the ERG's investigation shows that the risk of OS confounding for pom+dex patients is likely to be considerably smaller than for daratumumab patients. This is related with the fact that 72% of patients in MMY2002/GEN501 received subsequent therapies, while the corresponding estimate for MM-003 is 44%, but more importantly, in MM-003 patients received carfilzomib, lenalidomide and bortezomib in much smaller numbers than in MMY2002/GEN501 (2% vs 28% for carfilzomib; 5% vs 15% for lenalidomide and 18% vs 24% for bortezomib). Daratumumab patients also received pomalidomide (31%) while pom+dex patients did not receive any pomalidomide (or daratumumab) after the main treatment in MM-003. [85, 140]As discussed in the report, treatment with carfilzomib and retreatment with lenalidomide and bortezomib are not available in the UK and are likely to considerably increase overall survival as subsequent therapies for rrMM patients.

  Finally, there is an inconsistency in the company's proposed advantage of daratumumab. That is, it allows a higher proportion of patients to receive subsequent therapy. On one hand the company claims that the novel mode of action of daratumumab increases the likelihood of patients benefiting from subsequent therapy pointing to the fact that, "…*of the 148 patients treated with daratumumab 16mg/kg monotherapy in the MMY2002/GEN501 cohort, 72% went*

on to receive subsequent therapy compared with 39% of the 302 patients randomised to POM+DEX in MM-003". On the other hand, the company also states that "…c*linical opinion suggested that…this figure* [72%] *is high compared to what is seen in clinical practice*… [and that] *the proportion of patients who receive subsequent therapy after daratumumab is* [likely to be] *55%*". The company also assumed that the proportion for patients receiving subsequent therapy after pano+bort+dex is 55% in the model, making it equally likely for pano+bort+dex and daratumumab patients to receive subsequent therapy;

- **Statistical approach undertaken by the company to model survival outcomes:** The ERG has several concerns with the company's statistical approach to the economic analysis. The ERG considers that the curve fitting exercise undertaken by the company lacks transparency and consistency. This is related with the approach taken to model Gompertz curves and the lack of an appropriate assessment of the PH, PO and AFT assumptions consistently across modelled outcomes. The ERG disagrees with the company's assessment of PH for OS data and thus with the company's modelling approach. This has several implications considering the company's use of exponential models to fit the daratumumab unadjusted OS curves and application of a HR to estimate the OS curves for comparator treatments. The ERG is also concerned with the validity of the curve fitting exercise undertaken by the company for OS data as some of the OS extrapolated curves by the company seem to differ considerably from the ones obtained by the ERG. The company's original model included an option to run the cost-effectiveness analysis using independently fitted curves for OS. This could have overcome the PH issue, nonetheless, this would also imply using the 11-characteristics-adjusted daratumumab curves. Given the ERG's consideration that the company should be adjusting for the maximum number of characteristics possible across trials, the option to fit curves independently in the model is not ideal as it solves one problem but creates a potentially bigger one. The ERG preferred statistical approach is therefore not currently allowed for in the company's model. The ERG preferred approach would have been to use the independently fitted curves, however using the MAIC fully adjusted daratumumab curves for OS and PFS compared with unadjusted pom+dex and pano+bort+dex curves. The company has provided the ERG with these data (i.e. the fully MAIC-adjusted OS and PFS KM curves for daratumumab) at clarification. The ERG discusses the potential implications of these data however due to time constraints, and the remit of the ERG's review, does not use these KM data to fit and extrapolate curves for inclusion in the company's model. Analysis of the fully adjusted KM curves led to important conclusions:

    - The number of characteristics included in the MAIC adjustment drastically changes the positioning of the daratumumab OS adjusted KM curves in relation to pom+dex (and to a less but also important extent) in relation to pano+bort+dex. In fact the fully

adjusted, 28-characteristc adjusted OS curve for daratumumab shows a lower survival benefit with daratumumab compared with pom+dex before month 10, and a modest benefit after that point in time. This is a major departure from the 11-characteristic-adjusted OS curve, which crosses the pom+dex curve at month 4, to then show an impressive survival benefit compared with pom+dex. This represents an even bigger departure from the dependent fit approach (company's base case) where the daratumumab OS curve is consistently above the pom+dex OS curve. Conversely, the 5-characteristic-adjusted OS curve for daratumumab vs pano+bort+dex seems to underestimate the survival benefit for daratumumab when compared with the 16-characteristic-adjusted OS curve. This has crucial implications for the OS estimated curves and therefore the cost-effectiveness of daratumumab when compared with pom+dex;

- The number of characteristics included in the MAIC adjustment changes the positioning of the daratumumab PFS adjusted KM curves in relation to pom+dex and in relation to pano+bort+dex, although to a less extent than observed for OS data. Regardless of this, given that PFS curves are a key diver of treatment costs, the slightest shift in the curves is likely to have an impact on the cost-effectiveness analysis' results;

Given that the ERG's preferred methodological approach is not available as a modelling option in the company's Excel model, the ERG undertook some exploratory analysis to assess the impact of using fully adjusted HRs in the company's base case approach. To note is that this approach carries the majority of the flaws in the company's base case analysis. It uses a dependent fit approach and fitted curves which may not be reliable. Nonetheless, it is a step in the right direction compared with the company's approach, as it uses the fully adjusted HRs.

- **Time to treatment discontinuation data**: The estimation of TTD curves in the company's analysis lacks transparency and clarity throughout the STA. Time to treatment discontinuation was not a pre-specified outcome in the MMY2002 and GEN501 trials but instead resulted from a *post-hoc* analysis of patient level data. Therefore the ERG has little to no information on this clinical outcome. Secondly, the estimation of adjusted TTD curves for daratumumab through the "calibration approach" is a black box in the company's analysis. No further details were provided by the company other than the fact that "*…the TTD curves for daratumumab were calibrated to match the observed mean and median from MM-003*". Considering the uncertainty around the TTD data, the ERG considers that using these data in the economic analysis carries a potentially high risk. While the PFS curves and data are also not without problems, PFS curves were used as an exploratory approach to derive treatment costs, implying that patients receive treatment until progression;

- **Progression-free survival data:** All estimates of relative treatment effect for PFS (company's base case, company's analysis using the MY2002 population and ERG exploratory analysis) show non-statistically significant HRs for daratumumab against pom+dex and pano+bort+dex. Also important is that the HRs used to model PFS in the model have a counterintuitive effect on the final ICERs, when PFS is used to model treatment costs. A beneficial change in the relative effectiveness of daratumumab's PFS increases the final ICER, while a detrimental change in the relative effectiveness of daratumumab's PFS decreases the final ICER, when compared with pom+dex. This is because the beneficial effect of pom+dex penalises this treatment in terms of treatment costs.

- **Overall survival data**: The ERG's preferred, fully-adjusted HRs lead to a decrease in the HR for pom+dex (showing a smaller benefit in OS for daratumumab) but to a considerable increase in the pano+bort+dex HR. Equally noticeable, all the HRs using the ERG's preferred approach produce non-statically significant HRs against both comparators. In their exploratory analysis, the ERG also changed the baseline curve used to model survival with daratumumab, using the Weibull instead of the exponential. This helps alleviate the strong assumption of a constant hazard specific to the exponential curve.

The ERG conducted exploratory analyses as an academic exercise to investigate the direction of the change in the final ICER when different approaches and data are used in the economic model. Nonetheless the ERG stresses its opinion that the company's model and data analysis need further internal consistency checks and a thorough quality check before a robust ICER can be determined for daratumumab. To this, it adds the need of further analysis to arrive at an unconfounded OS estimate for daratumumab monotherapy.

In their exploratory analysis, the ERG arrives at two possible sets of ICERs, both of which need careful interpretation. The first set of ICERs show a dominated daratumumab against pom+dex and pano+bort+dex. This is because the analysis uses HRs of 1 for both PFS and OS, leaving the economic analysis reduced to a cost-minimisation exercise. The use of HRs of 1 reflects the lack of statistical significance of HRs for OS and PFS throughout the ERG analyses. In this scenario, the total costs for daratumumab are £85,327, while the total costs for pom+dex are £73,260 and £68,798 for pano+bort+dex.

The alternative set of ICERs, using the fully-adjusted, albeit non-statistically significant, HRs for OS and PFS produce a final ICER of £8,559 per QALY gained for daratumumab compared with pom+dex and £59,960 for the comparison of pano+bort+dex. However these results are extremely volatile. Firstly, these results depend on the synergy between PFS curves determining treatment costs and the fact that pom+dex shows a relative benefit to daratumumab for PFS outcomes, with a HR of 0.88 (95%

CI: 0.49 to 1.56). The very wide range and the lack of statistical significance of the PFS HRs imprint a great amount of uncertainty in the analysis. Thus ERG ran an additional exploratory analysis replacing the PFS HR for pom+dex with the value of 1.01 (reflecting a 1% gain in effectiveness for daratumumab against pom+dex). The final ICER went from £8,559 to £114,278 per QALY gained. This shows the fragility of the ICER for daratumumab against pom+dex, depending on the HR used for PFS (when treatment costs are determined by PFS curves). Secondly, these results are also highly dependent on the HRs for OS which are not only non-statistically significant, but show an incredible wide range of possible HRs. with 95% confidence intervals going from values such as 0.69 to 4.00. The OS HR for pom+dex is 1.14 (95% CI: 0.57 to 2.27) while the HR for pano+bort+dex is 1.64 (95% CI: 0.69 to 4.00). Therefore the ERG concludes that the "true" ICERs comparing daratumumab with pom+dex and with pano+bort+dex can lie anywhere between dominant and dominated in the analysis undertaken by the company.

8.1 Implications for research

The ERG considers there is a need for further research into:

- The relative effectiveness of daratumumab compared with pom+dex;
- Confirmation of the efficacy and safety of daratumumab in a population receiving subsequent treatments available in the UK for rrMM;
- Confirmation of the efficacy and safety of daratumumab in a population receiving no subsequent treatments for rrMM.

9 REFERENCES

1. National Institute for Health and Care Excellence (NICE). Daratumumab monotherapy for treating relapsed and refractory multiple myeloma. Final scope. In: National Institute for Health and Care Excellence (NICE), editor. 2016.

2. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia. 2009;23(1):3-9.

3. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003;78(1):21-33.

4. Moreau P, San Miguel J, Ludwig H, Schouten H, Mohty M, Dimopoulos M, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2013;24 Suppl 6:vi133-7.

5. UK CR. Myeloma2016 9 December 2016. Available from: http://www.cancerresearchuk.org/about-cancer/type/myeloma/.

6. Bianchi G, Anderson KC. Understanding biology to tackle the disease: Multiple myeloma from bench to bedside, and back. CA Cancer J Clin. 2014;64(6):422-44.

7. Prideaux SM, Conway O'Brien E, Chevassut TJ. The genetic architecture of multiple myeloma. Adv Hematol. 2014;2014:864058.

8. Palumbo A, Anderson K. Multiple myeloma. The New England journal of medicine. 2011;364(11):1046-60.

9. Barlogie B, Mitchell A, van Rhee F, Epstein J, Morgan GJ, Crowley J. Curing myeloma at last: defining criteria and providing the evidence. Blood. 2014;124(20):3043-51.

10. Bird J, Owen R, D'Sa S. Guidelines for the diagnosis and management of multiple myeloma.2014 19 December 2016. Available from: https://academy.myeloma.org.uk/wp-content/uploads/sites/2/2014/08/MYELOMA_GUIDELINE_Feb_2014_for_BCSH1.pdf.

11. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. Blood. 2008;111(5):2521-6.

12. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111(5):2516-20.

13. Usmani SZ, Ahmad T, Ng Y, al E, editors. Analyses of real world data on overall survival in multiple myeloma patients with at least 3 prior lines of therapy including a PI and an IMiD, or double refractory to a PI and an IMiD. American Society of Hematology; 2015; Orlando, Florida, USA.

14. Gooding S, Lau IJ, Sheikh M, Roberts P, Wong J, Dickens E, et al. Double Relapsed and/or Refractory Multiple Myeloma: Clinical Outcomes and Real World Healthcare Costs. PLoS ONE. 2015;10(9):e0136207.

15. Kumar SK, Lee JH, Lahuerta JJ, Morgan G, Richardson PG, Crowley J, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. Leukemia. 2012;26(1):149-57.

16. Streetly M, Kazmi M, Campbell T, al E. Clinical review of overall survival for myeloma patients progressing after both bortezomib and lenalidomide based therapy. British journal of haematology. 2014;165:68.

17. Tarant JL, Ashcroft J, Feyler S, al E. Treatment patterns & survival in multiple myeloma patients sequentially exposed to thalidomide, bortezomib & lenalidomide in a UK single centre. Blood. 2013:122.

18. Usmani S, Ahmadi T, Ng Y, Lam A, Desai A, Potluri R, et al. Analysis of Real-World Data on Overall Survival in Multiple Myeloma Patients With >/=3 Prior Lines of Therapy Including a Proteasome Inhibitor (PI) and an Immunomodulatory Drug (IMiD), or Double Refractory to a PI and an IMiD. The oncologist. 2016.

19. Wang TF, Ahluwalia R, Fiala MA, Trinkaus KM, Cox DP, Jaenicke M, et al. The characteristics and outcomes of patients with multiple myeloma dual refractory or intolerant to bortezomib and lenalidomide in the era of carfilzomib and pomalidomide. Leukemia & lymphoma. 2014;55(2):337-41.

20. Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. Blood. 2009;113(22):5412-7.

21. Kyle RA, Durie BG, Rajkumar SV, Landgren O, Blade J, Merlini G, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia. 2010;24(6):1121-7.

22. Wadhera RK, Rajkumar SV. Prevalence of monoclonal gammopathy of undetermined significance: a systematic review. Mayo Clin Proc. 2010;85(10):933-42.

23. UK N. Multiple myeloma.2016 12 December 2016. Available from: http://www.nhs.uk/Conditions/Multiple-myeloma/Pages/Introduction.aspx.

24. Silbermann R, Roodman GD. Myeloma bone disease: Pathophysiology and management. J Bone Oncol. 2013;2(2):59-69.

25. Laubach J, Garderet L, Mahindra A, Gahrton G, Caers J, Sezer O, et al. Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. Leukemia. 2016;30(5):1005-17.

26. Smith D, Yong K. Multiple myeloma. Bmj. 2013;346:f3863.

27. Cavo M, Rajkumar SV, Palumbo A, Moreau P, Orlowski R, Blade J, et al. International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation. Blood. 2011;117(23):6063-73.

28. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(26):2863-9.

29. Dimopoulos MA, Barlogie B, Smith TL, Alexanian R. High serum lactate dehydrogenase level as a marker for drug resistance and short survival in multiple myeloma. Ann Intern Med. 1991;115(12):931-5.

30. Rajan AM, Rajkumar SV. Interpretation of cytogenetic results in multiple myeloma for clinical practice. Blood Cancer J. 2015;5:e365.

31. Nooka AK, Kastritis E, Dimopoulos MA, Lonial S. Treatment options for relapsed and refractory multiple myeloma. Blood. 2015;125(20):3085-99.

32. Sonneveld P, Broijl A. Treatment of relapsed and refractory multiple myeloma. Haematologica. 2016;101(4):396-406.

33. Fonseca R, Bergsagel PL, Drach J, Shaughnessy J, Gutierrez N, Stewart AK, et al. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. Leukemia. 2009;23(12):2210-21.

34. Rajkumar SV. Multiple myeloma: 2014 Update on diagnosis, risk-stratification, and management. Am J Hematol. 2014;89(10):998-1009.

35. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

36. Mols F, Oerlemans S, Vos AH, Koster A, Verelst S, Sonneveld P, et al. Health-related quality of life and disease-specific complaints among multiple myeloma patients up to 10 yr after diagnosis: results from a population-based study using the PROFILES registry. Eur J Haematol. 2012;89(4):311-9.

37. Johnsen AT, Tholstrup D, Petersen MA, Pedersen L, Groenvold M. Health related quality of life in a nationally representative sample of haematological patients. Eur J Haematol. 2009;83(2):139-48.

38. Jordan K, Proskorovsky I, Lewis P, Ishak J, Payne K, Lordan N, et al. Effect of general symptom level, specific adverse events, treatment patterns, and patient characteristics on health-related quality of life in patients with multiple myeloma: results of a European, multicenter cohort study. Support Care Cancer. 2014;22(2):417-26.

39. Rizzo M, Xu Y, Panjabi S, Iheanacho I, editors. A systematic literature review of the economic burden in multiple myeloma. ISPOR 17th Annual European Congress; 2014; The Netherlands.

40. Rha SY, Park Y, Song SK, Lee CE, Lee J. Caregiving burden and the quality of life of family caregivers of cancer patients: the relationship and correlates. Eur J Oncol Nurs. 2015;19(4):376-82.

41. UK CR. Myeloma (statistics).2016 9 December 2016. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma.

42. National Institute for Health and Care Excellence (NICE). Management of myeloma2016 19 December 2016. Available from: https://pathways.nice.org.uk/pathways/myeloma/management-of-myeloma.

43. National Institute for Health and Care Excellence (NICE). Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib2015 19 December 2016. Available from: https://www.nice.org.uk/guidance/ta338.

44. National Institute for Health and Care Excellence (NICE). Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation2014 19 December 2016. Available from: https://www.nice.org.uk/guidance/ta311.

45. National Institute for Health and Care Excellence (NICE). Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy2014 19 December 2016. Available from: https://www.nice.org.uk/guidance/ta171.

46. National Institute for Health and Care Excellence (NICE). Bortezomib and thalidomide for the first‐line treatment of multiple myeloma2011 19 December 2016. Available from: https://www.nice.org.uk/guidance/ta228.

47. National Institute for Health and Care Excellence (NICE). Bortezomib monotherapy for relapsed multiple myeloma2007 19 December 2016. Available from: https://www.nice.org.uk/guidance/ta129.

48. National Institute for Health and Care Excellence (NICE). Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib: guidance. 2017.

49. National Institute for Health and Care Excellence (NICE). Managing relapse of myeloma2016 19 December 2016. Available from: https://pathways.nice.org.uk/pathways/myeloma/management-of-myeloma#path=view%3A/pathways/myeloma/managing-relapse-of-myeloma.xml&content=view-index.

50. (EMA) EMA. Assessment report: Darzalex2016 19 December 2016. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004077/WC500207295.pdf.

51. Electronic Medicines Compendium (eMC). Velcade 3.5mg powder for solution for injection. 2016 [updated 19 December 2016]. Available from: https://www.medicines.org.uk/emc/medicine/17109.

52. Yong K, Delforge M, Driessen C, Fink L, Flinois A, Gonzalez-McQuire S, et al. Multiple myeloma: patient outcomes in real-world practice. British journal of haematology. 2016;175(2):252-64.

53. Janssen Research & Development. Clinical Study Report: An open-label, multicenter, Phase 2 trial investigating the efficacy and safety of daratumumab in subjects with multiple myeloma who have received at least 3 prior lines of therapy (including a proteasome inhibitor and IMiD) or are double refractory to a proteasome inhibitor and an IMiD (54767414MMY2002; Phase 2). 2015.

54. Lonial S, Weiss BM, Usmani SZ, Singhal S, Chari A, Bahlis NJ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. The Lancet. 2016;387(10027):1551-60.

55. Janssen Research & Development. Clinical Study Report: Daratumumab (HuMax-CD38) safety study in multiple myeloma – open-label, dose-escalation followed by open-label, single-arm study (GEN501; Phase 1/2). 2015.

56. Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. New England Journal of Medicine. 2015;373(13):1207-19.

57. (FDA) UFaDA. Darzalex: approval letter2015 28 December 2016. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/761036Orig1s000ltr.pdf.

58. Khagi Y, Mark TM. Potential role of daratumumab in the treatment of multiple myeloma. Onco Targets Ther. 2014;7:1095-100.

59. Lin P, Owens R, Tricot G, Wilson CS. Flow cytometric immunophenotypic analysis of 306 cases of multiple myeloma. Am J Clin Pathol. 2004;121(4):482-8.

60. Santonocito AM, Consoli U, Bagnato S, Milone G, Palumbo GA, Di Raimondo F, et al. Flow cytometric detection of aneuploid CD38(++) plasmacells and CD19(+) B-lymphocytes in bone marrow, peripheral blood and PBSC harvest in multiple myeloma patients. Leuk Res. 2004;28(5):469-77.

61. Krejcik J, Casneuf T, Nijhof I, al E, editors. Immunomodulatory effects and adaptive immune response to daratumumab in multiple myeloma. American Society of Hematology; 2015; Orlando, Florids, USA.

62. de Weers M, Tai YT, van der Veer MS, Bakker JM, Vink T, Jacobs DC, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. J Immunol. 2011;186(3):1840-8.

63. Krejcik J, Casneuf T, Nijhof IS, Verbist B, Bald J, Plesner T, et al. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. Blood. 2016;128(3):384-94.

64. Overdijk MB, Verploegen S, Bogels M, van Egmond M, Lammerts van Bueren JJ, Mutis T, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. MAbs. 2015;7(2):311-21.

65. Marco J, Boross P, Overdijk MB, al E, editors. Daratumumab, a human CD38 antibody induces apoptosis of myeloma tumor cells via Fc receptor-mediated crosslinking. 54th American Society of Heamatology (ASH) Annual Meeting and Exposition; 8-11 December 2012; Atlanta, Georgia, USA.

66. Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117(18):4691-5.

67. (FDA) UFaDA. Guidance for Industry: clinical trial endpoints for the approval of cancer drugs and biologics2007 28th December 2016. Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf.

68. He Y, Wheatley K, Glasmacher A, Ross H, Djulbegovic B. Early versus deferred treatment for early stage multiple myeloma. Cochrane Database of Systematic Reviews. 2003(1).

69. Naumann-Winter F, Greb A, Borchmann P, Bohlius J, Engert A, Schnell R. First-line tandem high-dose chemotherapy and autologous stem cell transplantation versus single high-dose chemotherapy and autologous stem cell transplantation in multiple myeloma, a systematic review of controlled studies. Cochrane Database of Systematic Reviews. 2012(10).

70. Tan Y, Xu S, Li X, Chen J. Allogeneic stem cell transplantation with matched sibling donor versus autologous stem cell transplantation for newly diagnosed Multiple Myeloma. Cochrane Database of Systematic Reviews. 2013(4).

71. National Institute for Health and Care Excellence (NICE). Lenalidomide for the treatment of multiple myeloma in people who have received one prior therapy with bortezomib (part rev TA171) [ID667]. 2014.

72. National Institute for Health and Care Excellence (NICE). Bortezomib and thalidomide for the first‐line treatment of multiple myeloma (TA228). 2011. Available from: http://www.nice.org.uk/guidance/ta228 (Accessed August 2016).

73. Scottish Intermediate Guideline Network (SIGN). Scottish Intermediate Guideline Network (SIGN) Systematic Review Filter Available at: http://www.sign.ac.uk/methodology/filters.html#systematic (Assessed last on: 29 November 2016). 2015.

74. Usmani S, Waheed S, Szymonifka J, Panozzo S, Petty NM, Steward D, et al. Pomalidomide (Pom) in Relapsed and Refractory Multiple Myeloma (RRMM) - theUARK Compassionate Use Protocol. Blood. 2011;118(21):3995-.

75. Jimenez Zepeda VH, Duggan P, Neri PE, Bahlis NJ. Pomalidomide and Dexamethasone Is an Effective Regimen for Advanced-Stage Relapsed/Refractory Multiple Myeloma: Experience of a Single Center. Blood. 2014;124(21):5747-.

76. Krieger O, Machherndl-Spandl S, Binder M. Bendamustin - A novel therapeutic option in relapsed/refractory multiple myeloma. Onkologie. 2010;33:251-2.

77. Gentilini F, Brunetti GA, Finsinger P, Chisini M, Cartoni C, Foa R, et al. Bendamustine and Dexamethasone Is an Effective Salvage Regimen for Patient with Advanced Multiple Myeloma in a Home Care Unit Program. Blood. 2014;124(21):5753-.

78. Dimopoulos MA, Weisel KC, Song KW, Delforge M, Karlin L, Goldschmidt H, et al. Cytogenetics and long-term survival of patients with refractory or relapsed and refractory multiple myeloma treated with pomalidomide and low-dose dexamethasone. Haematologica. 2015;100(10):1327-33.

79. Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in healthcare. Available at https://wwwyorkacuk/media/crd/Systematic_Reviewspdf Accessed 21 March 2016. 2011.

80. San-Miguel JF, Hungria VT, Yoon SS, Beksac M, Dimopoulos MA, Elghandour A, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. The Lancet Oncology. 2014;15(11):1195-206.

81. Richardson PG, Schlossman RL, Alsina M, Weber DM, Coutre SE, Gasparetto C, et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. Blood. 2013;122(14):2331-7.

82. San Miguel J, Weisel K, Moreau P, Lacy M, Song K, Delforge M, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. The Lancet Oncology. 2013;14(11):1055-66.

83. Phan K, Tian DH, Cao C, Black D, Yan TD. Systematic review and meta-analysis: techniques and a guide for the academic surgeon. Ann Cardiothorac Surg. 2015;4(2):112-22.

84. Development JR. Scottish clinician consultation for daratumumab for the treatment of multiple myeloma. Data on file. 2016.

85. National institute for Health and Care Excellence (NICE). Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib [ID985]. Guidance in Development. 2016. Available from: https://www.nice.org.uk/guidance/GID-TA10038/documents/final-appraisal-determination-document (Accessed January 2017). 2016.

86. Ltd NPU. Panobinostat (Farydak®). Medical benefit and additional medical benefit, patient groups with therapeutically significant additional benefit.2015 6th January 2017. Available from: https://www.g-ba.de/downloads/92-975-1151/2015-09-25_Modul4A_Panobinostat.pdf.

87. San Miguel JF, Weisel KC, Song KW, Delforge M, Karlin L, Goldschmidt H, et al. Impact of prior treatment and depth of response on survival in MM-003, a randomized phase 3 study comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma. Haematologica. 2015;100(10):1334-9.

88. Signorovitch JE, Sikirica V, Erder MH, Xie J, Lu M, Hodgkins PS, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value Health. 2012;15(6):940-7.

89. Signorovitch JE, Wu EQ, Yu AP, Gerrits CM, Kantor E, Bao Y, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. Pharmacoeconomics. 2010;28(10):935-45.

90. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, NJ W. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE2016 9th January 2017. Available from: http://www.nicedsu.org.uk/TSD18%20Population%20adjustment%20TSD%20-%20FINAL.pdf.

91. Blade J, Samson D, Reece D, Apperley J, Bjorkstrand B, Gahrton G, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. British journal of haematology. 1998;102(5):1115-23.

92. National Institute for Health and Care Excellence (NICE). Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib: committee papers2017 17th January 2017. Available from: https://www.nice.org.uk/guidance/TA427/documents/committee-papers.

93. Usmani SZ, Weiss BM, Plesner T, Bahlis NJ, Belch A, Lonial S, et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma. Blood. 2016.

94. National Institute for Health and Care Excellence (NICE). Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib: NICE technology appraisal guidance [TA338]. Available from: https://www.nice.org.uk/guidance/ta338 Accessed on 11 January 2017. 2015.

95. National Institute for Health and Care Excellence (NICE). Panobinostat for multiple myeloma after at least 2 previous treatments (TA380). 2016. Available from: http://www.nice.org.uk/guidance/ta380 (Accessed August 2016).

96. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. National Institute for Health and Care Excellence (NICE),, 2013.

97. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. ScHARR, University of Sheffield, 2011.

98. Delea TE, El Ouagari K, Rotter J, Wang A, Kaura S, Morgan GJ. Cost-effectiveness of zoledronic acid compared with clodronate in multiple myeloma. Curr Oncol. 2012;19(6):e392-403.

99. Crott R, Versteegh M, Uyl-de Groot CA. An assessment of the external validity of mapping QLQ-C30 to EQ-5D preferences. Quali Life Res. 2013;22:1045-54.

100. Crott R, Versteegh M, Uyl-de-Groot C. An assessment of the external validity of mapping QLQ-C30 to EQ-5D preferences. Qual Life Res. 2013;22(5):1045-54.

101. van Agthoven M, Segeren CM, Buijt I, Uyl-de Groot CA, van der Holt B, Lokhorst HM, et al. A cost-utility analysis comparing intensive chemotherapy alone to intensive chemotherapy followed by myeloablative chemotherapy with autologous stem-cell rescue in newly diagnosed patients with stage II/III multiple myeloma; a prospective randomised phase III study. European journal of cancer (Oxford, England : 1990). 2004;40(8):1159-69.

102. Fragoulakis V, Kastritis E, Psaltopoulou T, Maniadakis N. Economic evaluation of therapies for patients suffering from relapsed-refractory multiple myeloma in Greece. Cancer Manag Res. 2013;5:37-48.

103. Uyl-de Groot CA, Buijt I, Gloudemans IJ, Ossenkoppele GJ, Berg HP, Huijgens PC. Health related quality of life in patients with multiple myeloma undergoing a double transplantation. Eur J Haematol. 2005;74(2):136-43.

104. Kharroubi SA, Edlin R, Meads D, Browne C, Brown J, McCabe C. Use of Bayesian Markov chain Monte Carlo methods to estimate EQ-5D utility scores from EORTC QLQ data in myeloma for use in cost-effectiveness analysis. Medical decision making : an international journal of the Society for Medical Decision Making. 2015;35(3):351-60.

105. Acaster S, Gaugris S, Velikova G, Yong K, Lloyd AJ. Impact of the treatment-free interval on health-related quality of life in patients with multiple myeloma: a UK cross-sectional survey. Support Care Cancer. 2013;21(2):599-607.

106. Rowen D, Young T, Brazier J, Gaugris S. Comparison of generic, condition-specific, and mapped health state utility values for multiple myeloma cancer. Value Health. 2012;15(8):1059-68.

107. Quinn C, Hirji I, Shingler SL, Davis C. Mapping Health State Utility Values From Eortc Data Collected From A Clinical Trial Population With Relapsed/Refractory Multiple Myeloma. Value Health. 2015;18(7):A468.

108. Proskorovsky I, Lewis P, Williams CD, Jordan K, Kyriakou C, Ishak J, et al. Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. Health and quality of life outcomes. 2014;12:35.

109. Hiten Naik, Doris Howell, Xin Qiu, Catherine Brown, Ashlee Vennettilli, Margaret Irwin, et al. Canadian cancer site-specific health utility values: Creating the basis for measuring value and costs of therapy. 2014 ASCO Quality Care Symposium2014.

110. Delforge M, Minuk L, Eisenmann J-C, Arnulf B, Canepa L, Fragasso A, et al. Health-related quality-of-life in patients with newly diagnosed multiple myeloma in the FIRST trial: lenalidomide plus low-dose dexamethasone versus melphalan, prednisone, thalidomide. Haematologica. 2015;100(6):826-33.

111. Cella D, Moreau P, Kuter D. An ongoing multinational observational study in multiple myeloma (preamble): a preliminary report of disease impact on quality of life. Haematologica. 2015;100:S23-4.

112. Ashaye AO, Zhang J, Bender RH, Altincatal A, S. P. Mapping Utility Scores from European organization for Treatment of Cancer Core-30 Questionnaire Scores (Eortc Qlq-C30) In Relapsed Multiple Myeloma. Value Health. 2015;18(3):A208.

113. Ashaye AO, Altincatal A, Bender RH, Zhang J, Panjabi S. Estimating Eortc-8d Health State Utility Values From Eortc Qlq-C30 Scores In Relapsed Multiple Myeloma. Value in Health.18(7):A468.

114. Moller J, Nicklasson L, Murthy A. Cost-effectiveness of novel relapsed-refractory multiple myeloma therapies in Norway: lenalidomide plus dexamethasone vs bortezomib. J Med Econ. 2011;14(6):690-7.

115. Usmani SZ, Cavenagh JD, Belch AR, Hulin C, Basu S, White D, et al. Cost-effectiveness of lenalidomide plus dexamethasone vs. bortezomib plus melphalan and prednisone in transplant-ineligible U.S. patients with newly-diagnosed multiple myeloma. J Med Econ. 2016;19(3):243-58.

116. Palumbo A, Dimopoulos M, San Miguel J, Harousseau JL, Attal M, Hussein M, et al. Lenalidomide in combination with dexamethasone for the treatment of relapsed or refractory multiple myeloma. Blood reviews. 2009;23(2):87-93.

117. Palumbo A, Davies F, Lee D, Dhanasiri S, Facon T, Zaki M, et al. Quality of Life Weights (Utilities) in Refractory or Relapsed and Refractory Multiple Myeloma (RRMM) Patients Using EORTC-8D and EQ-5D. Lymphoma and Myeloma 2013: An International Congress on Hematologic Malignancies; October 24-26, 2013; New York, NY2013.

118. Palumbo A, Davies F, Lee D, Dhanasiri S, Facon T, Zaki M, et al. Quality of Life Weights (Utilities) in Refractory or Relapsed and Refractory Multiple Myeloma (RRMM) Patients Using EORTC-8D and EQ-5D. Lymphoma and Myeloma. New York: US; 2013.

119. Brown RE, Stern S, Dhanasiri S, Schey S. Lenalidomide for multiple myeloma: cost-effectiveness in patients with one prior therapy in England and Wales. Eur J Health Econ. 2013;14(3):507-14.

120. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. British journal of cancer. 2006;95(6):683-90.

121. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Medical decision making : an international journal of the Society for Medical Decision Making. 2011;31(6):800-4.

122. Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. Eur J Health Econ. 2013;14(5):749-59.

123. Green C, Bryant J, Takeda A, Cooper K, Clegg A, Smith A, et al. Bortezomib for the treatment of multiple myeloma patients. Health Technol Assess. 2009;13 Suppl 1:29-33.

124. Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, et al. A systematic review of the role of bisphosphonates in metastatic disease. Health Technol Assess. 2004;8(4):1-176.

125. DuBois D, E. D. A Formula To Estimate The Approximate Surface Area If Height And Weight Be Known. Arch Intern Med (Chic). 1916;17:863-71.

126. European Medicines Agency. EPAR summary for the public, Imnovid (pomalidomide). 2013 [cited 2-16 4 December]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002682/WC500147720.pdf.

127. European Medicines Agency. EPAR Assessment Report, Farydak (panobinostat). 2016.

128. Electronic Medicines Compendium (eMC). Summary of product characteristics: Levact 2.5 mg/ml powder for concentrate for solution for infusion. 2015 [cited 2016 4 December]. Available from: https://www.medicines.org.uk/emc/medicine/23469/SPC/Levact+2.5+mg+ml+powder+for+concentrate+for+solution+for+infusion/.

129. Monthly Index of Medical Specialities (MIMS). 2016. Available from: http://www.mims.co.uk/ (Accessed December 2016).

130. BMJ Group and Pharmaceutical Press. 2016 [cited December 2016]. Available from: Available from: www.medicinescomplete.com.

131. Department of Health. NHS reference costs 2014-15. 2015.

132. Drugs and pharmaceutical electronic market information (eMit) [Internet]. 2016. Available from: http://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. (Accessed December 2016).

133. Celgene Ltd. TA338 Single technology appraisal (STA) manufacturer's submission: Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib. Available from: https://wwwniceorguk/guidance/ta338/history. 2014.

134. Janssen Research & Development. Clinical validation meeting for daratumumab. [Data on File.]. In press 2016.

135. (NHS). NHS. Blood and DTS pricing proposals for 2015/16. 2014.

136. Janssen Research & Development. Haematological Malignancy Research Network: Clinical management and outcomes in relapsed/refractory myeloma. [Data on File]. In press.

137. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess. 2004;8(36):iii-iv, ix-xi, 1-158.

138. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12:9.

139. National Institute for Health and Care Excellence (NICE). Carfilzomib for previously treated multiple myeloma [ID934]. 2016.

140. Federal Joint Committee. Pomalidomide (Addendum to Commission A15-42). Institute for Quality and Efficiency in Health Care, 2016.

141. Song KW, Dimopoulos MA, Weisel KC, Moreau P, Palumbo A, Belch A, et al. Health-related quality of life from the MM-003 trial of pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed and/or refractory multiple myeloma. Haematologica. 2015;100(2):e63-e7.

142. Leleu X, Attal M, Arnulf B, Moreau P, Traulle C, Marit G, et al. Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide–refractory multiple myeloma: Intergroupe Francophone du Myélome 2009-02. Blood. 2013;121(11):1968-75.

143. Richardson PG, Siegel DS, Vij R, Hofmeister CC, Baz R, Jagannath S, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood. 2014;123(12):1826-32.

144. Lacy MQ, Allred JB, Gertz MA, Hayman SR, Short KD, Buadi F, et al. Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of 2 dosing strategies in dual-refractory disease. Blood. 2011;118(11):2970-5.

145. DiCapua Siegel. DS, Agajanian. R, Gaur. R, Karamlou. K, Kaya. H, Sturniolo. M, et al. MM-014: A phase 2 trial evaluating efficacy, safety, and biomarkers of pomalidomide plus low-dose dexamethasone (POM + LoDEX) in relapsed/refractory multiple myeloma (RRMM) following second-line lenalidomide plus dexamethasone (LEN + DEX). Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014;32(5).

146. Ichinohe T, Kuroda Y, Okamoto S, Matsue K, Iida S, Sunami K, et al. A multicenter phase 2 study of pomalidomide plus dexamethasone in patients with relapsed and refractory multiple myeloma: the Japanese MM-011 trial. Experimental Hematology & Oncology. 2016;5(1):11.

147. Matsue K, Iwasaki H, Chou T, Tobinai K, Sunami K, Ogawa Y, et al. Pomalidomide alone or in combination with dexamethasone in Japanese patients with refractory or relapsed and refractory multiple myeloma. Cancer Science. 2015;106(11):1561-7.

148. Dimopoulos MA, Palumbo A, Weisel K, Ocio EM, Cavo M, Corradini P, et al. Safety and Efficacy in the Stratus (MM-010) Trial, a Single-Arm Phase 3b Study Evaluating Pomalidomide + Low-Dose Dexamethasone in Patients with Refractory or Relapsed and Refractory Multiple Myeloma. Blood. 2014;124(21):80-.

149. Miles O, Wells M. Efficacy of Pomalidomide after Progression Following Lenalidomide and Bortezomib-a Multicenter Retrospective Study. Clinical Lymphoma, Myeloma and Leukemia.15:e302.

150. Sonneveld P, Heyne N, Kueenburg E, Glasmacher AG, Kasserra C, Rosettani B, et al. MM-013: An ongoing phase 2 trial of pomalidomide and low-dose dexamethasone (POM + LoDEX) in relapsed/refractory multiple myeloma (RRMM) with moderate or severe renal impairment (RI) including patients (pts) undergoing hemodialysis. J Clin Oncol (Meeting Abstracts). 2014;32(15_suppl):TPS8626-.

151. Baz R, Martin TG, Alsina M, Shain KH, Cho HJ, Wolf JL, et al. Pomalidomide, Cyclophosphamide, and Dexamethasone Is Superior to Pomalidomide and Dexamethasone in Relapsed and Refractory Myeloma: Results of a Multicenter Randomized Phase II Study. Blood. 2014;124(21):303-.

152. Baz R, Martin TG, Alsina M, Shain KH, Cho HJ, Wolf JL, et al. Pomalidomide, cyclophosphamide, and dexamethasone is superior to pomalidomide and dexamethasone in relapsed and refractory myeloma: Results of a multicenter randomized phase II study. Blood. 2014;124.

153. Dechow. T, Aladoud. A, Hurtz. H. Overall response rate of patients wtih refractory multiple myeloma treated wtih pomalidomide and low dose dexamethasone after lenalidomide failure: interim results of the POSEIDON study. European Haematology Association. 2016.

154. Sriskandarajah. P, Pawlun. C, Boyle. E. Retrospective observational study of patients with relapsed/refractory myeloma treated with pomalidomide – the UK Experience. British Society of Haematology. 2015.

155. Montes-Gaisan C, Montes-Gaisán C, Cuesta A, Bermúdez A, Insunza A, Yánez L, et al. Pomalidomide in Refractory Multiple Myeloma (MMRR): A Single Center Experience. Clinical Lymphoma, Myeloma and Leukemia.15:e311.

156. Voorhees PM, Mulkey F, Hassoun H, Paba-Prada CE, Efebera YA, Hoke E, et al. Alliance A061202. a Phase I/II Study of Pomalidomide, Dexamethasone and Ixazomib Versus Pomalidomide and Dexamethasone for Patients with Multiple Myeloma Refractory to Lenalidomide and Proteasome Inhibitor Based Therapy: Phase I Results. Blood. 2015;126(23):375-.

157. Grey-Davies E, Bosworth JL, Boyd KD, Ebdon C, Saso R, Chitnavis D, et al. Bendamustine, Thalidomide and Dexamethasone is an effective salvage regimen for advanced stage multiple myeloma. British journal of haematology. 2012;156(4):552-5.

158. Lau I-J, Smith D, Aitchison R, Blesing N, Roberts P, Peniket A, et al. Bendamustine in combination with thalidomide and dexamethasone is a viable salvage option in myeloma relapsed and/or refractory to bortezomib and lenalidomide. Annals of hematology. 2015;94(4):643-9.

159. Musto P, Fraticelli VL, Mansueto G, Madonna E, Nozza A, Andriani A, et al. Bendamustine in relapsed/refractory multiple myeloma: the "real-life" side of the moon. Leukemia & lymphoma. 2015;56(5):1510-3.

160. Stöhr E, Schmeel FC, Schmeel LC, Hänel M, Schmidt-Wolf IGH, German Refractory Myeloma Study G. Bendamustine in heavily pre-treated patients with relapsed or refractory multiple myeloma. Journal of cancer research and clinical oncology. 2015;141(12):2205-12.

161. Caers J, Vekemans MC, Van De Broek I. Responding patients show durable responses to bendamustine in double refractory multiple myeloma patients. Haematologica. 2014;99:643-4.

162. Kim SJ, Bang S-M, Choi YS, Jo D-Y, Kim JS, Lee H, et al. Bendamustine in heavily pre-treated multiple myeloma patients: Results of a retrospective analysis from the Korean Multiple Myeloma Working Party. Blood research. 2016;51(3):193-9.

163. Lehenbauer-Dehm S, Alex M, Pecher G. Bendamustine in advanced multiple myeloma previously treated with bortezomid and lenalidomide containing regimen. Onkologie. 2012;35:145-6.

164. Mian M, Pescosta N, Luminari S. Phase II trial to investigate efficacy and safety of bendamustine, dexamethasone and thalidomide in relapsed or refractory multiple myeloma patients after treatment with lenalidomide and bortezomib. Haematologica. 2014;99:382-3.

165. Lonial S, Weiss BM, Usmani SZ, Singhal S, Chari A, Bahlis NJ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet (London, England). 2016.

166. Janssen Research & Development. An Open-label, Multicenter, Phase 2 Trial Investigating the Efficacy and Safety of Daratumumab in Subjects With Multiple Myeloma Who Have Received at Least 3 Prior Lines of Therapy (Including a Proteasome Inhibitor and IMiD) or are Double Refractory to a Proteasome Inhibitor and an IMiD. Clinical study report2015.

167. Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. New England Journal of Medicine. 2015;373:1207-19.

168. Janssen Research & Development. Daratumumab (HuMax-CD38) Safety Study in Multiple Myeloma – Open-label, Dose-Escalation Followed by Open-Label, Single-Arm Study. Clinical study report2015.

169. Richardson PG, Schlossman RL, Alsina M, Weber DM, Coutre SE, Gasparetto C, et al. PANORAMA 2: Panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. Blood. 2013;122:2331-7.

170. San Miguel J, Weisel K, Moreau P, Lacy M, Song K, Delforge M, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): A randomised, open-label, phase 3 trial. The Lancet Oncology. 2013;14:1055-66.

10 APPENDICES

10.1 Summary of studies assessing relevant comparators identified by the company's literature search

Table 90. Studies evaluating panobinostat (adapted from CS, Appendix 7, pg. 63, Table 8)

Study ID	Study design	Treatment arms	n	Population	Outcomes	Data availability	Quality grading
PANORAMA-1[80]	RCT Phase III Placebo-controlled Double-blind	Panobinostat 20 mg in combination with BORT 1.3 mg/m^2 plus DEX 20 mg Placebo in combination with BORT 1.3mg/m^2 plus DEX 20mg	387 381	Patients with rrMM who had received 1-3 prior treatments	Primary: PFS Secondary: OS, ORR, DoR, TTR, TTP, safety	Full published manuscript	High
PANORAMA-2[81]	RCT Phase II Single-arm Open-label	Panobinostat 20 mg in combination with BORT 1.3 mg/m^2 plus DEX 20 mg	55	Patients with rrMM who had received at least 2 prior treatments, including an IMiD, and who had BORT-refractory disease	Primary: ORR Secondary: OS, PFS, safety	Full published manuscript	Medium

Abbreviations: BORT, bortezomib; CS, company submission; DEX, dexamethasone; DoR, duration of response; ITC, indirect treatment comparison; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pg, page; rrMM, relapsed refractory multiple myeloma; TTP, time to progression; TTR, time to response.

Table 91. Studies evaluating pomalidomide (adapted from CS, Appendix 7, pg. 64, Table 9)

Study ID	Study design	Treatment arms	n	Population	Outcomes	Data availability	Quality grading
MM-003[82]	RCT Phase III Active-controlled Open-label	Pomalidomide 4 mg plus DEX 40mg High-dose DEX 40 mg	302 153	Patients with rrMM who had received prior treatment that included ≥2 cycles of lenalidomide and bortezomib (separate regimens or in combination) as well as adequate alkylator therapy	Primary: PFS Secondary: OS, ORR, TTP, DoR, safety, QoL.	Full published manuscript	High

IFM 2009-02[142]	RCT Phase II, Dose-controlled Open-label	Pomalidomide 4 mg plus DEX 40 mg: Pomalidomide on Days 1–21 Pomalidomide on Days 1–28	 43 41	Patients with relapsed MM after at least 1 prior regimen who were considered to be non-responders to the last line of LEN and to the last line of BORT	Primary: ORR Secondary: safety, TTR, DoR, TTP, PFS, EFS, OS	Full published manuscript	Medium
MM-002[143]	Dose-escalation study/RCT Phase I/II Active-controlled (RCT) Open-label	RCT phase: Pomalidomide 4 mg plus DEX 40 mg Pomalidomide 4 mg	 113 108	Patients with rrMM who had received ≥2 prior therapies including LEN and BORT and were refractory to their last treatment	**Phase I:** MTD **Phase II:** Primary: PFS Secondary: ORR, TTR, DoR, OS, safety	Full published manuscript	Medium
NCT00558896[144]	Non-RCT Phase II Single-group assignment Open-label	Pomalidomide plus DEX 40 mg: Pomalidomide 2 mg Pomalidomide 4 mg	 35 35	Patients included those with rrMM refractory to both lenalidomide and bortezomib therapy (subgroup of interest).	Primary: CR Secondary: OS, PFS, DoR, safety	Full published manuscript	Medium
MM-014[145]	Single-arm trial Phase II Open-label	Pomalidomide 2–4 mg plus DEX 40 mg	85[a]	Patients with rrMM who had received at least 2 prior therapies including LEN+DEX at second line to which they had relapsed from or become refractory	OS, second primary malignancies, subsequent treatment	Study protocol	Low (no data available)
MM-011[146]	Single-arm trial Phase II Open-label	Pomalidomide 4 mg plus DEX 20–40 mg	36	Japanese patients with rrMM who had received ≥2 prior therapies	Primary: ORR Secondary: PFS, safety	Full published manuscript	Low
MM-004[147]	Dose-escalation study Phase I Open-label	Treatment phase: Pomalidomide plus DEX 40 mg: Pomalidomide 2 mg Pomalidomide 4 mg	 3 3	Patients with rrMM who had received ≥2 lines of therapy including ≥2 cycles of LEN and BORT (separate regimens or in combination) as well as adequate alkylator therapy, and were refractory to their last treatment	Primary: MTD Secondary: ORR, DoR, PFS, PK, safety	Full published manuscript	Low
STRATUS[148]	Single-arm trial Phase IIIb Open-label	Pomalidomide 4mg plus DEX 40 mg	456	Patients with rrMM who had treatment failure with prior LEN and BORT and adequate prior alkylator therapy	Primary: safety Secondary: POM exposure, ORR, DoR,	Abstract only	Unclear (abstract only)

					PFS, OS and cytogenetic analysis		
Miles 2015[149]	Real-world comparison of POM use in UK hospitals to data from MM-003 trial	Pomalidomide 4 mg plus DEX 40 mg[b]	38	Patients with rrMM who had received prior LEN and BORT	Response, toxicity	Abstract only	Unclear (abstract only)
MM-013[150]	Non-RCT Phase II Single-group assignment Open-label	Pomalidomide 4 mg plus DEX 40 mg (20 mg for patients >75 years)	36	Patients with rrMM who had at least 1 prior antimyeloma therapy including LEN and moderate to severe RI. Patients had received a median of 4 (range: 2–7) prior therapies	Primary: ORR Secondary: assessment of renal response, time to renal response, PFS, TTP, OS, safety and PK	Abstract only	Unclear (abstract only)
NCT01432600[151]	Dose-escalation study/RCT Phase I/II Active-controlled (RCT) Open-label	RCT phase: Pomalidomide 4 mg plus DEX 40 mg (20 mg for patients >75 years) Pomalidomide 4 mg plus DEX 40 mg (20 mg for patients >75 years) plus cyclophosphamide	 36 34	Patients with rrMM after at least 2 prior therapies and who were LEN refractory	Response, PFS, safety	Abstract only[152]	Unclear (abstract only)
POSEIDON[153]	Retrospective	Pomalidomide 4 mg plus DEX 20 mg	138	Patients with rrMM who have received ≥2 prior lines of therapy including both lenalidomide and bortezomib, and who have demonstrated disease progression or were refractory to their last line of treatment	ORR, safety	Abstract only	Unclear (abstract only)
Sriskandarajah 2015[154]	Retrospective study	Pomalidomide[c]	32	Patients with rrMM presumed to have had at least 2 prior regimens, including LEN and BORT in line with CDF terms	Response, PFS, safety	Abstract only	Unclear (abstract only)
Montes-Gaison 2015[155]	Retrospective study	Pomalidomide 2–4 mg plus DEX 40 mgb	10	Patients with rrMM with treatment failure to LEN and BORT	Response, TTP, safety	Abstract only	Unclear (abstract only)

Alliance A061202[156]	Dose-escalation study/RCT Phase I/II Active-controlled (RCT) Open-label	RCT phase: Pomalidomide plus ixazomib plus DEX Pomalidomide plus DEX	 – –	Patients with rrMM after at least 2 prior therapies with double refractory disease (refractory to lenalidomide- and PI-based treatment)	Primary: PFS Secondary: ORR, DoR, OS, TNT, safety	Abstract only for Phase I	Low (no data available)
UARK Pom[74]	Compassionate use programme	Pomalidomide 4 mg plus dexamethasone 12–40mg	23	Patients with rrMM and prior exposure or resistant to other IMiDs and bortezomib	Response, survival, safety	Abstract only	Unclear (abstract only)
Zepeda 2014[75]	Retrospective study	Pomalidomide 2–4 mg plus dexamethasone 20 mg or 40 mg	31	Patients with rrMM after 2 or more therapies including lenalidomide, bortezomib or thalidomide	Primary: PD	Abstract only	Unclear (abstract only)

[a] Planned sample size.

[b] A cohort of patients subsequently received concurrent oral cyclophosphamide if progressive disease after initial response but data extracted for POM+DEX treated patients only.

[c] Presumed to be POM+DEX as UK practice with pomalidomide access through the CDF.

Abbreviations: BORT, bortezomib; CDF, cancer drugs fund; CS, company submission; DEX, dexamethasone; DoR, duration of response; EFS, event-free survival; ITC, indirect treatment comparison; LEN, lenalidomide; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; pg, page; PI, proteasome inhibitor; PK, pharmacokinetics; p.o, orally; POM, pomalidomide; QoL, quality of life; RCT, randomised controlled trial; RI, renal impairment; rrMM, relapsed refractory multiple myeloma; TNT, time to next treatment; TTP, time to progression; TTR, time to response.

Table 92. Studies evaluating bendamustine (adapted from CS, Appendix 7, pg. 68, Table 10)

Study ID	Study design	Treatment arms	n	Population	Outcomes	Data availability	Quality grading
Grey-Davies 2012[157]	Retrospective	Bendamustine 60 mg/m^2 plus thalidomide 50–200 mg plus DEX 20 mg	23	Patients with advanced stage MM who had received bendamustine within a compassionate use program in the UK. Patients had received a median of 5 (range: 3–7) prior lines of therapy	Safety, response, survival	Letter to the editor	Low
Lau 2015[158]	Retrospective	Bendamustine 60–100 mg/m^2 plus thalidomide 50–100 mg plus DEX 160 mg/cycle	30	Patients with rrMM who are double relapsed and/or refractory to bortezomib and lenalidomide	ORR, PFS, OS, safety	Full published manuscript	Low
Musto 2015[159]	Retrospective	Bendamustine ± steroids Bendamustine plus bortezomib Bendamustine plus lenalidomide	39 18 16	Patients with rrMM who had received salvage therapy with bendamustine within a compassionate use program All patients receiving bendamustine ± steroids had previously received both bortezomib and lenalidomide	ORR, PFS, OS, safety	Full published manuscript	Low
Stohr 2015[160]	Retrospective	Bendamustine 60–300 mg/m^2 ± steroids 40 mg	58	Patients with rrMM who had heavily pre-treated disease. Results reported for patients who had received >3 prior regimens (n=32)	Primary: OS, EFS Secondary: ORR, safety, influence of predictors on OS and EFS	Full published manuscript	Low
BHS MM[161]	Single-arm	Bendamustine	20	Patients with rrMM who had a prior history of relapse after both bortezomib and lenalidomide treatment	ORR, PFS, OS, safety	Abstract only	Unclear (abstract only)
Gentilli 2014[77]	Single-arm	Bendamustine 60 mg/m^2 plus DEX 20 mg	8	Patients with rrMM in a home care unit programme who had previously received lenalidomide and bortezomib	Response, PFS, TTP, safety	Abstract only	Unclear (abstract only)
KMM125[162]	Retrospective	Bendamustine 100 mg/m^2 plus prednisone	22	Patients with rrMM who had heavily pre-treated disease including	Response, safety	Abstract only	Unclear (abstract only)

				treatment with bortezomib and lenalidomide			
Krieger 2010[76]	Retrospective	Bendamustine 70–90 mg/m^2 plus corticosteroids	15	Patients with rrMM. Patients had received a median of 4 (range: 2–9) prior lines of therapy	Safety, response	Abstract only	Unclear (abstract only)
Lehenbauer-Dehm 2012[163]	Retrospective	Bendamustine 60–90 mg/m^2	15	Patients with rrMM previously treated with IMiDs and bortezomib alone or in distinct combinations	ORR, PFS, safety	Abstract only	Unclear (abstract only)
Mian 2014[164]	Phase II Single-arm	Bendamustine 60 mg/m^2 plus thalidomide 200 mg plus DEX 20 mg	18	Patients with rrMM after treatment with bortezomib and lenalidomide or who are ineligible to these drugs	Safety, ORR	Abstract only	Unclear (abstract only)
Abbreviations: CS, company submission; ITC, indirect treatment comparison; DEX, dexamethasone; EFS, event-free survival; IMiD, immunomodulatory drug; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pg, page; rrMM, relapsed and refractory multiple myeloma; TTP, time to treatment progression.							

10.2 Quality assessment

Table 93. Quality assessment for MMY2002 (adapated from CS, Appendix 4, pg. 57, Table 7)

	Company assessment		ERG assessment	
Study question	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias
Were attempts made to minimise selection bias?	Yes. Patients were randomly assigned to 8 mg/kg or 16 mg/kg daratumumab monotherapy using an IWRS. Randomisation was balanced by using randomly permuted blocks and stratified by ISS staging and refractory status.	Low	Yes. Patients in Part 1 Stage 1 were randomised in a 1:1 ratio to either 8 mg/kg or 16 mg/kg daratumumab using an IWRS. Randomisation was balanced using permuted blocks and the sample was stratified by ISS staging and refractory status. Part 1 Stage 2 and Part 2 of study were not randomised as all people enrolled received daratumumab 16 mg/kg.	Low
Do the selected patients represent the eligible population for the intervention?	In part. All patients enrolled were in line with licence terms; however, patients represent a heavily pre-treated and highly refractory cohort within the licensed population. Any bias caused by this would be against daratumumab monotherapy.	Medium (negative bias)	In part. As noted by the company, people enrolled within MMY2002 are in line with the licence, the positive opinion issued by the EMA and the population of interest to the decision problem set out by NICE. However, eligibility criteria for MMY2002 stipulate receipt of at least 3 prior lines of therapy, which means that the population in MMY2002 has been more heavily pre-treated prior to daratumumab than would be expected for the licensed population. In addition, prior therapies received should be	Medium

			considered for individual decision-making settings. For example, some of the listed therapies received before daratumumab are not available treatment options to clinicians in the UK (e.g., carfilzomib).	
Did the setting reflect UK practice?	In part. Daratumumab was administered by IV in the hospital setting, as would be the case in UK practice, and the majority of patients were treated with the licensed dose. Baseline demographics and disease characteristics generally representative of typical patients presenting with rrMM in UK clinical practice; however, patients represent a heavily pre-treated and highly refractory cohort and previous treatments include agents yet to be routinely funded in the UK. Any bias caused by this would be against daratumumab monotherapy.	Medium (negative bias)	No. As noted by the company, the population in MMY2002 is heavily pre-treated and seems more refractory to treatment than that of GEN501. Importantly, people received treatments prior and subsequent to daratumumab that are not available treatment options within the UK. The direction of bias resulting from differences in treatment pathways cannot be determined.	High
Were all participants accounted for at study conclusion?	Yes.	Low	Yes. All enrolled people were accounted for. In addition, everyone that received at least one dose of daratumumab were included in safety and efficacy analyses.	Low
Were outcome measures reliable? And were all clinically relevant outcome measures assessed?	Yes. Efficacy assessed in terms of response and survival which are the key outcome measures relevant to patients and clinicians alike. Outcome measures were in line with trial validated methodology (IMWG) and response assessments performed by a central laboratory and reviewed by an IRC.	Low	In part. Primary outcome was objective response rate as assessed by an IRC. Secondary outcomes included PFS and OS. All reported outcomes are standard outcomes for assessment in oncological conditions and are clinically relevant. However, it should be noted that single-arm studies, such as MMY2002 Stage 2, are not suitable for recording time-to-event outcomes, such as PFS and OS.	Low (for primary outcome)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Analyses included all treated patients with standard censoring methods used to account for missing data. The most common reason for study withdrawal in both studies was disease progression, which is accounted for within the efficacy assessments.	Low	Unclear. ITT analysis was not specified but methods suggest all people that received one dose of daratumumab were included in the analysis. Censoring methods were appropriate. Most people withdrew from the study due to disease progression.	Unclear
Are the study results internally valid?	Yes.	Low	No. Although MMY2002 was conducted and analysed in line with the study protocol, as an observational study, the	High

	Analyses conducted in accordance with approved statistical methods.		study is open to bias, as is well recognised for this study design, and results should be interpreted with caution.	
Are the findings externally valid?	Yes. Analyses are all reflective of evidence on which treatment decisions will be made in clinical practice.	Low	No (considering the UK perspective). Population does not reflect the population that will be eligible for treatment within the UK (due to exposure to treatments not currently available within the UK, including carfilzomib).	High

Abbreviations: CS, company submission; IMiD, immunomodulatory agent; IMWG, International Myeloma Working Group; IRC, independent review committee; ISS, International Staging System; ITT, intention-to-treat; IV, intravenous; IWRS, interactive web response system; OS, overall survival; PFS, progression-free survival; pg, page; PI, proteasome inhibitor; rrMM, relapsed refractory multiple myeloma.

Source: Lonial et al. 2016[165]; Janssen et al. 2015.[166]; Lokhorst et al. 2015[167]; Janssen et al. 2015.[168]

Table 94. Quality assessment for GEN501 (adapated from CS, Appendix 4, pg. 57, Table 7)

	Company assessment		ERG assessment	
Study question	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias
Were attempts made to minimise selection bias?	Yes. Patients were sequentially allocated to treatment.	Low	No. Patients were not randomised to treatment in GEN501 Part 1.	High
Do the selected patients represent the eligible population for the intervention?	In part. All patients enrolled were in line with license terms; however, patients represent a heavily pre-treated and highly refractory cohort within the licensed population. Any bias caused by this would be against daratumumab monotherapy.	Medium (negative bias)	In part. As noted by the company, people enrolled within GEN501 are in line with the licence, the positive opinion issued by the EMA and the population of interest to the decision problem set out by NICE. However, baseline characteristics indicate that people in GEN501 Part 2 have been more heavily pre-treated prior to daratumumab than would be expected for the licensed population. In addition, prior therapies received should be considered for individual decision-making settings. For example, some of the listed therapies received before daratumumab are not available treatment options to clinicians in the UK (e.g., carfilzomib).	Medium
Did the setting reflect UK practice?	In part. Daratumumab was administered by IV in the hospital setting as would be the case in UK practice and the majority of patients were treated with the license dose. Baseline demographics and disease characteristics generally representative of typical patients presenting with rrMM in UK clinical practice; however, patients represent a	Medium (negative bias)	No. As noted by the company, the population in GEN501 Part 2 (from which evidence is derived) is heavily pre-treated. Importantly, people received treatments prior and subsequent to daratumumab that are not available treatment options within the UK. The direction of bias resulting from differences in treatment pathways cannot	High

	heavily pre-treated and highly refractory cohort, and previous treatments include agents yet to be routinely funded in the UK. Any bias caused by this would be against daratumumab monotherapy.		be determined. Additionally, baseline demographics relating to cytogenetics and ISS staging were not recorded, which precludes assessment and comparison of the performance status of the GEN501 population.	
Were all participants accounted for at study conclusion?	Yes.	Low	Unclear. No details were given as to whether all patients enrolled for accounted for in analyses.	High
Were outcome measures reliable? And were all clinically relevant outcome measures assessed?	Yes. Efficacy assessed in terms of response and survival which are the key outcome measures relevant to patients and clinicians alike. Outcome measures were in line with trial validated methodology (IMWG) and response assessments performed by a computerised algorithm.	Low	In part. Primary outcome was safety rather than an outcome assessing clinical efficacy of daratumumab. Objective response rate, PFS and OS were recorded as secondary outcomes. All reported outcomes are standard outcomes for assessment in oncological conditions and are clinically relevant. However, it should be noted that single-arm studies, such as GEN501 Part 2, are not suitable for recording time-to-event outcomes, such as PFS and OS. Additionally, clinical outcomes were assessed using a computerised algorithm that was developed using MMY2002 data and validated by the MY2002 IRC.	Low (for safety and objective response)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Analyses included all treated patients with standard censoring methods used to account for missing data. The most common reason for study withdrawal in both studies was disease progression, which is accounted for within the efficacy assessments.	Low	Unclear. It is unclear from the study methods whether all people were accounted for in analyses. Censoring and data management processes were appropriate.	Unclear
Are the study results internally valid?	Yes. Analyses conducted in accordance with approved statistical methods.	Low	No. Although GEN501 was conducted and analysed in line with the study protocol, as an observational study, the study is open to bias, as is well recognised for this study design, and results should be interpreted with caution.	High
Are the findings externally valid?	Yes. Analyses are all reflective of evidence on which treatment decisions will be made in clinical practice.	Low	No (considering the UK perspective). Population does not reflect the population that will be eligible for treatment within the UK (due to exposure to treatments not currently available within the UK, including carfilzomib).	High

Abbreviations: AE, adverse event; CS, company submission; EMA, European Medicines Agency; IMiD, immunomodulatory agent; IMWG, International Myeloma Working Group; IRC, independent review committee; ISS, International Staging System; IV, intravenous; IWRS, interactive web response system; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pg, page; PI, proteasome inhibitor; rrMM, relapsed refractory multiple myeloma.
Sources: Lonial et al. 2016[165]; Janssen et al. 2015.[166]; Lokhorst et al. 2015[167]; Janssen et al. 2015.[168]

Table 95. Quality assessment of the PANORMA 2 study (adapted from CS, Appendix 8, pg. 73, Table 12)

	Company assessment		ERG assessment	
Study question	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias
Were attempts made to minimise selection bias?	Single group assignment.	Medium	No Single group study, open label design.	High
Do the selected patients represent the eligible population for the intervention?	Yes. All patients enrolled were generally in line with license terms for daratumumab.	Low	In part People enrolled to PANORAMA 2 are in line with the marketing authorisation for panobinostat and the population specified in NICE recommendations for use in rrMM: NICE recommends pano+bort+dex for 'adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent', However, baseline characteristics indicate that the median number of prior therapies received was 4, which suggests a more heavily pre-treated population than would be expected than would be expected for population eligible for treatment with daratumumab or pano+bort+dex.	Medium
Did the setting reflect UK practice?	Yes. Panobinostat was initiated in the hospital setting and administered in combination with bortezomib and dexamethasone as would be the case in UK practice. Baseline demographics and disease characteristics generally representative of typical patients presenting with rrMM in UK clinical practice.	Low	Yes. As noted by the company, panobinostat was administered in PANORAMA 2 as it would be in UK clinical practice. Importantly, baseline characteristics suggest that prior therapies received before enrolment into PANORAAMA 2 are analogous to those used in UK clinical practice: reported characteristics suggest that no one received carfilzomib or pomalidomide prior to pan+bort+dex.	Low
Were all participants accounted for at study conclusion?	Yes.	Low	Yes. All patients accounted for, with details of discontinuation rate and reason for discontinuation.. Primary reason for study discontinuation was disease progression (56.4%),	Low

			AE (18.2%), withdrawn consent (9.1%) and death (1.8%)	
Were outcome measures reliable? And were all clinically relevant outcome measures assessed?	Yes. Efficacy assessed in terms of response and survival which are the key outcome measures relevant to patients and clinicians alike. Outcome measures were in line with trial validated methodology (EBMT and IMWG).	Low	In part Primary outcome was ORR. Secondary outcomes included PFS, OS and AE. It is unclear whether an IRC evaluated clinical response and other outcomes. Reported outcomes are standard outcomes for assessment in oncological conditions and are clinically relevant. However, it should be noted that single-arm studies, such as PANORAMA 2, are not suitable for recording time-to-event outcomes, such as PFS and OS.	High
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Analyses included all treated patients. No details were given on methods to account for missing data	Unclear	Unclear. ITT analysis was not specified but methods suggest that all people enrolled in PANORAMA 2 were included in the analysis. Details on methods to account for missing data are not provided.	Unclear
Are the study results internally valid?	Yes. Analyses conducted in accordance with approved statistical methods.	Low	No. As an observational study, PANORAMA 2 is open to bias, as is well recognised for this study design, and results should be interpreted with caution.	High
Are the findings externally valid?	Yes. Analyses are all reflective of evidence on which treatment decisions will be made in clinical practice.	Low	Yes. Population enrolled in PANORAMA 2 is representative of UK clinical practice.	Low

Abbreviations: AE, adverse event; CS, company submission; EBMT, European Society for Blood and Marrow Transplantation; IMWG, International Myeloma Working Group; ORR, overall response rate; OS, overall survival; pano+bort+dex, panobinostat+bortezomib+dexamethasone; PFS, progression-free survival; pg, page; rrMM, relapsed and refractory multiple myeloma.
Source: Richardson et al. 2013.[169]

Table 96. Quality assessment of MM-003 study (adapted from CS, Appendix 8, pg. 77, Table 14)

	Company assessment		ERG assessment	
Study question	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias
Was randomisation carried out appropriately?	Yes.	Low	Yes. Patients were randomised in a 2:1 ratio to either pom+LoDEX or HiDEX. Randomisation was stratified by	Low

	Patients were randomised in a 2:1 ratio with stratification according to age, disease status and number of previous treatments.		age (≤75 years vs >75 years), disease status (refractory vs relapsed and refractory vs bortezomib intolerant) and number of previous treatments (two vs three or more).	
Was the concealment of treatment allocation adequate?	Yes. Patients were randomised using an IVRS.	Low	Yes. Allocation carried out using an IVRS .	Low
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes. Patient characteristics between treatment arms were well balanced; prognostic factors including number of previous treatments were evenly distributed.	Low	Yes. Patient baseline characteristics were well balanced between groups.	Low
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Open-label study. Potential impact on the risk of bias for primary outcome analysis as it was investigator assessed.	Medium	No Open-label RCT. Reported in full publication that outcomes were assessed by investigators not masked to treatment. However, subsequent publication reports that an independent Response Adjudication Committee (IRAC) reviewed all efficacy data in a blinded manner to ensure an unbiased assessment. Given that the MAIC carried out by the company is based on the full publication, the ERG assumes that the risk of bias in MM-003 in this context is high.	High
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No. Comparable rates of discontinuation with the most common reason for treatment discontinuation attributed to PD, accounted for within efficacy assessments.	Low	No Although rate of discontinuation was high, a similar proportion of people discontinued from each arm (80% for pom+LoDEX vs 92% for HiDEX). Most people discontinued as a result of disease progression or adverse event.	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. Results for primary and secondary outcomes presented in primary publication.	Low	No. Primary and secondary outcomes reported as described in methods.	High

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. However, high cross-over rates limits interpretation of OS analysis using the ITT principle.	Medium	Yes. ITT used and appropriate methods used to adjust for missing data.	Low
Was statistical powering such to detect a significant difference between treatment groups?	Yes.	Low	Yes. Detail of statistical power calculation for sample size discussed. The required number of people for determined power was recruited.	Low
Abbreviations: CS, company submission; HiDEX, high-dose dexamethasone; ITT, intention-to-treat; IVRS, interactive voice response system; OS, overall survival; PD, progressive disease; PFS, progression-free survival; pg, page; pom+LoDEX, pomalidomide plus low-dose dexamethasone. Source: San Miguel et al. 2013.[170]				

10.3 International Uniform Response Criteria Consensus Recommendations

Table 97. International Uniform Response Criteria Consensus Recommendations (reproduced from CSR for MMY2002[53])

Response	Response Criteria
Stringent complete response (sCR)	• CR as defined below, plus • Normal FLC ratio, and • Absence of clonal PCs by immunohistochemistry, immunofluorescencea or 2- to 4-color flow cytometry
Complete response (CR)*	• Negative immunofixation on the serum and urine, and • Disappearance of any soft tissue plasmacytomas, and • <5% PCs in bone marrow
Very good partial response(VGPR)*	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, or • ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours
Partial response (PR)	• ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours • If the serum and urine M-protein are not measurable, a decrease of ≥50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥50% reduction in bone marrow PCs is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% • In addition to the above criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
Minimal response (MR)	• In subjects with relapsed refractory myeloma adopted from the EBMT criteria • ≥25% but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by50% to 89% • In addition to the above criteria, if present at baseline, 25% to 49% reduction in the size of soft tissue plasmacytomas is also required • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR, or progressive disease

Progressive disease (PD)†	Any one or more of the following criteria:
	• Increase of 25% from lowest response value in any one of the following:
	  • Serum M-component (absolute increase must be ≥0.5 g/dL)
	  • Urine M-component (absolute increase must be ≥200 mg/24 hours)
	• Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL)
	• Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥10%)
	• Bone marrow plasma cell percentage: the absolute percentage must be >10%
	• Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas. A definite increase is defined as a 50% (and at least 1 cm) increase as measured

	serially by the sum of the products of the cross-diameters of the measurable lesion • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the PC proliferative disorder

All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither.

Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

* Clarifications to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such subjects requires a >90% decrease in the difference between involved and uninvolved FLC levels.

† Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in subjects without measurabledisease by M protein and by FLC levels; "25% increase" refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the "lowest response value" does not need to be a confirmed value.

[a] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of >4:1 or <1:2.

Clinical Relapse

Clinical relapse is defined using the definition of clinical relapse in the IMWG criteria.[66] In the IMWG criteria, clinical relapse is defined as requiring one or more of the following direct indicators of increasing disease or end-organ dysfunction that are considered related to the underlying plasma cell proliferative disorder:

1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, magnetic resonance imaging, or other imaging
2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
3. Hypercalcemia (>11.5 mg/dL; >2.875mM/L)
4. Decrease in hemoglobin of more than 2 g/dL (1.25 mM) or to less than 10 g/dL
5. Rise in serum creatinine by more than or equal to 2 mg/dL (≥77 mM/L)
6. Hyperviscosity

In some subjects, bone pain may be the initial symptom of relapse in the absence of any of the above features. However, bone pain without imaging confirmation is not adequate to meet these criteria in studies.

Abbreviations: EBMT, European Group for Blood and Marrow Transplantation; FLC, free light chain; PC, plasma cell.

10.4 PANORAMA 2: patient demographics and methods

Table 98. Key study characteristics of PANORAMA 2 (reproduced from CS, Appendix 8, pg. 71, Table 11)

Characteristic	Description
Location	12 sites in the US
Trial design	A Phase II, two-stage, single-arm, open-label multicentre study of oral panobinostat in combination with bortezomib and dexamethasone in patients with rrMM
Method of allocation	Single arm trial
Key inclusion criteria	≥18 years of age; relapsed and bortezomib-refractory MM (progressed on or within 60 days of the last bortezomib-containing regimen); received at least 2 prior lines of therapy; been exposed to an IMiD; measurable disease, defined as M protein ≥10g/L or urine M protein ≥200 mg per 24 hours, based on IMWG 2003 definitions; ECOG PS ≤2; absolute neutrophil count ≥1.0x10^9/L; platelet count ≥70x10^9/L; electrolyte levels within normal limits and transaminase levels ≤2.5 x ULN
Key exclusion criteria	Primary refractory disease; prior MM therapy with a DACi; history of allogeneic stem cell transplant with active graft-versus-host disease requiring immunosuppressive therapy and/or peripheral Grade ≥2

Study drugs	Patients were treated in two phases, both with a 2-week-on/1-week-off schedule. Phase 1 treatment (N=55) consisted of eight 3-week cycles of oral panobinostat 20 mg, 3 times per week on Weeks 1 and 2 + bortezomib 1.3 mg/m^2 IV 2 times per week on Weeks 1 and 2 + oral dexamethasone 20 mg, 4 times per week on Weeks 1 and 2 on days of and after bortezomib use. Patients who showed evidence of clinical benefit in phase 1 treatment continued study therapy in phase 2 treatment, which consisted of 6-week cycles of panobinostat 3 times per week on Weeks 1, 2, 4 and 5 + bortezomib once per week on Weeks 1, 2, 4 and 5 + dexamethasone on the days of and after bortezomib until disease progression, death, toxicity or withdrawal of consent
Primary outcome(s)	ORR, defined as the proportion of patients with a best overall disease response of better than or equal to partial response (PR; CR or near-CR or PR)
Secondary outcomes(s)	PFS, OS, TTP, TTR
Efficacy evaluations	Disease assessments were based on modified EBMT 1998 criteria, with the exploratory objective of VGPR determined by IMWG 2008 uniform criteria. Disease assessments—performed every 3 weeks, with responses confirmed after 6 weeks—entailed measurements of serum M protein (serum protein electrophoresis), urine M protein (urine protein electrophoresis), serum-free light chains, immunoglobulins (serum immunofixation), urine proteins (urine immunofixation), and evaluation of soft tissue plasmacytomas. In addition, bone marrow aspirate for plasma cell count was assayed at screening and for complete response (CR) confirmation, and skeletal surveys were performed at screening and during the study if they were clinically indicated. Patients who discontinued study treatment for reasons other than documented disease progression continued to have disease assessments performed every 6 weeks until documented disease progression or death. After disease progression, patients were followed every 3 months for survival for up to 2 years. Safety was monitored throughout the trial and up to 28 days after the last dose of study treatment. Adverse events (AEs) were assessed according to Common Terminology Criteria for Adverse Events version 4.0. Electrocardiogram monitoring was performed throughout the first 8 cycles. The Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity subscale version 4.0 was used to determine the presence and intensity of neuropathic pain and/or peripheral neuropathy at baseline, Day 1 of cycle 1, and every 6 weeks thereafter
Statistical analysis	Additional statistical tests were performed at a 2-sided significance level of .05. Point estimates and exact 95% confidence intervals were calculated for response rates, and Kaplan–Meier estimates were used to summarise PFS and OS. All authors had access to the primary trial data
Sample size, power calculation	Sample size was estimated based on a 2-stage design to test the null hypothesis of a response rate of P < 10% vs an alternative hypothesis of a response rate of P ≤ 10%. Using a 1-sided type I error rate of 0.05 and 80% power, 47 evaluable patients were required for the study. At least 4 responses were required in stage 1 (n=24) to enrol an additional 23 patients in stage 2, and at least 9 of 47 patients at the end of stage 2 were needed to reject the null hypothesis
Data cuts and follow-up, median months (range)	Data are presented as of February 20, 2012. Median follow-up: 8.3 months
Abbreviations: CS, company submission; ECOG, Eastern Cooperative Oncology Group; EBMT, European Society for Blood and Marrow Transplantation; IMiD, immunomodulatory agent; IMWG, International Myeloma Working Group; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression free survival; PS, performance status; TTP, time to progression; TTR, time to response; US, United States; VGPR, very good partial response.	

Table 99. Baseline characteristics of population enrolled in PANORAMA 2 [81]

Characteristic	Result (N=55)
Female/male, n (%)	26/29 (47.3/52.7)
Median age, y (range)	61 (41–-88)
Age, ≥65 y, n (%)	21 (38.2)
ECOG performance status, n (%)	
0	26(47.3)

1	25 (45.5)
2	4 (7.3)
Baseline serum albumin (g/L), median (range)	36.9 (30.6–48.9)
Baseline serum M protein (g/L), median (range)	26.0 (0–66.0)
Baseline urine M protein (mg/24 h), median (range)	283 (0–9628)
ISS staging, n (%)	
Stage 1	18 (32.7)
Stage 2	23 (41.8)
Stage 3	13 (23.6)
Missing[a]	1 (1.8)
Immunoglobulin subtype, n (%)	
IgG	35 (63.6)
IgA	12 (21.8)
IgM	1 (1.8)
Indeterminate	7 (12.7)
Light-chain subtype, n (%)	
Kappa	37 (67.3)
Lambda	16 (29.1)
Indeterminate	2 (3.6)
FISH, n (%)	
Normal	2 (3.6)
Any abnormality[b]	35 (63.6)
del(17p), t(4;14), or t(14;16)	14 (25.5)
del(13q)	5 (9.1)
t(11;14)	14 (25.5)
3+	1 (1.8)
Median time since diagnosis, months (range)	54.8 (7.5–263.6)
Prior regimens, median (range)	4 (2–11)
Prior therapy, n (%)	
Bortezomib	55 (100.0)
Dexamethasone	55 (100.0)
Lenalidomide	54 (98.2)
Thalidomide	38 (69.1)
Prior autologous stem cell transplant, n (%)	31 (56.4)
Median cumulative duration of prior bortezomib[c], months (range)	8.7 (1.6–42.6)
Prior bortezomib regimens, median (range)	2 (1–6)
Progressed while on last bortezomib regimen, n (%)	40 (72.7)
Progressed ≤60 d after last bortezomib regimen, n (%)	15 (27.3)
Bortezomib in most recent prior regimen, n (%)	27 (49.1)
Dexamethasone in most recent prior regimen, n (%) 37 (67.3)	
Dexamethasone in last bortezomib-containing regimen, n (%)	45 (81.8)
Best response at last treatment, n (%)	
Complete response	1 (1.8)
Partial response	11 (20.0)
Minimal response	10 (18.2)
Stable disease	8 (14.5)

Progressive disease	17 (30.9)
None	5 (9.1)
Unknown	3 (5.5)

[a] One patient did not have baseline beta-2 microglobulin measurement.

[b] Not all subcategories of abnormalities are presented, and patients could present with more than 1 abnormality.

[c] One patient had missing data.

Abbreviations: del, deletion; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; Ig, immunoglobulin; ISS, International Staging System; t, translocation.

10.5 MM-003: patient demographics and methods

Table 100. Key study characteristics of MM-003 (reproduced from CS, Appendix 8, pg. 74, Table 13)

Characteristic	Description
Location	93 centres in Australia, Canada, Europe, Russia and the USA.
Trial design	Multicentre, open-label, randomised Phase III trial to compare the efficacy and safety of pomalidomide plus low-dose dexamethasone with high-dose dexamethasone in patients with rrMM.
Method of allocation	Patients were randomly assigned in a 2:1 ratio with a validated interactive voice and internet response system using a randomly permuted block within strata. Stratification factors were age (≤75 years vs >75 years), disease status (refractory vs relapsed and refractory vs bortezomib intolerant), and number of previous treatments (two vs three or more).
Key inclusion criteria	Patients were included if they were refractory to their previous treatment; judged to have refractory or relapsed and refractory disease; had received at least two previous consecutive cycles of bortezomib and lenalidomide, alone or in combination; had adequate alkylator treatment (at least six cycles of alkylator treatment, or progressive disease after at least two cycles of alkylator treatment, or received alkylator treatment as part of a stem-cell transplant); older than 18 years. Patients must have failed (progressive disease on or before 60 days of treatment, progressive disease ≤6 months after achieving partial response, or intolerance to bortezomib) treatment with bortezomib or lenalidomide. Also included were patients who developed treatment intolerance after a minimum of two cycles of bortezomib and had developed progressive disease on or before 60 days after completing their last treatment.
Key exclusion criteria	Patients were ineligible if they had previously received pomalidomide; had hypersensitivity to thalidomide, lenalidomide, or dexamethasone; or had resistance to high-dose dexamethasone (progressive disease on or within 60 days of the last dose used in their previous treatment). Patients were also considered ineligible if they had peripheral neuropathy of Grade 2 or more; substantial cardiac disease (New York Heart Association Class III or IV, congestive heart failure, myocardial infarction on or within 12 months or unstable or poorly controlled angina); or showed any of the following laboratory abnormalities: absolute neutrophil count of less than 1×10^9 per L, platelet count of less than 75×10^9 per L ($<30 \times 10^9$ per litre if ≥50% of bone marrow nucleated cells were plasma cells); creatinine clearance of less than 45 mL/min according to the Cockroft-Gault formula or 24-hour urine collection; corrected serum calcium greater than 3·5 mmol/L; total bilirubin greater than 34·2 µmol/L; haemoglobin less than 80 g/L (4·9 mmol/L); or liver enzyme concentrations greater than three times the upper limit of normal.
Study drugs	POM+DEX (N=302): pomalidomide 4 mg/day on Days 1-21 of a 28-day cycle, orally plus low dose dexamethasone 40 mg/day on Days 1, 8, 15 and 22, orally DEX (N=153): high dose dexamethasone 40 mg/day on Days 1-4, 9-12 and 17-20 of a 28-day cycle Treatment was continued until progressive disease or unacceptable toxicity. Dexamethasone dose was reduced to 20 mg/day in all patients over 75 years and dose modifications were in accordance with institutional guidelines. Pomalidomide was withheld for Grade ≥4 neutropenia, febrile neutropenia and thrombocytopenia; Grade ≥3 venous thromboembolism, constipation, peripheral neuropathy and rash; Grade ≥2 hypothyroidism or hyperthyroidism; and all other Grade

	≥3 treatment-related AEs. On Day 1 of the next treatment cycle, the dose of pomalidomide was to be reduced by 1mg. Patients progressing on DEX could receive pomalidomide at the same dose, but without dexamethasone in a companion trial (MM-003 C). At the time of the final PFS analysis, the IDMC indicated that the trial met the primary endpoint and the upper boundary for superior OS had been crossed despite 45 patients in the DEX group crossing over to receive pomalidomide. In accordance with predefined stopping rules, the committee recommended that patients assigned to DEX who had not progressed should have access to pomalidomide (± dexamethasone).
Permitted and disallowed concomitant medications	Appropriate concomitant treatments for adverse events were permitted. Thromboprophylaxis was required for patients receiving pomalidomide or those at high risk of developing thrombosis. Choice of thromboprophylaxis and use of myeloid and erythroid growth factors was left to the physician's discretion.
Primary outcome(s)	PFS.
Secondary outcomes(s)	OS; ORR, defined as the proportion of patients who achieved at least a partial response; TTP; DoR; Safety; QoL.
Efficacy evaluations	The study used the IMWG 12 or EBMT for assessment of response (EBMT used for minor response only). Disease evaluations were performed by investigator assessment for primary analysis of PFS and ORR. Severity of AEs was graded in accordance with the CTCAE (version 4.0). SAEs were defined as fatal, life-threatening, requiring or prolonging hospitalisation, causing persistent or substantial disability or incapacity, involving a congenital anomaly or a birth defect, or constituting any other important medical event. Efficacy assessments were done in the ITT population (all randomly assigned patients), and safety assessment was done in the safety population (all patients who received at least one dose of study treatment). Follow-up for OS and new cancers (second primary malignancy) was planned to occur every 84 days for up to 5 years after randomisation.
Statistical analysis	PFS was estimated with the K-M product-limit method, and a log-rank test (stratified) was used as the primary analytic method to compare survivorship functions between groups. OS was only to be tested if the difference in PFS between treatment groups was significant. Alpha was controlled at the 0·05 level with a two-sided test for both PFS and OS. The final OS analysis was to be done after 212 patients from both treatment groups died during the study. An interim survival analysis was also planned at either the same time as the final PFS analysis or when 106 deaths (50% overall survival information) had occurred, whichever happened later (conducted at the time of final OS when 134 deaths had occurred). The O'Brien Fleming boundary for superiority was used for the interim survival analysis and was based on the actual numbers of events (deaths). The alpha level for the final survival analysis was to be adjusted accordingly. Statistical analysis was done with the SAS software (version 9.2).
Sample size, power calculation	Target accrual was 426 patients (284 in the POM+DEX group and 142 in the DEX group) to have 242 PFS events (disease progression or death) with 85% power to detect a 50% improvement in median PFS (hazard ratio [HR] 1·5 for POM+DEX vs DEX) at a two-sided significance level of 0·05. An interim analysis was planned for PFS using a group sequential procedure at 121 PFS events (50% information). If the futility boundary was crossed, the IDMC could stop the trial.
Data cuts and follow-up, median months (range)	Final PFS and interim OS, September 7 2012: follow-up = 4.2 (2.0-7.1) Updated PFS and final OS, March 1 2013: follow-up = 10.0 (7.2-13.2)
Abbreviations: AE, adverse event; CS, company submission; CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; DEX, high-dose dexamethasone; DoR, duration of response; EBMT, European Society for Blood and Marrow Transplantation; IDMC, independent data monitoring committee; IMWG, International Myeloma Working Group; ITT, intention-to-treat; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pg, page; POM+DEX, pomalidomide plus dexamethasone; QoL, quality of life; rrMM, relapsed refractory multiple myeloma; SAE, serious adverse events; TTP, time to progression.	

Table 101. Baseline characteristics of the ITT population in MM-003[92]

Characteristic	Pomalidomide + LoDEX	HiDEX

	(N=302)	(N=153)
Age (years)		
Mean (SD)	63.6 (9.3)	63.7 (9.6)
Median (min, max)	64 (35, 84)	65 (35, 87)
Age >65 years, n (%)	135 (44.7)	72 (47.1)
Sex, males, n (%)	181 (59.9)	87 (56.9)
Race, white, n (%)[a]	244 (80.8)	113 (73.9)
Baseline beta-2-microglobulin (mg/L)		
N	289	146
Median (min, max)	4.6 (1.6 to 31.8)	4.4 (1.6 to 30.0)
ISS, n (%)*		
I/II	197 (65.2)	93 (60.8),
III	93 (30.8)	54 (35.3)
Missing	12 (4.0)	6 (3.9)
Baseline ECOG performance status, n (%)		
0	110 (36.4)	36 (23.5)
1	138 (45.7)	86 (56.2)
2	52 (17.2)	25 (16.3)
3	0 (0.0)	3 (2.0)
Missing	2 (0.7)	3 (2.0)
Median (min, max) time from first pathological diagnosis (years)	5.3 (0.6, 30.0)	6.1 (0.9, 21.1)
Cytogenetic risk, n (%)		
High risk[b]	130 (43.0)	57 (37.3)
Non high risk	91 (30.1)	47 (30.7)
Modified high risk[c]	77 (25.5)	35 (22.9)
Missing	81 (26.8)	49 (32.0)
Baseline renal function (CrCl)		
<30 mL/min	2 (0.7)	3 (2.0)
30-<45 mL/min	28 (9.3)	15 (9.8)
45-<60 mL/min	65 (21.5)	41 (26.8)
60-<80 mL/min	97 (32.1)	41 (26.8)
≥80 mL/min	108 (35.8)	52 (34.0)
Missing	2 (0.7)	1 (0.7)
Median (min, max) number of prior anti-myeloma therapies	5 (2, 14)	5 (2, 17)
Previous treatments		
BOR	302 (100.0)	153 (100.0)
LEN	302 (100.0)	153 (100.0)
Alkylators	299 (99.0)	150 (98.0)
DEX	295 (97.7)	152 (99.3)
Autologous stem-cell transplantation	214 (70.9)	105 (68.6)
THAL	173 (57.3)	93 (60.8)
Refractory multiple myeloma	249 (82.5)	125 (81.7)
Refractory to LEN	286 (94.7)	141 (92.2)
Refractory to BOR	238 (78.8)	121 (79.1)

Refractory to both BOR and LEN	225 (74.5)	113 (73.9)
Refractory to THAL	90 (29.8)	48 (31.4)
Intolerant to BOR	45 (14.9)	23 (15.0)

[a] Race/ethnicity was not permitted to be collected by law in some regions.

[b] High risk is defined as any cytogenetic abnormality in 13q14, 17p13, 4p16/14q32 or 14q32/16q23.

[c] Modified risk is defined as any cytogenetic abnormality in 17p13 or 4p16/14q32.

Source: * Data were obtained from the CSR except for ISS which was obtained from San Miguel 2013. Data cut-off: 01 March 2013.

Abbreviations: BOR, bortezomib; CrCl, creatinine clearance; DEX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; HiDEX, high-dose dexamethasone; ISS, International Staging System; ITT, intention to treat; LEN, lenalidomide; LoDEX, low-dose dexamethasone; POM, pomalidomide; SCT, stem cell transplantation; SD, standard deviation; THAL, thalidomide.

Daratumumab for treating relapsed and refractory multiple myeloma [ID933]

ERRATUM

This report was commissioned by the NIHR HTA Programme as project number 16/10/05

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the company's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
16, 24, 56, 72, 77, 79, 84	Text amended in the sentences flagged by the company to reflect that that pomalidomide was available through the Cancer Drugs Fund. After consulting with clinical experts, the ERG has amended the text to read (or something similar depending on the section) "However, other therapies given prior to daratumumab in MMY2002 and GEN501 included carfilzomib and pomalidomide, both of which will have had limited use in UK clinical practice as a treatment for rrMM: carfilzomib has never been an available treatment option outside of clinical trials and a compassionate use scheme, and pomalidomide was available for treatment of rrMM through the Cancer Drugs Fund for a limited period between April 2013 and September 2015, when it was de-listed."
19, 95, and 126	Number of people receiving subsequent treatment marked as commercial in confidence.
20, 95, 126	The sentence "median OS of those receiving [redacted]" has been amended to "For MMY2002, median OS of those receiving [redacted]".
20, 127, 129	95.6% amended to 95.8%
23	The sentence "The PFS HRs used in the company's base case are 1.24 (95% CI: 0.92 to 1.68) for pom+dex and 1.74 (95% CI: 1.24 to 2.26) for pano+bort+dex" has been amended to "The PFS HRs used in the company's base case are 1.24 (95% CI: 0.92 to 1.68) for pom+dex and 1.09 (95% CI: 0.74 to 1.61) for pano+bort+dex".
26, 187, 260	The sentence "The ERG interprets this trend in the data as a possible consequence of the effect of daratumumab as a subsequent therapy" has been replaced with "The ERG interprets this trend in the data as a possible consequence of the effect of pomalidomide as a subsequent therapy".
27, 229	The marking on Figure A and Figure 44 has been amended from academic in confidence to commercial in confidence.
29	The sentence "The company's base case approach … is also likely to overestimate the survival benefit compared with pano+bort+dex" has been replaced with "The company's base case approach … underestimates the survival benefit compared with pano+bort+dex".
33	Figure I has been labelled as "ERG's preferred approach to OS curves".
35	Figure K has been labelled as "ERG's preferred approach to PFS curves".
58	The sentence "The FDA approval aligns with the company's positioning of daratumumab as an alternative treatment at fourth-line and higher (Table 6)..." has been amended to "The FDA approval partly aligns with the company's positioning of daratumumab as an alternative treatment at fourth-line and higher (Table 6)...".
74	The sentence "Over the duration of the study, 90 people (85%) discontinued treatment with daratumumab. The most common reason for discontinuation was disease progression (82 people [77%])" has been replaced with "Over the duration of the study (data cut off December 2015), 100 people (94.3%) discontinued treatment with daratumumab. The most common reason for discontinuation was disease progression (92 people [86.8%])".
131	The sentence "All HRs presented by the ERG are the inverse of the company's reported HRs (i.e. 1/company's HRs) to reflect the comparator treatment as the base. Therefore an HR> 1 reflects a gain in survival with daratumumab and a HR<1 reflects a loss in survival with daratumumab" has been added.

137	The sentence “the company states that the unique mechanism of action associated with daratumumab monotherapy appears to change the natural course of disease in rrMM as its favourable safety profile is potentially associated with a disease reset. This culminates in an improved health status of patients, allowing them to receive further active treatments (and retreatment with drugs received previously) to re-stabilise their disease” has been replaced with “the company states that the unique mechanism of action associated with daratumumab monotherapy appears to change the natural course of disease in rrMM and is potentially associated with a disease reset. This, along with its favourable safety profile culminates in an improved health status of patients, allowing them to receive further active treatments (and retreatment with drugs received previously) to re-stabilise their disease”.
145, 211	The sentence “Time to treatment discontinuation is used by the company to model treatment costs for daratumumab and pom+dex. This is done by subtracting the PFS curve from the TTD curve for each treatment, to obtain time on treatment for daratumumab and pom+dex patients (TOT = P(PFS)-P(TTD)).” has been replaced with “Time to treatment discontinuation is used by the company to model treatment costs for daratumumab and pom+dex. This is done by using the TTD curve to calculate treatment costs. The TTD curve is subtracted from the PFS curve for each treatment, to obtain PFS (off Tx) for daratumumab and pom+dex patients (PFSOT = P(PFS)-P(TTD)).”
183	The sentence “The company included all the comparators specified in the NICE scope” has been replaced with “The company included most of the comparators specified in the NICE scope”.

practice, but that it is common for a population enrolled in a clinical trial to be younger than the representative population seen in clinical practice.

To consider the generalisability of the populations from which evidence is derived to UK clinical practice, the ERG considers it important to discuss therapies received prior to fourth-line treatment in the UK setting. When a person with rrMM reaches fourth-line treatment in the UK, they will have been exposed to lenalidomide in combination with dexamethasone (len+dex) and bortezomib. Nearly all people in both MMY2002 and GEN501 Part 2 had received lenalidomide and bortezomib as part of their previous disease management. However, other therapies given prior to daratumumab in MMY2002 and GEN501 included carfilzomib and pomalidomide, both of which will have had limited use in UK clinical practice as a treatment for rrMM: carfilzomib has never been an available treatment option outside of clinical trials and a compassionate use scheme, and pomalidomide was available for treatment of rrMM through the Cancer Drugs Fund for a limited period between April 2013 and September 2015, when it was de-listed. A person who has not been exposed to a treatment is more likely to have a better outcome on receiving that treatment compared with a person who is re-treated with that intervention. In terms of number of and type of prior therapies received, the ERG's clinical experts advised that the population of GEN501 Part 2 is more closely aligned with the population who would most likely be eligible for daratumumab therapy in the UK. However, the company is positioning daratumumab as a treatment at the fourth line and greater, a setting that is better reflected by MMY2002 as most people enrolled have had three prior therapies. With the exception of number of lines of prior therapy in GEN501 part 2, the ERG's clinical experts fed back that neither study alone accurately represents the baseline characteristics of people in England most likely to receive daratumumab in clinical practice. In the context of daratumumab given at the fourth-line and higher in the UK, because of prior therapies received and differences in baseline characteristics across MMY2002 and GEN501 Part 2, the ERG considers the submitted evidence to partially represent people with rrMM in England who would most likely be eligible for treatment with daratumumab.

All clinically relevant outcomes were reported in the CS, with the exception of time to next treatment and health-related quality of life (HRQoL).

As data on clinical effectiveness of daratumumab are derived from the follow-up of a single group from each of MMY2002 and GEN501 Part 2, neither study has a comparator group that is relevant to this STA and there is no direct evidence of daratumumab in comparison with another intervention. In the final scope issued by NICE, the comparators of interest were identified as:

- panobinostat with bortezomib and dexamethasone (pano+bort+dex);
- len+dex.

achieve the first response was 0.99 months, ranging from 0.9 to 5.6 months. Based on TTR, for people who respond to treatment with daratumumab, response is rapid, and shrinkage of tumours typically occurs within the first month of treatment. Median DOR in MMY2002 was 6.82 months (95% CI: 5.55 months to 11.07 months). Median PFS and OS were 3.7 months (95% CI: 2.8 months to 4.6 months) and 18.6 months (95% CI: 13.7 months to not reached), respectively, in MMY2002. In pomalidomide-naïve people, median PFS was 3.98 months (95% CI: 2.60 months to 7.39 months). Median OS could not be determined for those without prior exposure to pomalidomide. Results for pomalidomide-naïve people are *post hoc* analyses and should be interpreted with caution.

The ERG considered that the OS benefit reported for daratumumab in MMY2002 was substantially longer than would be expected based on the comparatively short PFS, given the typically poor prognosis of people at this stage of MM. The company proposes that the large difference between PFS and OS is not unexpected and is likely as a result of daratumumab's novel mode of action and immunomodulatory activity. However, a longer OS compared with PFS has been reported in other studies in people with rrMM, with one potential explanation proposed to be progression in disease being diagnosed biochemically, with clinical manifestation of relapse not occurring until months later.

Confounding of OS due to subsequent therapy given at disease progression is recognised in studies evaluating treatments in oncological conditions. In MMY2002, people who progressed received carfilzomib and re-treatment with lenalidomide or bortezomib, none of which are available treatment options in the UK. Carfilzomib, lenalidomide and bortezomib are likely to be associated with prolonged OS compared with other treatment options available in the UK setting for the population of interest.

The company reports that 71% of people (n=[redacted]) in MMY2002 went on to receive another intervention subsequent to treatment with daratumumab, which, as acknowledged by the company and its experts, is a large proportion and is likely to be smaller in clinical practice should daratumumab be approved (~55%). The ERG notes that the estimate of 55% of people going on to receive further therapy after daratumumab is similar to the proportion of people receiving subsequent treatment in MM-003 (44%). The company proposes that the high number of people receiving additional treatment after daratumumab is attributable to the "*...novel and unique MoA associated with daratumumab, alongside the favourable safety profile, that culminate in an improved health status of patients*". As the company outlines in their response to clarification, the more favourable adverse effect profile of daratumumab gives people, "*time to recover from the cumulative toxicity of previous treatments allowing a greater proportion of patients to receive subsequent therapy*." Additionally, the company proposes that the, "*novel MoA of daratumumab, which includes immune-mediated mechanisms, increases the likelihood of benefitting from subsequent therapy*". To evaluate the potential impact of confounding in OS due to therapies received after daratumumab, during clarification the ERG requested OS for MMY2002 and

GEN501 Part 2 based on those receiving no subsequent treatment, and those receiving any subsequent treatment. For MMY2002, median OS of those receiving [redacted].

In terms of safety, daratumumab was well tolerated and resulted in no patient death or treatment discontinuation due to drug toxicity. Three deaths occurred due to TEAEs, one case each of viral HIN1 infection, pneumonia and aspiration pneumonia. IRRs are a known AE of daratumumab, as reported in the SmPC. In the integrated analysis of MMY2002 and GEN501 Part 2, 48% of people experienced IRRs, with most IRRs (95.8%) occurring at the first infusion. Respiratory, thoracic and mediastinal disorder (nasal congestion, cough, allergic rhinitis, throat infection and dyspnoea) were the most common group of IRR, occurring in 36.5% of patients across all infusions. The number of IRRs reduced with each subsequent infusion. According to the company, IRRs were managed with pre- and post-infusion medications that included antihistamines, corticosteroids and paracetamol/ acetaminophen. All patients who experienced IRRs were able to continue daratumumab therapy at a full dose with these supportive treatments.

To address the lack of evidence from RCTs on comparative effectiveness of daratumumab, the company carried out a MAIC comparing daratumumab versus the identified relevant comparators of pom+dex and pano+bort+dex for PFS and OS. The company followed reported methods. The ERG's preferred dataset from the MAIC differs from that of the company. Based on guidance from the DSU, the ERG considers that the most adjusted dataset to be the most appropriate, which included adjustment for ISS and cytogenetics (therefore based on MMY2002 alone). For pomalidomide-naïve people, results for the MAIC are based on the dataset from the integrated analysis of MMY2002 and GEN501 Part 2.

For PFS, using the ERG's preferred dataset, results from the MAIC show no significant difference between daratumumab and pano+bort+dex (HR 0.85, 95% CI: 0.39 to 1.88) or pom+dex (HR 1.14, 95% CI: 0.64 to 2.03). The direction of the effect favours daratumumab compared with pano+bort+dex, but not when compared with pom+dex. In people without prior exposure to pomalidomide (based on integrated analysis), the MAIC found no statistically significant difference in PFS between daratumumab and pom+dex (HR 0.51, 95% CI: 0.24 to 1.06).

For OS, using the ERG's preferred dataset, the results generated by MAIC show no significant difference between daratumumab and pano+bort+dex (HR 0.61, 95% CI: 0.25 to 1.45) or pom+dex (HR 0.88, 95% CI 0.44 to 1.77). In the MAIC of the integrated dataset, in people without prior exposure to pomalidomide, daratumumab was associated with a statistically significant reduction in risk of mortality compared with pom+dex (HR 0.33, 95% CI: 0.17 to 0.66).

trials and PANORAMA2. The PFS HRs used in the company's base case are 1.24 (95% CI: 0.92 to 1.68) for pom+dex and 1.09 (95% CI: 0.74 to 1.61) for pano+bort+dex.

The company uses an exponential model to estimate OS curves for daratumumab. To estimate the OS curves for pom+dex and pano+bort+dex, the company applied the weighted HRs from the MAIC analysis matching the top 11 baseline characteristics while the OS HR for pano+bort+dex was derived when matching the five top baseline characteristics across patients in the daratumumab trials and PANORAMA2. The OS HRs used in the company's base case are 1.74 (95% CI: 1.24 to 2.46) for pom+dex and 1.19 (95% CI: 0.73 to 1.92) for pano+bort+dex.

The company assumes that patients' quality of life varies according to progression status and whether or not patients experience adverse reactions to the different treatments received. The health state utility values (HSUVs) used in the base case analysis are taken from a paper by Palumbo *et al.* which analyses EQ-5D data collected in the MM-003 trial. The EQ-5D data were valued using the UK general population time trade-off values, which resulted in a utility value of 0.61 for the pre-progression state and of 0.57 for the progressive disease state. The utility decrements attributed to AEs in the model are based on published estimates and the company's clinical experts' input.

The costs considered in the economic model consist of pharmacological costs (treatment acquisition, administration and concomitant treatment costs), disease management costs, AEs costs, subsequent therapy costs and end of life costs.

The company's primary base case results present an ICER of £55,766 per QALY gained for daratumumab compared with pom+dex and an ICER of £32,593 per QALY gained for daratumumab compared with pano+bort+dex. The ICER comparing daratumumab with bendamustine is £56,574 per QALY gained.

ERG commentary on the robustness of evidence submitted by the company

1.4.1 Strengths

Clinical

The CS contained a systematic review that addressed the decision problem outlined in the final scope issued by NICE. The company's search strategies were well designed.

Economic

The ERG is generally satisfied with the company's model structure and the patients' flow through the model. The partitioned survival approach employed by the company is appropriate. The company included a range of scenario analyses which attempted to explore some of the methodological and structural uncertainty in the analysis.

1.4.2 Weaknesses and areas of uncertainty

Clinical

Although the ERG is satisfied that the company's search strategy was comprehensive, the omission of a long-term follow-up study from the evidence base identified by the company generates some uncertainty that not all relevant evidence has been identified.

A key limitation of the submission is the lack of direct randomised evidence comparing daratumumab versus an active intervention of interest. Although two RCTs of daratumumab are ongoing, they are evaluating daratumumab in combination with other interventions, and so will not inform the decision problem that is the focus of this STA. Of the studies identified to inform the MAIC, one was a well-conducted RCT, but data from the trial are being used as an uncontrolled observational study and the second is an uncontrolled observational study.

Considering the populations from which evidence is derived, the ERG noted differences in the patient baseline characteristics between MMY2002 and GEN501 Part 2 including number of prior lines of therapy, the prior therapies received and the therapies to which people were refractory. Due to a lack of data presented in GEN501 Part 2 concerning disease stage and cytogenetic status, it is unclear how the population groups compare on these baseline demographics. Overall, the ERG considers that the available evidence on the clinical efficacy of daratumumab monotherapy for the treatment of rrMM is of limited quality due to the study design. However, the ERG also acknowledges that MMY2002 and GEN501 Part 2, at this time, represent the best available evidence on the clinical effectiveness of daratumumab monotherapy.

The ERG has concerns around the generalisability of the studies to the UK population most likely to be eligible for treatment with daratumumab. In MMY2002 and GEN501 Part 2, some of the therapies people had received prior to trial entry will have had limited use in UK clinical practice as a treatment for rrMM (carfilzomib and pomalidomide). Moreover, some of the subsequent treatments given on disease progression are not available treatment options in this setting in UK clinical practice, which

The fact that ERG kept on finding mistakes in data handling and labelling increases the probability that some other similar mistakes were not identified. It is impossible to foresee the impact of such potentially unidentified mistakes. It is the ERG's opinion that the company's model and data analysis need further internal consistency checks and a thorough quality check before a robust ICER can be determined for daratumumab. The ERG summarises the key issues surrounding the cost-effectiveness of daratumumab below. These are related with:

- **Pre-treatment with pomalidomide**: Even though the ERG lacks confidence in the validity of the data sent through by the company at the clarification stage, the data suggest that there is no difference in PFS across pom-naïve and non-pom-naïve patients and that OS outcomes are better for pom-naïve patients than for the overall trial population. The ERG interprets this trend in the data as a possible consequence of the effect of pomalidomide as a subsequent therapy. It can be hypothesised that given that pre-treatment with pomalidomide does not seem to influence PFS, the considerable difference in the OS curves across the pom-naïve and the overall trial population is due to the effect that pomalidomide would have as a subsequent treatment in the pom-naïve patients, compared to the effect that pomalidomide would have as a subsequent treatment in patients pre-treated with pomalidomide. Unfortunately the ERG cannot validate this hypothesis given the uncertainty around the data and the fact that company did not provide the OS KM curve for patients subsequently treated with pomalidomide, despite the ERG's request for such data;

- **Subsequent treatments received in MMY2002/GEN501**: The ERG is concerned with the highly confounded OS estimates in the company analysis. The ERG considers that the evidence put forward by the company is not robust enough to determine the cost-effectiveness of daratumumab monotherapy alone. To determine this, we would need to be able to disentangle further the estimate of OS for daratumumab alone vs daratumumab followed by other treatments. Similarly, if we are to consider the cost-effectiveness of daratumumab monotherapy followed by subsequent rrMM therapies, then the effectiveness of daratumumab would need adjusting for the impact of subsequent therapies currently not available in the UK. This is particularly important in this case given the lack of RCT data for daratumumab. While in theory this confounding effect might also apply to the comparator treatments, as pom+dex and pano+bort+dex patients could receive subsequent therapies in MM-003 and PANORAMA2, respectively, the ERG's investigation shows that the risk of OS confounding for pom+dex patients is likely to be considerably smaller than for daratumumab patients. This is related with the fact that 72% of patients in MMY2002/GEN501 received subsequent therapies, while the corresponding estimate for MM-003 is 44%, but more importantly, in MM-003 patients received carfilzomib, lenalidomide and bortezomib in much smaller numbers than in

MMY2002/GEN501 (2% vs 28% for carfilzomib; 5% vs 15% for lenalidomide and 18% vs 24% for bortezomib). Daratumumab patients also received pomalidomide (31%) while pom+dex patients did not receive any pomalidomide (or daratumumab) after the main treatment in MM-003. As discussed in the report, treatment with carfilzomib and retreatment with lenalidomide and bortezomib are not available in the UK and are likely to considerably increase overall survival as subsequent therapies for rrMM patients (Figure A).

[redacted]

Finally, there is an inconsistency in the company's proposed advantage of daratumumab. That is, it allows a higher proportion of patients to receive subsequent therapy. On one hand the company claims that the novel mode of action of daratumumab increases the likelihood of patients benefiting from subsequent therapy pointing to the fact that, "…*of the 148 patients treated with daratumumab 16mg/kg monotherapy in the MMY2002/GEN501 cohort, 72% went on to receive subsequent therapy compared with 39% of the 302 patients randomised to POM+DEX in MM-003*". On the other hand, the company also states that, "…*clinical opinion suggested that…this figure* [72%] *is high compared to what is seen in clinical practice*… [and that] *the proportion of patients who receive subsequent therapy after daratumumab is* [likely to be] *55%*". The company also assumed that the proportion for patients receiving subsequent therapy after pano+bort+dex is 55% in the model, making it equally likely for pano+bort+dex and daratumumab patients to receive subsequent therapy;

- **Statistical approach undertaken by the company to model survival outcomes:** The ERG has several concerns with the company's statistical approach to the economic analysis. The ERG considers that the curve fitting exercise undertaken by the company lacks transparency

This has crucial implications for the OS estimated curves and therefore the cost-effectiveness of daratumumab when compared with pom+dex and pano+bort+dex. The company's base case approach overestimates the survival benefit of daratumumab compared with pom+dex and underestimates the survival benefit compared with pano+bort+dex. Analysis of Figure B, Figure C and Figure D show that the dependent fit approach is unlikely to be appropriate for the estimation of cost-effectiveness for daratumumab.

Figure B. Company's base case OS curves for daratumumab, pom+dex and pano+bort+dex

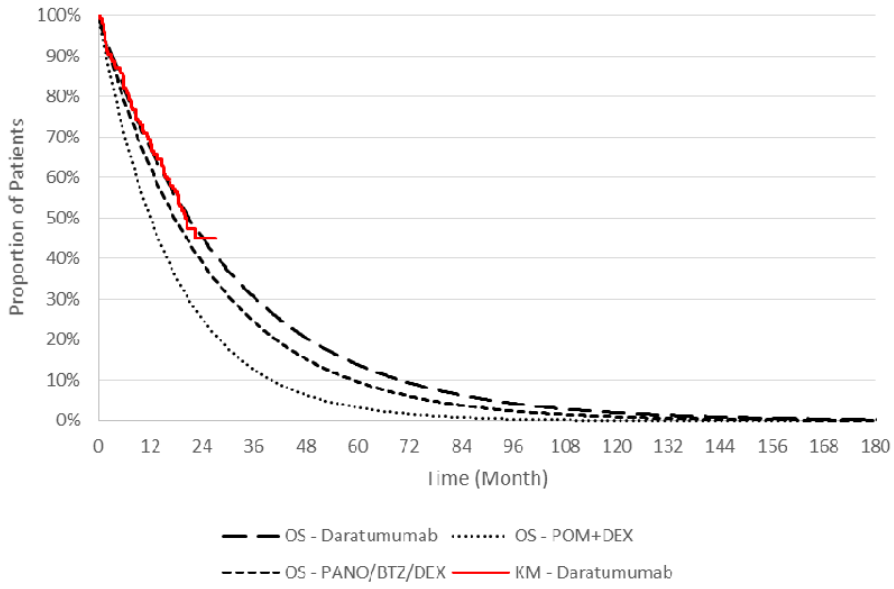


Figure H. Company's indepdendent fit approach to OS curves

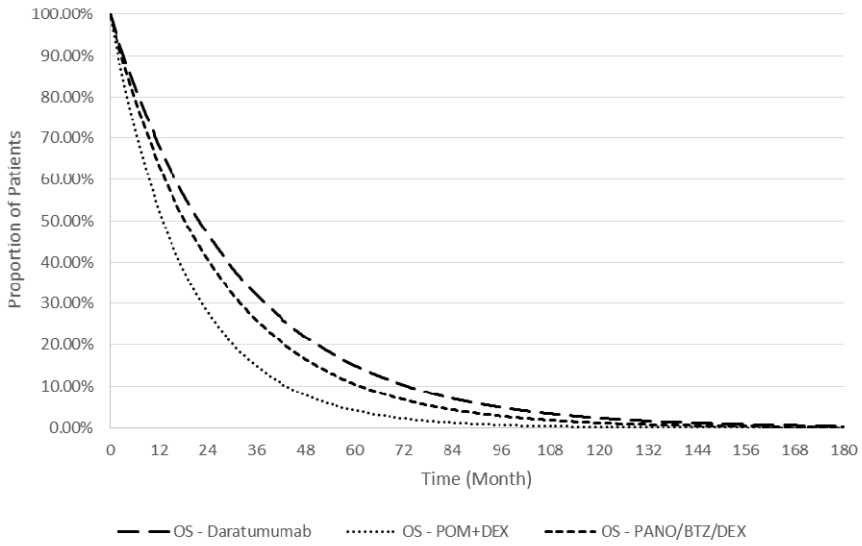
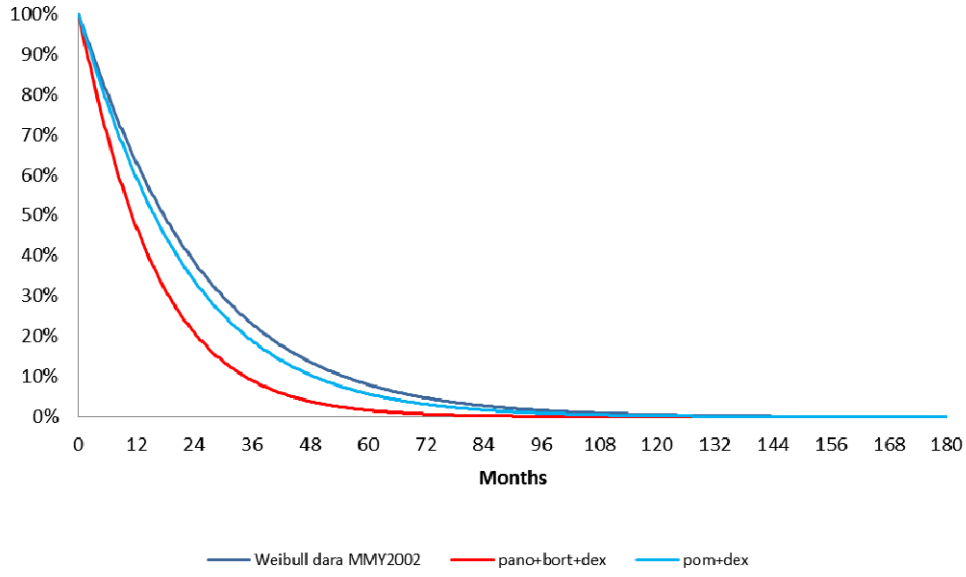
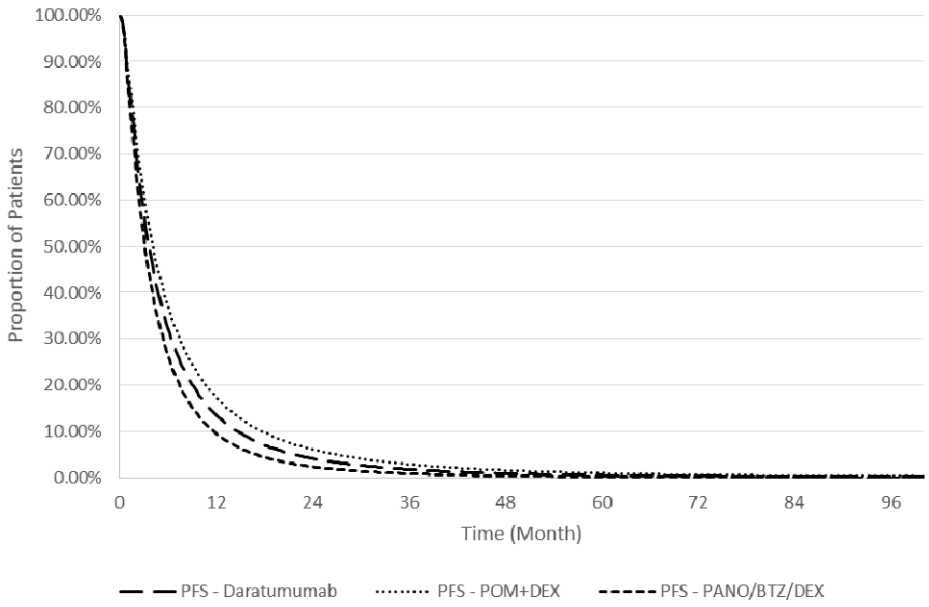


Figure I. ERG's preferred approach to OS curves



All estimates of relative treatment effect for PFS (company's base case, company's analysis using the MY2002 population and ERG exploratory analysis) show non-statistically significant HRs for daratumumab against pom+dex and pano+bort+dex. The ERG's preferred HRs lead to a decrease in the HR for pom+dex (reflecting a loss in the relative effectiveness of daratumumab) to the extent that pom+dex becomes more effective than daratumumab in delaying disease progression (Figure K). Conversely

Figure K. ERG's preferred approach to PFS curves



- **Time to treatment discontinuation data**: The estimation of TTD curves in the company's analysis lacks transparency and clarity throughout the STA. Time to treatment discontinuation was not a pre-specified outcome in the MMY2002 and GEN501 trials but instead resulted from a *post-hoc* analysis of patient level data. Therefore the ERG has little to no information on this clinical outcome. Secondly, the estimation of adjusted TTD curves for daratumumab through the "calibration approach" is a black box in the company's analysis. No further details were provided by the company other than the fact that, "…*the TTD curves for daratumumab were calibrated to match the observed mean and median from MM-003*". Considering the uncertainty around the TTD data, the ERG considers that using these data in the economic analysis carries a potentially high risk. While the PFS curves and data are also not without problems, PFS curves were used as an exploratory approach to derive treatment costs, implying that patients receive treatment until progression;

- **Estimation of utility and subsequent treatment costs**: The ERG also has some concerns with the utility data used and with the application of disutility values to AEs. Similarly, the ERG found some issues in the company's estimation of subsequent treatment costs. These are described in the ERG report in detail but pale in significance when compared with the issues aforementioned.

common for a population enrolled in a clinical trial to be younger than the representative population seen in clinical practice.

Table 7. Summary of baseline characteristics discussed in Section 3.1 of ERG report

Baseline characteristic	MMY2002 N=106	GEN501 N=42
Mean number of prior lines of therapy (SD)	5.6 (2.35)	4.9 (2.61)
Number of people refractory to the last line of therapy (%)	103 (97.2%)	32 (76.2%)
Mean time since initial diagnosis of MM (SD)	6.06 (4.06) years	84.64 (53.49) months
Age (SD), years	62.9 (10.00)	63.8 (8.27)
Number of people with ECOG score 1 (%)	69 (65.1%)	28 (66.7%)
Number of people with ECOG score 2 (%)	8 (7.5%)	2 (4.8%)
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ERG, Evidence Review Group; MM, multiple myeloma; SD, standard deviation.		

In UK clinical practice, before receiving daratumumab, people with rrMM will have been exposed to len+dex and bortezomib. Nearly all people in both MMY2002 and GEN501 Part 2 had received lenalidomide and bortezomib as part of their previous disease management (≥95% for each treatment; Table 9). Other therapies given prior to daratumumab in MMY2002 and GEN501 included carfilzomib and pomalidomide, both of which will have had limited use in UK clinical practice as a treatment for rrMM: carfilzomib has never been an available treatment option outside of clinical trials and a compassionate use scheme, and pomalidomide was available for treatment of rrMM through the CDF for a limited period between April 2013 and September 2015, when it was de-listed. Carfilzomib was given prior to daratumumab in 50% of people in MMY2002 and 19% of people in GEN501 Part 2. Correspondingly, 63% and 36% of people in MMY2002 and GEN501 Part 2, respectively, received pomalidomide prior to daratumumab. In terms of number of and type of prior therapies received, the ERG's clinical experts advised that the population of GEN501 Part 2 is more closely aligned with the population who would most likely be eligible for daratumumab therapy in the UK.

The final scope for the decision problem defines the population relevant to this STA to be people with rrMM that has previously been treated with a PI and an IMiD and who have demonstrated disease progression on the last therapy (Table 6): the population specified in the final scope mirrors the population for which the EMA approved marketing authorisation of daratumumab, that is, "...patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy".[50] Given the specified population criteria, both MMY2002 and GEN501 Part 2 are relevant to the decision problem. However, the company is positioning daratumumab as a treatment at the

3.2 Intervention

The CS provides an overview on the regulatory status and mode of action of daratumumab, which, as per the final scope issued by NICE, is the intervention of interest to the decision problem. In September 2015, the company applied to the EMA for a marketing authorisation for daratumumab.[50] After reviewing the submission through the accelerated application procedure, in April 2016 the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on allowing the company to market daratumumab in the European Union, with the approval of marketing authorisation following in May 2016.[50] In addition, due to the classification of MM as a rare disease, daratumumab had previously been granted orphan drug status (in 2013). The positive opinion issued by the CHMP is subject to review, and, in the case of daratumumab, continued approval is dependent on findings from two ongoing Phase III trials that evaluate daratumumab in combination with lenalidomide and dexamethasone (len+dex) in one trial (MMY3003; ClinicalTrials.gov identifier NCT02076009) and with bortezomib plus low dose dexamethasone (bort+dex) in the second trial (MMY3004; ClinicalTrials.gov identifier NCT02136134). The ERG notes that the ongoing Phase III studies are not relevant to the decision problem that is the focus of this STA, which is evaluating the clinical and cost effectiveness of daratumumab when given as a monotherapy.

As noted by the company, in November 2015, the US Food and Drug Administration (FDA) approved the use of daratumumab (monotherapy) for the treatment of rrMM, indicating the population suitable for treatment with daratumumab to be those "...with multiple myeloma (MM) who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and immunomodulatory agent".[57] The FDA approval aligns with the company's positioning of daratumumab as an alternative treatment at fourth-line and higher (Table 6), which is a narrowing of the population specified in the final scope (see Section 3.1). As discussed in Section 2.2, the ERG's clinical experts have indicated that, given treatment options for rrMM available at this time, they consider the company's restriction of daratumumab to an option at fourth line and greater to be appropriate.

Daratumumab is a human monoclonal antibody that is known to target CD38, a transmembrane glycoprotein that is expressed on the surface of many immune cells, including plasma cells and myeloma cells. The exact mode of action of daratumumab has yet to be elucidated, but it is thought that daratumumab triggers apoptosis (cell death) of tumour cells through several mechanisms, as described in the CS and presented in Box 5. The CS also provides a figure illustrating the proposed modes of action of daratumumab (Figure 2). A key tenet of the company's application to NICE is the proposed unprecedented benefit afforded by daratumumab, which the company attributes to "...the novel and unique multifactorial MoA [mechanism of action] of daratumumab which appears to

studies to establish clinical efficacy of daratumumab compared with relevant comparators. In addition, estimates of clinical effectiveness of daratumumab are based on data from single arms from MMY2002 and GEN501 Part 2, as will be discussed in Section 4.1.4 and 4.2.

4.1.4 Quality assessment

The company provided assessments of the quality for the two studies MMY2002 and GEN501 using criteria that was adapted from an RCT assessment tool to assess non-RCT studies. The ERG notes that the company does not specify the source of the implemented quality assessment checklist. Domains included in the assessment were: selection bias; population eligibility; whether the study is reflective of UK practice; methods to account for missing participants; outcomes measured; type of analyses; and internal and external validity of results. Each of the domains was assessed as being at a 'low', 'medium' or 'high' risk of bias, with additional qualitative justifications provided. Summaries of the company's assessments, together with those of the ERG, for MMY2002 and GEN501 Part 2 are provided in Appendix 10.2. Details of quality assessments of studies investigating the efficacy of relevant comparators are covered in Section 4.4.

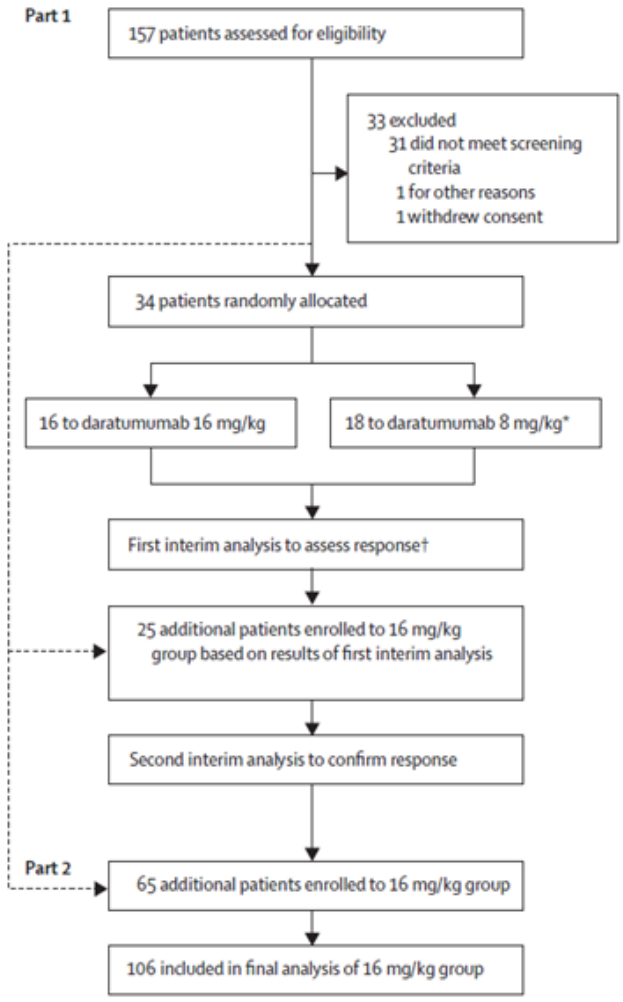
The company assessed both trials as being of low risk of bias, with the exception of patients in both studies being more heavily pre-treated than would be expected in UK clinical practice. In addition, based on the marketing authorisation issued by the European Medicines Agency (EMA), the populations enrolled in MMY2002 and GEN501 Part 2 only partially represent the licensed population.

The ERG's quality assessments of MMY2002 and GEN501 Part 2 differ from those of the company in some domains. The ERG's opinion is that, as long-term single-arm studies, both MMY2002 and GEN501 Part 2 are at a high risk of bias due to the inherent bias associated with their study design, which relates to the internal validity of the studies. In addition, in the context of how closely the studies reflect UK clinical practice, as discussed in Section 3.1, the ERG notes that some treatments received before enrolment to the studies will have had limited use in UK clinical practice as a treatment for rrMM (carfilzomib and pomalidomide), which weakens the external validity of the studies for the decision problem that is the focus of this STA (discussed in more detail in Section 4.2.3). The difference in prior treatments compared with the population in the UK that would likely be eligible for treatment with daratumumab is due to the disparate treatment options available in the countries in which the studies were carried out (as noted earlier, there was no study site in the UK).

Both studies initially assessed daratumumab at different doses and/or dosing schedules. In MMY2002, people were randomised to different doses (8 mg/kg vs 16 mg/kg of daratumumab). By contrast, in GEN501, people were sequentially allocated to different dosing schedules, with no randomisation (study is at a high risk of selection bias). As previously discussed in Section 3.1, both

company highlights that three people moved to the 16 mg/kg dose but were not included in efficacy analyses. People that responded to and tolerated daratumumab 16 mg/kg at the first interim analysis continued treatment (N=16). In Stage 2 of Part 1, after the initial interim analysis, a further 25 people were enrolled and received daratumumab 16 mg/kg. Part 2 of the study was an expansion of Part 1 to further evaluate the selected daratumumab dose of 16 mg/kg, for which a further 65 patients were enrolled into the study. Thus, the total study population of MMY2002 consisted of 106 patients that received daratumumab 16 mg/kg dose across both Part 1 and Part 2 of the study in a predominantly non-randomised manner. Over the duration of the study (data cut off December 2015), 100 people (94.3%) discontinued treatment with daratumumab. The most common reason for discontinuation was disease progression (92 people [86.8%]). Five people (4.7%) discontinued daratumumab because of AEs not related to treatment, and three people (2.8%) withdrew due to symptoms related to disease progression.

Figure 5. Patient flow diagram of MMY2002 study (reproduced from the company's clarification response, pg. 71, Figure 1)



- June 2015: interim analysis for OS with a median follow-up of 15.2 months (range of 1.2-21.4 months);
- December 2015: final data cut-off (ORR, DoR, PFS and OS) with a median follow-up of 20.5 months (range of 1.2-27 months).

The ERG notes that the primary outcome measure of safety was assessed at the earlier cut-off of January 2015.

4.2.3 Baseline characteristics

Baseline characteristics of people in MMY2002 and GEN501 Part 2 are summarised in Table 9. Although, in both studies patients received various doses of daratumumab, as noted in Section 3.1, here the ERG focuses on the licensed dose of daratumumab of 16 mg/kg.

People in MMY2002 and GEN501 Part 2 had a similar median age of around 64 years and the proportions of patients with ECOG performance status 0, 1 or 2 were also similar. However, the proportion of men was larger in GEN501 Part 2 (64%) compared with MMY2002 (49%), and time since initial diagnosis was longer in GEN501 Part 2 than in MMY2002 (5.8 years versus 4.8 years, respectively). However, counterintuitively the median number of lines of prior treatments was lower in GEN501 Part 2 than in MMY2002 (4 versus 5, respectively). As discussed in Section 3.1, the ERG proposes one potential reason for this observation is that people in MMY2002 had shorter periods of response to prior treatments before enrolment in the study, and thus could be more refractory to treatment than those enrolled in GEN501 Part 2. It is noted that a larger proportion of people in MMY2002 (97%) was refractory to the last line of treatment compared with GEN501 Part 2 (76%; Table 9), which would be expected based on the inclusion criteria for MMY2002 that people could be double-refractory to PI and IMiD. In addition, there were differences between the studies in refractoriness to individual treatments (Table 9). For example, 48% of patients in MMY2002 were refractory to carfilzomib compared with 17% of people in GEN501 Part 2 (Table 9). Alternatively, the difference in median time since diagnosis may be attributable to variation in clinical practice in management of rrMM across the countries hosting trial sites for the two studies.

The ERG's clinical experts highlight that with each subsequent line of therapy patients are likely to have a poorer prognosis. In addition, with each line of therapy, the patient is also exposed to more toxic treatments. As noted in Section 3.1, some of the prior treatments people had received at enrolment will have had limited use in UK clinical practice as a treatment for rrMM (carfilzomib and pomalidomide): carfilzomib has never been an available treatment option outside of clinical trials and a compassionate use scheme, and pomalidomide was available for treatment of rrMM through the CDF for a limited period between April 2013 and September 2015, when it was de-listed. Pomalidomide is known to be associated with severe AEs. Therefore, patients that were pom+dex-naïve at baseline are likely to have a better performance status

Refractory to PI/IMiD, n (%)	101 (95)	27 (64)
PI only	3 (3)	3 (7)
IMiD only	1 (1)	4 (10)
Refractory to PI + IMiD + alkylating agent, n (%)	79 (75)	21 (50)
Refractory to, n (%):		
Bortezomib	95 (90)	30 (71)
Carfilzomib	51 (48)	7 (17)
Lenalidomide	93 (88)	31 (74)
Pomalidomide	67 (63)	15 (36)
Thalidomide	29 (27)	12 (29)
Alkylating agent	82 (77)	25 (60)

Abbreviations: CS, company submission; Dara, daratumumab; ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory agent; ISS, International Staging System; PI, proteasome inhibitor

As outlined in Section 2.1 of the ERG report, there are key characteristics that can have an influential role in how patients respond to treatment, including ISS stage and cytogenetics. In GEN501 Part 2, data on the cytogenetic profile and ISS staging were not recorded, which makes it difficult to draw conclusions on the comparability of baseline characteristics of people in MMY2002 and GEN501 Part 2, as well as whether the study population in GEN501 Part 2 is representative of the rrMM population in the UK.

For the data that are available, as touched on in Section 3.1, the baseline characteristics of neither MMY2002 nor GEN501 Part 2 fully represent the population in UK clinical practice who would likely be eligible for treatment with daratumumab. In both trials, some patients has received prior carfilzomib, a treatment undergoing a NICE technology assessment but not currently approved. In addition, a substantial proportion of patients had also previously been given pomalidomide, which was recently (January 2017) approved as a fourth-line treatment in the UK. Given the proposed position of daratumumab by the company as a fourth-line therapy, pomalidomide would be a direct comparator and would not be given to rrMM patients prior to daratumumab. Importantly, in the context of the decision problem, the number of people in the UK who would likely be eligible for treatment with daratumumab and will have received pomalidomide as a prior treatment at the time of writing is likely to be low. Fewer patients in GEN501 Part 2 had been treated with carfilzomib or pomalidomide compared with MMY2002. Therefore, in terms of type of prior therapy received, GEN501 Part 2 is more representative of UK clinical practice. At the clarification stage, the company provided a more detailed breakdown of number of prior lines of therapy at enrolment, which is summarised in Table 10. These data show that a larger proportion of patients that received less than 3 prior treatments in GEN501 Part 2 (21.43%) compared with MMY2002 (1.89%). Therefore, despite both study populations being heavily pre-treated, the ERG considers the MMY2002 study population to be more aligned with the proposed positioning of daratumumab, in terms of number of prior treatments.

IMiDs) or who were refractory to both a PI and an IMiD. By contrast, the primary goal of GEN501 was to assess safety and tolerability of daratumumab. The population enrolled in GEN501 Part 2 were those with MM whose disease was relapsed or relapsed and refractory to two prior lines of therapy and who did not have further established treatment options.

The outcomes assessed in the studies and presented in the CS are clinically relevant. Outcomes were captured at three time points in both MMY2002 and GEN501 Part 2. However, the same outcomes were not recorded at the same time points, with longer follow-up for ORR in GEN501 Part 2 compared with MMY2002.

Comparison of baseline characteristics across MMY2002 and GEN501 Part 2 identified differences in characteristics associated with prognosis and outcome. Based on the median number of prior therapies (five in MMY2002 vs four in GEN501 Part 2), and the proportion of people who were refractory to their last treatment (97.2% in MMY2002 and 76.2%), the ERG notes that people in MMY2002 are more heavily pre-treated and are more refractory to treatment than those in GEN501 Part 2. In addition, information on ISS stage and cytogenetics, characteristics that are also associated with prognosis, were not recorded for GEN501 Part 2.

The ERG has concerns around the generalisability of the studies to the UK population most likely to be eligible for treatment with daratumumab. In MMY2002 and GEN501 Part 2, some of the therapies people had received prior to trial entry will have had limited use in UK clinical practice as a treatment for rrMM (carfilzomib and pomalidomide). Moreover, some of the subsequent treatments given on disease progression are not available treatment options in this setting in UK clinical practice.

Within the CS, the company presents results for an integrated analysis of MMY2002 and GEN501 Part 2. Given the differences between the studies in baseline characteristics, the ERG considers it inappropriate to combine the data of the two studies. Furthermore, the ERG considers the methods used by the company to pool the data to be inappropriate (discussed further in Section 4.2). However, the ERG acknowledges the company has taken a pragmatic approach to combining the studies to increase the sample size and power of the analysis.

4.3 Clinical results

Before discussing the clinical effectiveness results, the ERG wishes to address a comment made by the company in their response to clarification questions. The company stated “During the clarification stage, Janssen requested further information on the rationale and priority of the additional analyses requested. As this was not forthcoming, Janssen have addressed priority questions in the order presented below. In addition to this, Janssen requested clarification on some questions for which it was unclear what was required. As no clarification was received, Janssen have interpreted these

bortezomib are not available treatment options in the UK. Carfilzomib, lenalidomide and bortezomib are likely to be associated with prolonged OS compared with other treatment options available in the UK setting for the population of interest.

Considering the proportion of people who go on to receive another therapy, for MMY2002, the company reports that 71% of people (n=[redacted]) in MMY2002 received another intervention subsequent to treatment with daratumumab, which, as acknowledged by the company, is considerably higher than the corresponding patient group in MM-003 (39% of 202 people). The company proposes that the high number of people receiving additional treatment after daratumumab is attributable to the "...novel and unique MoA associated with daratumumab, alongside the favourable safety profile, that culminate in an improved health status of patients". As the company outlines in their response to clarification, the more favourable adverse effect profile of daratumumab gives people "time to recover from the cumulative toxicity of previous treatments allowing a greater proportion of patients to receive subsequent therapy." Additionally, the company proposes that the "novel MoA of daratumumab, which includes immune-mediated mechanisms, increases the likelihood of benefitting from subsequent therapy".

The ERG considers it important to contextualise the reported numbers of people receiving subsequent treatment in MMY2002 and MM-003. At a median follow-up of 9.3 months, 55% (n=58) of people in MMY2002 had received subsequent treatment.[53] The proportion reported by the company in the CS (71%) is based on more mature data at a median follow-up of 20.7 months. It should be noted that the company's experts' believe that it is unlikely that 71% of people will receive treatment after daratumumab in clinical practice, which is reflected in the costing of subsequent treatment in the economic model (costed at 55% of people receive subsequent treatment with no adjustment to efficacy).

Considering MM-003, median follow-up for the reported 39% of people receiving subsequent treatment in MM-003 was 10.0 months.[82] In a subsequent publication, at a median follow-up of 15.4 months, 44.4% (n=134) of people had gone on to receive subsequent treatment.[87] The clinical experts acting for the company (Celgene) in the STA for pom+dex asserted that the proportion of people receiving subsequent treatment is likely to be larger in clinical practice.[85] Taking all comments together, the ERG considers that there is likely to be little difference in the number of people going on to receive treatment after daratumumab compared with after pom+dex.

To evaluate the potential impact of confounding in OS due to therapies received after daratumumab, during clarification the ERG requested OS for MMY2002 and GEN501 Part 2 based on those receiving no subsequent treatment, and those receiving any subsequent treatment. The company kindly provided the data, which are presented in Table 16. For MMY2002, median OS of those receiving [redacted]

exposure to pomalidomide. Results for pomalidomide-naïve people are *post hoc* analyses and should be interpreted with caution.

The ERG considered that the OS benefit reported for daratumumab in MMY2002 was substantially longer than would be expected based on the comparatively short PFS, given the typically poor prognosis of people at this stage of MM. The company proposes that the large difference between PFS and OS is not unexpected and is likely as a result of daratumumab's novel mode of action and immunomodulatory activity. However, a longer OS compared with PFS has been reported in other studies in people with rrMM, with one potential explanation proposed to be progression in disease being diagnosed biochemically, with clinical manifestation of relapse not occurring until months later.[82]

Confounding of OS due to subsequent therapy given at disease progression is recognised in studies evaluating treatments in oncological conditions. In MMY2002, people who progressed received carfilzomib and re-treatment with lenalidomide or bortezomib, none of which are available treatment options in the UK. Carfilzomib, lenalidomide and bortezomib are likely to be associated with prolonged OS compared with other treatment options available in the UK setting for the population of interest, and, hence, the OS benefit reported for daratumumab in MMY2002 is likely to be an overestimate of what would be expected in UK clinical practice.

The company reports that 71% of people (n=[redacted]) in MMY2002 went on to receive another intervention subsequent to treatment with daratumumab, which, as acknowledged by the company and its experts, is a large proportion and is likely to be smaller in clinical practice should daratumumab be approved (~55%). The ERG notes that the estimate of 55% of people going on to receive further therapy after daratumumab is similar to the proportion of people receiving subsequent treatment in MM-003 (44%). The company proposes that the high number of people receiving additional treatment after daratumumab is attributable to the "...novel and unique MoA associated with daratumumab, alongside the favourable safety profile, that culminate in an improved health status of patients". As the company outlines in their response to clarification, the more favourable adverse effect profile of daratumumab gives people "time to recover from the cumulative toxicity of previous treatments allowing a greater proportion of patients to receive subsequent therapy." Additionally, the company proposes that the "novel MoA of daratumumab, which includes immune-mediated mechanisms, increases the likelihood of benefitting from subsequent therapy". To evaluate the potential impact of confounding in OS due to therapies received after daratumumab, during clarification the ERG requested OS for MMY2002 and GEN501 Part 2 based on those receiving no subsequent treatment, and those receiving any subsequent treatment. For MMY2002, median OS of those receiving [redacted].

In terms of safety, daratumumab was well tolerated and resulted in no patient death or treatment discontinuation due to drug toxicity. Three deaths occurred due to TEAEs, one case each of viral HIN1 infection, pneumonia and aspiration pneumonia. IRRs are a known AE of daratumumab, as reported in the SmPC.[51] In the integrated analysis of MMY2002 and GEN501 Part 2, 48% of people experienced IRRs, with most IRRs (95.8%) occurring at the first infusion. Respiratory, thoracic and mediastinal disorder (nasal congestion, cough, allergic rhinitis, throat infection and dyspnoea) were the most common group of IRR, occurring in 36.5% of patients across all infusions. The number of IRRs reduced with each subsequent infusion. According to the company, IRRs were managed with pre- and post-infusion medications that included antihistamines, corticosteroids and paracetamol/ acetaminophen. All patients who experienced IRRs were able to continue daratumumab therapy at a full dose with these supportive treatments.

To address the lack of evidence from RCTs on comparative effectiveness of daratumumab, the company carried out a MAIC comparing daratumumab versus the identified relevant comparators of pom+dex and pano+bort+dex for PFS and OS. The company followed reported methods. The ERG's preferred dataset from the MAIC differs from that of the company. Based on guidance from the DSU, the ERG considers that the most adjusted dataset to be the most appropriate, which included adjustment for ISS and cytogenetics (therefore based on MMY2002 alone). For pomalidomide-naïve people, results for the MAIC are based on the dataset from the integrated analysis of MMY2002 and GEN501 Part 2. The ERG highlights that there were inconsistencies across analyses in factors adjusted for within the MAIC.

For PFS, results from the MAIC show no significant difference between daratumumab and pano+bort+dex (HR 0.85, 95% CI: 0.39 to 1.88) or pom+dex (HR 1.14, 95% CI: 0.64 to 2.03). The direction of the effect favours daratumumab compared with pano+bort+dex, but not when compared with pom+dex. In people without prior exposure to pomalidomide (based on integrated analysis), the MAIC found no statistically significant difference in PFS between daratumumab and pom+dex (HR 0.51, 95% CI: 0.24 to 1.06).

For OS, using the ERG's preferred dataset, the results generated by MAIC show no significant difference between daratumumab and pano+bort+dex (HR 0.61, 95% CI: 0.25 to 1.45) or pom+dex (HR 0.88, 95% CI 0.44 to 1.77). In the MAIC of the integrated dataset, in people without prior exposure to pomalidomide, daratumumab was associated with a statistically significant reduction in risk of mortality compared with pom+dex (HR 0.33, 95% CI: 0.17 to 0.66).

Again, the ERG considers it important to note that OS data are confounded by differences between MMY2002 and the comparator studies that have not been adjusted for. For example, in MM-003, which informs the MAIC versus pom+dex, the most commonly used subsequent therapies were dexamethasone, cyclophosphamide, bortezomib and bendamustine, which may have been used alone

- MAIC for OS found no significant difference between daratumumab and pano+bort+dex (HR 0.61, 95% CI: 0.25 to 1.45) or pom+dex (HR 0.88, 95% CI 0.44 to 1.77) in OS. Daratumumab

was associated with a statistically significant reduction in risk of mortality compared with pom+dex in pomalidomide-naïve people (HR 0.33, 95% CI: 0.17 to 0.66).

- The adverse effects reported for the integrated analysis dataset were consistent with the SmPC for daratumumab. IRRs are a known AE associated with use of daratumumab. In the integrated analysis of MMY2002 and GEN501 Part 2, 48% of people experienced IRRs, with most IRRs (95.8%) occurring at the first infusion. Respiratory, thoracic and mediastinal disorder (nasal congestion, cough, allergic rhinitis, throat infection and dyspnoea) were the most common group of IRR, occurring in 36.5% of patients across all infusions.

4.4.1 Clinical issues

- Evidence on clinical effectiveness of daratumumab is derived from long-term follow up of a single-arm from two separate studies, and thus is based on observational data and is at a high risk of bias.

- Single-arm studies are not considered appropriate design to capture time to event outcomes such as PFS and OS.

- Based on differences in baseline characteristics between MMY2002 and GEN501 Part 2, the ERG considers it inappropriate to combine data from the two studies for the purposes of estimating clinical effectiveness of daratumumab.

- ERG has concerns around the validity of the methods used by the company to carry out the reported integrated analysis of MMY2002 and GEN502 Part 2 to estimate clinical effectiveness of daratumumab.

- No estimates of clinical effectiveness from head-to-head studies.

- Long-term follow-up of a key study omitted from company's report. The ERG cannot definitively conclude that all relevant evidence has been identified.

- The ERG has concerns around the generalisability of MMY2002 and GEN501 Part 2 to UK clinical practice. Some treatments given as prior therapies and as subsequent treatments on progression are not available treatment options to clinicians in the UK in this setting.

- OS data are confounded by the use of subsequent treatment. Although this is the case in most studies, the ERG thinks it particularly noteworthy in the context of the decision problem

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and the *de novo* economic evaluation submitted by the company. Due to mistakes or discrepancies identified before and during the clarification process, the company provided two versions of the written submissions of the economic evidence along with three electronic versions of the Microsoft Excel® based economic model. The focus of the ERG report is therefore on the updated company submission (CS) and the third version, updated, economic model.

All HRs presented by the ERG are the inverse of the company's reported HRs (i.e. 1/company's HRs) to reflect the comparator treatment as the base. Therefore an HR> 1 reflects a gain in survival with daratumumab and a HR<1 reflects a loss in survival with daratumumab.

5.2 Summary of the company's key results

The company presented results for the pairwise analysis of daratumumab compared with pom+dex, pano+bort+dex and bendamustine. The base case and probabilistic results are presented in Table 28 and Table 29, respectively, for daratumumab at list price.

Table 28. Pairwise base case results from the company's updated model (CS, addendum to company evidence submission, Table 2)

Treatment	Total			Incremental			ICER (Dara vs comparator) at list prices
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Daratumumab	£81,422	1.31	2.54				
Pom+dex	£49,921	0.75	1.46	£31,501	0.56	1.07	£55,766
Pano+bort+dex	£74,530	1.10	2.14	£6,892	0.21	0.39	£32,593
Bendamustine-based therapy	£38,327	0.55	1.10	£43,095	0.76	1.44	£56,574
Abbreviations in table: bort, bortezomib; dex, dexamethasone; dara, daratumumab; year; ICER, incremental cost-effectiveness ratio; LY, life year; pano, panobinostat; pom, pomalidomide; QALY, quality-adjusted life year.							

Table 29. Mean PSA from company's updated model (CS, addendum to company's evidence submssion, Table 7)

Treatment	Total			Incremental			ICER (Dara vs Comparator)
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Daratumumab	£80,197	1.32	2.55				
Pom+dex	£49,653	0.76	1.50	£30,544	0.56	1.06	£54,987
Pano+bort+dex	£74,516	1.14	2.22	£5,681	0.18	0.33	£31,079
Bendamustine-based therapy	£39,313	0.56	1.13	£40,884	0.76	1.43	£54,149
Abbreviations in table: dex, dexamethasone; pano, panobinostat; bort, bortezomib; LY, life years; pom, pomalidomide; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; dara, daratumumab							

The company also reports that daratumumab is well tolerated and has a favourable safety profile, which is particularly important for rrMM patients who have been exposed to the continuous toxicity associated with other rrMM treatments. In fact, the company states that the unique mechanism of action associated with daratumumab monotherapy appears to change the natural course of disease in rrMM and is potentially associated with a disease reset. This, along with its favourable safety profile culminates in an improved health status of patients, allowing them to receive further active treatments (and retreatment with drugs received previously) to re-stabilise their disease.

Treatment effectiveness within the model was implemented through a partitioned survival method, which uses the estimated OS and PFS data from the MMY2002/GEN501 integrated trial analysis to determine mortality and disease progression at each cycle of the economic model. Treatment effectiveness was also included in the model through the observed lower rates of adverse events (AEs) related with daratumumab. The clinical impact of subsequent treatments received after daratumumab was implicitly included in the economic model through the use of overall OS data from MMY2002 and GEN501, given that patients received further rrMM treatment after daratumumab. Disease progression on subsequent therapy is not captured within the economic model.

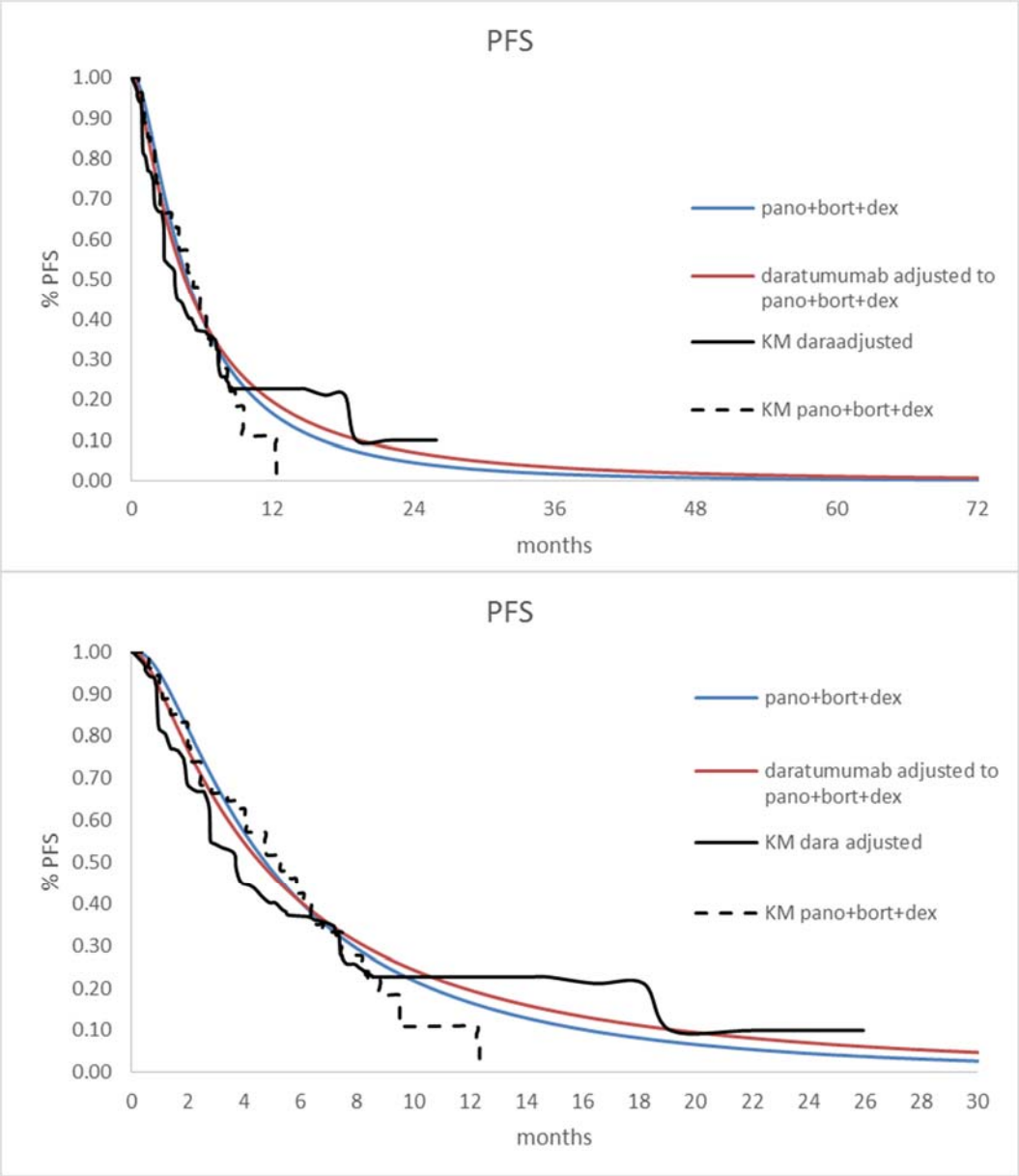
5.2.1.1 Statistical approach

In this section the ERG provides an overview of the statistical approach undertaken to estimate parametric survival models using OS, PFS and time to treatment discontinuation (TTD) data from MMY2002 and GEN50 and the process of deriving the occupancy for the PFT, PFOT, PD and death states of the model in the base case analysis. The ERG also reports the results of the company analysis of PFS and TTD data. The mortality section of the ERG report (Section 5.4.4) describes the results of the company analysis of OS data in the base case economic analysis.

In their base case analysis, the company decided to use the integrated patient-level data from MMY2002 and GEN501 (described in Section 4 of the ERG report). In order to extrapolate OS, PFS and TTD data into the model time horizon the company fitted a variety of parametric curves to the integrated data. The company reports fitting clinical data from the trials with exponential, Weibull, log-logistic, lognormal and generalised gamma models in accordance with guidance from NICE Technical Support Document (TSD) 14.[97] The company adds that the fit of each parametric model was compared with the observed KM data and that statistical fit was assessed using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). It is also reported that the clinical plausibility of each extrapolation was assessed by a consultant haematologist practicing within the NHS in England.

Once the best-fitting model was selected, survival curves were derived through the use of survival functions and were then used to estimate the proportion of patients in each health state for every cycle of the economic model. The company did not report how the estimated survival curves for daratumumab

Figure 16. Indepedently fitted PFS curves for daratumumab vs pano+bort+dex



5.2.1.2 Time to treatment discontinuation

Time to treatment discontinuation is used by the company to model treatment costs for daratumumab and pom+dex. This is done by using the TTD curve to calculate treatment costs. The TTD curve is subtracted from the PFS curve for each treatment, to obtain PFS (off Tx) for daratumumab and pom+dex patients (PFSOT = P(PFS)-P(TTD)). The company estimated TTD curves for daratumumab using the integrated data from MMY2002 and GEN50. For pom+dex, only mean and median TTD could be obtained from the literature, therefore the TTD curves for daratumumab were calibrated to match the observed mean and median from MM-003. The company could not find TTD data for pano+bort+dex or bendamustine therefore patients were assumed to be treated until progression, or when the maximum number of treatment cycles was reached for these two treatments.

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Sensitivity analysis	Probabilistic sensitivity analysis	Unfortunately, the ERG had insufficient time to fully validate the PSA undertaken by the company.
Abbreviations used in the table: EQ-5D, EuroQoL 5-Dimension; HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; TA, technology appraisal.		

Table 54. Philip's checklist[137]

Dimension of quality	Comments
Structure	
S1: Statement of decision problem/objective	Clearly stated.
S2: Statement of scope/perspective	Clearly stated (UK NHS and PSS) and consistent with the scope.
S3: Rationale for structure	The model structure is consistent with previously used models in rrMM and has been validated by clinical experts.
S4: Structural assumptions	The chosen structure is appropriate.
S5: Strategies/ comparators	The company included most of the comparators specified in the NICE scope: pano+bort+dex, pom+dex and bendamustine-based therapy. However, both the company and the ERG's clinical experts consider that bendamustine-based therapy is not an appropriate comparator since it is not currently licensed for use in the NHS in this patient population. [1]
S6: Model type	Appropriate but not clearly stated. The model was based on the area under the curve (AUC) approach however the company did not provide details on the approach taken.
S7: Time horizon	A life time horizon of 15 years is used in the base case analysis, by when less than 1% of patients in all treatment arms of the model are alive.
S8: Disease states/pathways	The health states included in the model are generally appropriate.
S9: Cycle length	The cycle length is appropriate. No half-cycle correction was applied due to the short length of cycles.
Data	
D1: Data identification	The ERG disagrees with the company's approach of limiting the cost-effectiveness search to a specific intervention (daratumumab), as this led the company to exclude relevant sources of data. As the cost-effectiveness search was limited by intervention and the ERG is unaware of how the company searched for TA submissions, it is difficult to predict why some relevant QoL data (identified by the ERG on the SMC pomalidomide submission) were missed by the company.
D2: Pre-model data analysis	The ERG considers that the curve fitting exercise undertaken by the company lacks transparency and consistency. The ERG disagrees with the company's assessment of PH and therefore the company's modelling approach. To derive the survival curves for pom+dex and pano+bort+dex the weighted HRs derived from the MAIC were applied to the estimated daratumumab unadjusted survival curves derived from the integrated MMY2002/GEN501 data for OS and PFS. The ERG considers that the company's MAIC results should have adjusted for the maximum number of characteristics possible across trials (Section 4). The ERG theoretically preferred modelling approach is not allowed for in the company's model. This consists on the use the independently fitted

patients for PFS) but also the ERG would expect to see the same numbers of patients at risk as the number of patients who were pom-naïve in the trials, instead of the overall trial population as the company data suggests.

Despite the fact that the pom-naïve population survival curves included the same number of patients as the entire trial population curves, the actual KM curves provided by the company were different from the entire trial population KM curves in the integrated dataset and in the individual trial datasets. This suggests that some sort of adjustment might have been carried by the company to the entire trial population KM curves. Without knowing what this adjustment was, or if these are the correct data for pom-naïve patients, the ERG cannot attest to the validity of the subgroup analysis the company carried for pom-naïve patients.

Table 55. Number of patients at risk in OS and PFS curves for the pom-naïve population

Population	Number of total patients	Number of patients at risk at the beginning of pom-naïve KM OS curves	Number of patients at risk at the beginning of pom-naïve KM PFS curves
MMY2002/GEN501 integrated population	148	n/a	n/a
MMY2002 population	106	n/a	n/a
GEN501 population	42	n/a	n/a
MMY2002/GEN501 integrated pom-naïve population	49	66	148
MMY2002 pom-naïve population	43	106	106
GEN501 pom-naïve population	6	42	42
Abbreviations in table: KM, Kaplan Meier; OS, overall survival; PFS, progression-free survival; pom, pomalidomide.			

Nonetheless, and for inclusiveness purposes, the ERG notes that the HRs for the pom-naïve subgroup analysis ran by the company (reported in Table 56 below) show that daratumumab compared with pom+dex is less effective in the pom-naïve population than in the overall trial population (albeit not statistically significant for PFS). This is understandable in theory as one could anticipate that pre-treated pomalidomide patients will respond less well to retreatment with pomalidomide compared with a pom-naïve population. The ERG also presents the KM curves forward by the company in Figure 22. Even though the ERG cannot validate the data reported in the figure and table below, it is still worth noting that the data trends observed in the company's data suggest. That is, while there seems to be no difference for PFS across pom-naïve and non-pom-naïve patients, there is a considerable difference in OS between pom-naïve and non-pom-naïve patients, with OS being better for pom-naïve patients than for the overall trial population. The ERG interprets this trend in the data as a possible consequence of the effect of pomalidomide as a subsequent therapy. It can be hypothesised that given that pre-treatment with pomalidomide does not seem to influence PFS, the considerable difference in the OS curves across

directions. While the HR for pom+dex decreases (reflecting a loss in the relative effectiveness of daratumumab) the HR for pano+bort+dex increases, reflecting a better performing daratumumab.

5.2.1.3 Time to treatment discontinuation

Time to treatment discontinuation is used by the company to model treatment costs for daratumumab and pom+dex. This is done by using the TTD curve to calculate treatment costs. The TTD curve is subtracted from the PFS curve for each treatment, to obtain PFS (off Tx) for daratumumab and pom+dex patients (PFSOT = P(PFS)-P(TTD)). The company estimated TTD curves for daratumumab using the integrated data from MMY2002 and GEN501. For pom+dex, only mean and median TTD could be obtained from the literature, therefore the TTD curves for daratumumab were calibrated to match the observed mean and median from MM-003.

The estimation of TTD curves in the company's analysis is another example of the lack of transparency and clarity throughout this STA. Firstly, the ERG could not find TTD as a specified outcome in the MMY2002 CSR or in GEN501 CSR. After a request for clarification, the company explained that TTD was not a pre-specified outcome in the MMY2002 and GEN501 trials but instead resulted from a *post-hoc* analysis of the patient level data. Therefore, the ERG has little to no information on this clinical outcome. Secondly, the estimation of adjusted TTD curves for daratumumab through the, "calibration approach" is a black box in the company's analysis. No further details were provided by the company other than the fact that, *"the TTD curves for daratumumab were calibrated to match the observed mean and median from MM-003".* A mean and median TTD of 4.7 months and 2.9 months was observed for pom+dex in the MM-003 trial, respectively. [43]

The daratumumab TTD and PFS curves are compared in Figure 35, which shows that the extrapolated curves separate with a higher rate of discontinuation than progression. The ERG notes that different functions were used to fit PFS and TTD (i.e. lognormal and log-logistic), and that may also lead to a more accentuated difference in the curves. The PFS and TTD curves for pom+dex indicate that patients are more likely to discontinue treatment for reasons other than progression compared to daratumumab. This would make sense considering the advantageous safety profile of daratumumab compared with pom+dex. Considering the uncertainty around the TTD data and estimation, the ERG considers that using these data in the economic analysis carries a potentially high risk. While the PFS curves and data are also not without problems, PFS curves could be used as an exploratory approach to derive treatment costs, implying that patients receive treatment until progression. Figure 36 shows the time on treatment (TOT = P(PFS)-P(TTD)) for daratumumab and pom+dex patients compared with the respective PFS curves. Analysis of the curves in Figure 36 shows that when

subsequent treatments received in MMY2002 and GEN501 in the NHS. This is explored in the next subsection of the report.

Table 71. Estimates of OS from post-hoc subgroup analysis

Dataset	Subgroup	Median OS (95% CI)	Sample size
Integrated	Bortezomib as a subsequent treatment	[redacted]	[redacted]
	Carfilzomib as a subsequent treatment	[redacted]	[redacted]
	Lenalidomide as a subsequent treatment	[redacted]	[redacted]
	Pomalidomide as a subsequent treatment.	[redacted]	[redacted]
MMY2002	No subsequent treatment	[redacted]	[redacted]
	Any subsequent treatment.	[redacted]	[redacted]
GEN501	No subsequent treatment	[redacted]	[redacted]
	Any subsequent treatment.	[redacted]	[redacted]

Key: CI, confidence interval; NE, not evaluable; OS, overall survival.

[redacted]

[redacted]

5.2.1.3.1 Availability of the subsequent treatments received in MMY2002 and GEN501 in the NHS

Around 72% of the population in MMY2002/GEN501 received further treatment after daratumumab for rrMM. Considering that daratumumab is being positioned by the company as a fourth line treatment option, there would not be many options for subsequent treatments available for these patients in the NHS. Daratumumab patients received subsequent carfilzomib (28%), lenalidomide (15%), bortezomib (24%) and pomalidomide (31%), among other treatments. As demonstrated above, these treatments are likely to have a great impact on daratumumab's OS, despite being received at a later point in time.

which appears to change the natural course of disease, such that the disease is effectively reset". Additionally, the company proposes that the novel mode of action of daratumumab increases the likelihood of patients benefiting from subsequent therapy. Given that no study comparing daratumumab with another active comparator is available, together with the differences across the studies that form the evidence base for the MAIC, the ERG considers that it is unclear whether the survival benefit associated with daratumumab is unprecedented. As the company acknowledges, across trial simple comparison (with no analysis) of effect estimates is inappropriate

Economic

The ERG has serious concerns with the robustness of the economic analysis undertaken by the company. The ERG encountered several errors and discrepancies in the different versions of the economic model, CS and data provided by the company to the ERG after the clarification stage. The specificities of this STA allied with the submission of multiple model versions and the limited time available for the ERG review, make it very likely that some mistakes were not detected by the ERG. The key aspects of this STA are as follows:

- The absence of RCT evidence;
- The possible permutations for the data analysis (three datasets for daratumumab – MMY2002; GEN501 and integrated; two different trials for the two comparator; two subgroups of relevance related with subsequent therapies and pre-treatment received by patients; two possible modelling approaches – dependent or independent fit and finally the variation in the adjustment factors included in the MAIC).

The fact that ERG kept on finding mistakes in data handling and labelling increases the probability that some other similar mistakes were not identified. It is impossible to foresee the impact of such potentially unidentified mistakes. It is the ERG's opinion that the company's model and data analysis need further internal consistency checks and a thorough quality check before a robust ICER can be determined for daratumumab.

The ERG summarises the key issues surrounding the cost-effectiveness of daratumumab below. These are related with:

- **Pre-treatment with pomalidomide**: The ERG is concerned about the validity of the data sent through by the company at the clarification stage. However, the data suggest that there is no difference in PFS across pom-naïve and non-pom-naïve patients and that OS outcomes are better for pom-naïve patients than for the overall trial population. The ERG interprets this trend in the data as a possible consequence of the effect of pomalidomide as a subsequent therapy. It

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID933]

You are asked to check the ERG report from BMJ Evidence Centre to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by the end of**, 6 February 2017** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Robustness of the economic analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 26 of the ERG report it is stated that: "Due to mistakes and/or discrepancies identified before and during the clarification process, the company provided two versions of the written submission of the economic evidence along with three electronic versions of the Microsoft Excel® based economic model The ERG has serious concerns with the robustness of the economic analysis undertaken by the company as it has encountered several errors and discrepancies in the different versions of the economic model, CS and data forward by the company to the ERG after the clarification stage. The specificities of this STA allied with the submission of multiple model versions and the limited time available for the ERG review, make it very likely that some mistakes were not detected." On page 27 of the ERG report it is	Janssen request that the ERG removes these statements, and other similar statements, as they do not present a balanced case of the review process, and mislead the reader regarding the consistency of the economic model.	Janssen is happy for any errors identified by the ERG or Janssen before, during or after the clarification process to be detailed in the ERG report – this is right and proper. However, Janssen considers that the text used by the ERG inflates the facts and may introduce unnecessary mistrust of Janssen's economic model in to the Appraisal Committee's consideration of the evidence. Whilst it is factually accurate that some minor errors and cosmetic inaccuracies were present in the submitted model. These did not have a substantial impact on the ICERs. Moreover the reason that three versions of the Microsoft Excel® based economic model were submitted was in no small part a result of the ERGs approach to identifying and addressing these minor errors. That is, the ERG chose to request a corrected model and submission addendum for the correction of minor errors identified ahead of the	The ERG thanks the company for their comment. Not a factual error.

stated that: "The fact that ERG kept on finding mistakes in data handling and labelling increases the probability that some other similar mistakes were not identified. It is impossible to foresee the impact of such potentially unidentified mistakes. It is the ERG's opinion that the company's model and data analysis need further internal consistency checks and a thorough quality check before a robust ICER can be determined for daratumumab" On page 37 of the ERG report it also states that: "Nonetheless the ERG stresses its opinion that the company's model and data analysis need further internal consistency checks and a thorough quality check before a robust ICER can be determined for daratumumab" On pages 136 and 137 of the ERG report these statements are reiterated and on page 136 it is also stated that: "After the submission of the third model, the ERG still found a considerable amount of serious errors in the economic model		clarification process. The ERG then requested another corrected model and submission addendum following additional minor errors identified during the clarification process. It is a direct consequence of this piecewise approach to the identification and correction of errors that three versions of the economic model were submitted. We did not anticipate that the ERG's unorthodox requests outside of the normal clarification stage, which we were happy to help with, would be used as a tool with which to unfairly criticise and discredit the analysis. It is also important to note that all of the minor errors identified by the ERG before, during and after the clarification period have resulted in decreased base case ICERs. One error identified by Janssen before clarification increased the ICERs (see table 1 below). In short, it is not only incorrect but also inflammatory, for the ERG to infer, explicitly or otherwise, that the model's robustness should be questioned in the manner set out in the ERG report. We state this given (1) the extent of quality control the	

(described throughout the report)." All of the above statements are then reiterated on pages 182, 183 and 263 of the ERG report		model has undergone, and (2) the transparency and helpfulness with which we have approached this submission process. Janssen apologise for the minor errors present in the model, however, the tone of language used by the ERG to describe this inflates the facts. Janssen considers that this text could result in an unfair consideration of the evidence by the Appraisal Committee.	

Table 1. Summary of errors identified by the ERG or by Janssen before, during or after the clarification stage

Appraisal stage	Description of errors	Identified by	Impact of correcting the error on the base case results
Before clarification	Utility decrements not applied due to incorrect cell referencing within the model	ERG	vs POM+DEX: increased by £2,557 vs PANO+BORT+DEX: increased by £9,151 vs Bendamustine: increased by £1,862
	Incorrect dosing schedule	Janssen	
During clarification	Incorrect proportion of patients assumed to experience nausea (all grades)	ERG	vs POM+DEX: reduced by £595 vs PANO+BORT+DEX: reduced by £667 vs Bendamustine: reduced by £449
	Positive rather than negative values for some disutilities		
Post clarification	Incorrect rates of peripheral neuropathy	ERG	vs POM+DEX: reduced by £2,295 vs PANO+BORT+DEX: reduced by £4,344 vs Bendamustine: reduced by £1,592
	Incorrect disutility applied to POM+DEX and bendamustine		
	Incorrect calculation of the proportion of patients receiving each subsequent treatment		
	Incorrect acquisition cost for subsequent treatments		

Issue 2 Errors in data submitted during the clarification stage

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 136 of the ERG report it is stated that: "The ERG encountered several errors and discrepancies in the data forwarded by the company to the ERG at the clarification stage. For example, all the overall survival Kaplan-Meier curves for subsequent treatments were labelled with the incorrect treatment (for instance, what the company reported as being the subsequent pomalidomide overall survival Kaplan-Meier curve, was actually the subsequent lenalidomide overall survival Kaplan-Meier curve, as the ERG discovered later). As a consequence, the ERG lacks overall confidence in the Excel model and in the company analysis of data."	Janssen request that the ERG modifies this and similar statements to disentangle errors in the data submitted as part of the clarification response with the consistency of the economic model. Issues with the data submitted at clarification do not affect the consistency of the submitted model, rather they are a result of the numerous additional data and analyses requested by the ERG and the fact that there was not sufficient time within the clarification process for data to be analysed and validated.	At the clarification stage, the ERG requested a substantial amount of additional analyses. In total the ERG requested 83 additional analyses, including: • MAIC analyses of OS and PFS vs pom+dex, using GEN501 data (12 analyses) • MAIC analyses of OS and PFS vs pano+bort+dex, using GEN501 data (14 analyses) • Post-hoc subgroup analysis of pom-naïve patients from GEN501 (3 analyses) • Post-hoc subgroup analyses of pom-naïve patients from MMY2002 (7 analyses) • MAIC of OS and PFS vs pom+dex using post-hoc subgroup analysis of pom-naïve patients in GEN501 (2 analyses) • MAIC of OS and PFS vs pano+bort+dex using post-hoc subgroup analysis of pom-naïve patients in GEN501 (2 analyses)	Not a factual error.

		• Post-hoc subgroup analyses of OS in people receiving bortezomib as a subsequent treatment in the integrated trial data • Post-hoc subgroup analyses of OS in people receiving carfilzomib as a subsequent treatment in the integrated trial data • Post-hoc subgroup analyses of OS in people receiving lenalidomide as a subsequent treatment in the integrated trial data • Post-hoc subgroup analyses of OS in people receiving pomalidomide as a subsequent treatment in the integrated trial data • Post-hoc subgroup analyses of OS in people receiving no subsequent treatment in the integrated trial data • MAIC of OS using post-hoc subgroup analyses of people receiving bortezomib as a subsequent treatment in the integrated trial data vs pom+dex (3 analyses) • MAIC of OS using post-hoc subgroup analyses of people receiving carfilzomib as a subsequent treatment in the integrated trial data vs pom+dex (8 analyses) • MAIC of OS using post-hoc subgroup analyses of people receiving	

		lenalidomide as a subsequent treatment in the integrated trial data vs pom+dex (2 analyses) • MAIC of OS using post-hoc subgroup analyses of people receiving pomaildomide as a subsequent treatment in the integrated trial data vs pom+dex (3 analyses) • MAIC of OS using post-hoc subgroup analyses of OS in people receiving no subsequent treatment in the integrated trial data vs pom+dex • MAIC of OS using post-hoc subgroup analyses of people receiving bortezomib as a subsequent treatment in the integrated trial data vs pano+bort+dex (2 analyses) • MAIC of OS using post-hoc subgroup analyses of people receiving carfilzomib as a subsequent treatment in the integrated trial data vs pano+bort+dex (3 analyses) • MAIC of OS using post-hoc subgroup analyses of people receiving lenalidomide as a subsequent treatment in the integrated trial data vs pano+bort+dex (3 analyses) • MAIC of OS using post-hoc subgroup analyses of people receiving pomaildomide as a subsequent treatment in the integrated trial data vs pano+bort+dex (2 analyses)	

		• MAIC of OS using post-hoc subgroup analyses of OS in people receiving no subsequent treatment in the integrated trial data vs pano+bort+dex • Post-hoc subgroup analyses of OS in people receiving no subsequent treatment in the MMY2002 trial • Post-hoc subgroup analyses of OS in people receiving any subsequent treatment in the MMY2002 trial • MAIC of OS using post-hoc subgroup analyses of people receiving no subsequent treatment in the MMY2002 trial vs pom+dex (this analysis was not possible) • MAIC of OS using post-hoc subgroup analyses of people receiving no subsequent treatment in the MMY2002 trial vs pano+bort+dex (this analysis was not possible) • MAIC of OS using post-hoc subgroup analyses of people receiving any subsequent treatment in the MMY2002 trial vs pom+dex (this analysis was not possible) • MAIC of OS using post-hoc subgroup analyses of people receiving any subsequent treatment in the MMY2002 trial vs pano+bort+dex (this analysis was not possible)	

		• MAIC analysis for TTD (this analysis was not possible) • mean treatment duration, with respective minimum and maximum treatment period for each of the treatments received in a sequential order for the integrated dataset. • mean treatment duration, with respective minimum and maximum treatment period for each of the treatments received in a sequential order for MMY2002 • mean treatment duration, with respective minimum and maximum treatment period for each of the treatments received in a sequential order for GEN501 In addition to this the ERG requested 93 files of K-M data and 49 files of weights used in the MAICs. Furthermore, the ERG requested 2 new models (one based on MMY2002 and one based on GEN501) and 5 additional post-hoc subgroup analyses to be included in these models. The ERG also requested that individual curves be fitted to PFS data. Janssen made every effort to obtain and provide all the information requested by the ERG and apologise for any mistakes in data labelling. Given the time constraints of the clarification process and the fact that new statistical	

		procedures had to be created to run many of these analyses, it is not surprising that errors crept in. A more focussed set of requests from the ERG would have allowed time for validation. Janssen consider that it is important to disentangle mistakes made in response to clarification requests and the robustness of the submitted economic model.	

Issue 3 Incorrect HRs

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Throughout the ERG report, HRs are reported incorrectly On page 23: "The PFS HRs used in the company's base case are 1.24 (95% CI: 0.92 to 1.68) for pom+dex and 1.74 (95% CI: 1.24 to 2.26) for pano+bort+dex" On page 23: "The OS HRs used in the company's base case are 1.74 (95% CI: 1.24 to 2.46) for pom+dex and 1.19 (95% CI: 0.73 to 1.92) for pano+bort+dex" On page 37: "Thus the ERG ran an additional exploratory analysis replacing the PFS HR for pom+dex with the value of 1.01 (reflecting a 1% gain in effectiveness for daratumumab	Janssen request that the ERG corrects these as follows: On page 23: "The PFS HRs used in the company's base case are **0.81** (95% CI: **0.60 to 1.09**) for pom+dex and for **1.09** (95% CI: **0.74 to 1.61**) pano+bort+dex" On page 23: "The OS HRs used in the company's base case are **0.57** (95% CI: **0.41 to 0.81**) for pom+dex and **0.84** (95% CI: **0.52 to 1.37**) for pano+bort+dex" On page 37: "Thus the ERG ran an additional exploratory analysis replacing the PFS HR for pom+dex with the value of	Factually inaccurate	The ERG would like to point out that all HRs presented by the ERG and reported by the company in the first column are the inverse of the company's HRs (i.e. 1/company's HR) to reflect the comparator treatment as the base. So an HR> 1 reflects a gain in survival with daratumumab and a HR<1 reflects a loss

against pom+dex)"

On page 37:

"Secondly, these results are also highly dependent on the HRs for OS which are not only non-statistically significant, but show an incredible wide range of possible HRs with 95% confidence intervals going from 0.69 to 4.00. The OS HR for pom+dex is 1.14 (95% CI: 0.57 to 2.27) while the HR for pano+bort+dex is 1.64 (95% CI: 0.69 to 4.00)."

Table 32, page 144:

Daratumumab compared with	Weighted HR from MAIC	95% confidence interval	Number of characteristics matched
Pom+dex	1.241	(0.920; 1.675)	11
Pano+bort+dex	0.920	(0.623; 1.357)	5

Abbreviations in table: bort, bortezomib; dex, dexamethasone; MAIC, matched adjusted indirect comparison; pano, panobinostat; pom, pomalidomide.

Table 35, page 152:

Daratumumab compared with	Weighted HR from MAIC	95% confidence interval	Number of characteristics matched
Pom+dex	1.742	(1.238; 2.457)	11
Pano+bort+dex	1.186	(0.733; 1.919)	5

Abbreviations in table: bort, bortezomib; dex, dexamethasone; HR, hazard ratio; MAIC, matched adjusted indirect comparison; pano, panobinostat; pom, pomalidomide.

On page 190 of the ERG report, the HRs reported in

1.01 (reflecting a 1% **reduction** in effectiveness for daratumumab against pom+dex)"

On page 37:

"Secondly, these results are also highly dependent on the HRs for OS which are not only non-statistically significant, but show an incredible wide range of possible HRs with 95% confidence intervals going from **0.44** to **1.77**. The OS HR for pom+dex is **0.88** (95% CI: **0.44 to 1.77**) while the HR for pano+bort+dex is **0.61** (95% CI: **0.25 to 1.45**)."

Table 32, page 144:

Daratumumab compared with	Weighted HR from MAIC	95% confidence interval	Number of characteristics matched
Pom+dex	**0.81**	**(0.60, 1.09)**	11
Pano+bort+dex	**1.09**	**(0.74, 1.61)**	5

Abbreviations in table: bort, bortezomib; dex, dexamethasone; MAIC, matched adjusted indirect comparison; pano, panobinostat; pom, pomalidomide.

Table 35, page 152:

Daratumumab compared with	Weighted HR from MAIC	95% confidence interval	Number of characteristics matched
Pom+dex	**0.57**	**(0.41, 0.81)**	11
Pano+bort+d	**0.84**	**(0.52, 1.37)**	5

in survival with daratumumab. For transparency purposes, the ERG has added a sentence at the beginning of the report explaining this.

The ERG thanks the company for pointing out some discrepancies in the values reported by the ERG and the company. However, these are not factual errors as the source of the discrepancies originate from the company submission reporting different values from those used in the company's economic model, a fact that the ERG did not notice upon writing their report. More specifically:

1) The values mentioned by the company on Table 56 (page 190) for

Table 56 are incorrect.

Daratumumab compared with	Weighted HR from MAIC	95% confidence interval	Number of characteristics matched
Pom+dex OS pom-naïve	1.639	(1.242; 2.165)	11
Pom+dex PFS pom-naïve	1.139	(0.897; 1.447)	11
Pom+dex OS base case	1.742	(1.238; 2.457)	11
Pom+dex PFS base case	1.241	(0.920; 1.675)	11
MAIC, matched adjusted indirect comparisson			

On page 199:

"HR (1.74; 95% CI: 1.24 to 2.26) across daratumumab and pom+dex"

On page 206:

"To note is that when the HRs are fully adjusted for the maximum number of patients' characteristics the HRs change the direction of the effect (for example, the HR for daratumumab vs pom+dex goes from 1.24 to 0.88).."

Table 59, page 206

Comparison	Hazard ratio	95% confidence interval
ex		
Abbreviations in table: bort, bortezomib; dex, dexamethasone; HR, hazard ratio; MAIC, matched adjusted indirect comparison; pano, panobinostat; pom, pomalidomide.		

On page 190 Table 56.

Daratumumab compared with	Weighted HR from MAIC	95% confidence interval	Number of characteristics matched
Pom+dex OS pom-naïve	**0.40**	**(0.20, 0.80)**	11
Pom+dex PFS pom-naïve	**0.57**	**(0.31, 1.05)**	11
Pom+dex OS base case	**0.57**	**(0.41, 0.81)**	11
Pom+dex PFS base case	**0.81**	**(0.60, 1.09)**	11
MAIC, matched adjusted indirect comparisson			

On page 199:

"HR (**0.57** (95% CI: **0.41 to 0.81**)) across daratumumab and pom+dex"

On page 206:

"To note is that when the HRs are fully adjusted for the maximum number of patients' characteristics the HRs change the direction of the effect (for example, the HR for daratumumab vs pom+dex goes from **0.81** to **1.14**."

pomalidomide naïve patients do not match the values reported by the company in their economic model. The company's economic model reports HRs for pom+dex of 0.61 (0.46 to 0.81) for OS and 0.88 (0.69 to 1.12) for PFS and not 0.40 (0.20 to 0.80) and 0.57 (0.31 to 1.05) as suggested by the company in the second column of this table. The values reported by the ERG therefore correspond to the inverse HRs reported in the company's model.

2) The values mentioned by the company on Table 60 (page 209) for the company's analysis of MMY2002 do not match the values used by the company in the economic model. The company's economic model uses PFS HRs

11 characteristics adjusted for daratumumab vs pom+dex (company's base case)	1.241	(0.920; 1.675)
5 characteristics adjusted for daratumumab vs pano+bort+dex (company's base case)	0.920	(0.623; 1.357)
28 characteristics adjusted for daratumumab vs pom+dex (ERG's preferred approach)	0.877	(0.493; 1.563)
16 characteristics adjusted for daratumumab vs pano+bort+dex (ERG's preferred approach)	1.176	(0.532; 2.564)

Abbreviations in table: bort, bortezomib; dex, dexamethasone; pano, panobinostat; pom, pomalidomide.

Table 60, page 209

Comparison	Hazard ratios	95% confidence interval
11 characteristics adjusted for daratumumab vs pom+dex (integrated population, company's base case)	1.241	(0.920; 1.675)
5 characteristics adjusted for daratumumab vs pano+bort+dex (integrated population,	0.920	(0.623; 1.357)

Table 59, page 206

Comparison	Hazard ratio	95% confidence interval
11 characteristics adjusted for daratumumab vs pom+dex (company's base case)	**0.81**	**(0.60, 1.09)**
5 characteristics adjusted for daratumumab vs pano+bort+dex (company's base case)	**1.09**	**(0.74, 1.61)**
28 characteristics adjusted for daratumumab vs pom+dex (ERG's preferred approach)	**1.14**	**(0.64, 2.03)**
16 characteristics adjusted for daratumumab vs pano+bort+dex (ERG's preferred approach)	**0.85**	**(0.39, 1.88)**

Abbreviations in table: bort, bortezomib; dex, dexamethasone; pano, panobinostat; pom, pomalidomide.

Table 60, page 209

Comparison	Hazard ratios	95% confidence interval
11 characteristics adjusted for daratumumab vs pom+dex (integrated population, company's	**0.81**	**(0.60, 1.09)**

for pom+dex of 1.07 (0.75 to 1.54) and not 0.95 (0.64 to 1.40) as suggested by the company in the second column of this table. The values reported by the ERG therefore correspond to the inverse HRs used in the company's model. It would appear that the company's model uses the investigator-assessed PFS HR for pom+dex instead of the IRC-assessed HR in this instance.

The ERG agrees with the company that the HR reported in page 23 represents a factual inaccuracy. The sentence "The PFS HRs used in the company's base case are 1.24 (95% CI: 0.92 to 1.68) for pom+dex and 1.74 (95% CI: 1.24 to 2.26) for pano+bort+dex" was therefore replaced with "The PFS HRs

company's base case)		
11 characteristics adjusted for daratumumab vs pom+dex (MMY2002 population, company's scenario analysis)	0.935	(0.651; 1.340)
5 characteristics adjusted for daratumumab vs. pano+bort+dex (MMY2002 population, company's scenario analysis)	0.832	(0.535; 1.294)
28 characteristics adjusted for daratumumab vs pom+dex (ERG's preferred approach)	0.877	(0.493; 1.563)
16 characteristics adjusted for daratumumab vs pano+bort+dex (ERG's preferred approach)	1.176	(0.532; 2.564)
Abbreviations in table: bort, bortezomib; dex, dexamethasone; pano, panobinostat; pom, pomalidomide.		

Table 64, page 218

Comparison	Hazard ratios	95% confidence interval
11 characteristics adjusted for daratumumab vs	1.742	(1.238; 2.457)
base case)		
5 characteristics adjusted for daratumumab vs pano+bort+dex (integrated population, company's base case)	**1.09**	**(0.74, 1.61)**
13 characteristics adjusted for daratumumab vs pom+dex (MMY2002 population, company's scenario analysis)	**0.95**	**(0.64, 1.40)**
8 characteristics adjusted for daratumumab vs. pano+bort+dex (MMY2002 population, company's scenario analysis)	**1.20**	**(0.77, 1.87)**
28 characteristics adjusted for daratumumab vs pom+dex (ERG's preferred approach)	**1.14**	**(0.64, 2.03)**
16 characteristics adjusted for daratumumab vs pano+bort+dex (ERG's preferred approach)	**0.85**	**(0.39, 1.88)**
Abbreviations in table: bort, bortezomib; dex, dexamethasone; pano, panobinostat; pom, pomalidomide.		

Table 64, page 218

used in the company's base case are 1.24 (95% CI: 0.92 to 1.68) for pom+dex and 1.09 (95% CI: 0.74 to 1.61) for pano+bort+dex"

pom+dex (company's base case)		
5 characteristics adjusted for daratumumab vs pano+bort+dex (company's base case)	1.186	(0.733; 1.919)
28 characteristics adjusted for daratumumab vs pom+dex (ERG's preferred approach)	1.136	(0.565; 2.273)
16 characteristics adjusted for daratumumab vs pom+dex 28 characteristics adjusted for daratumumab vs. pano+bort+dex (ERG's preferred approach)	1.639	(0.690; 4.000)

Table 66, page 222

Comparison	Hazard ratios	95% confidence interval
11 characteristics adjusted for daratumumab vs pom+dex (integrated population, company's base case)	1.742	(1.238; 2.457)
5 characteristics adjusted for daratumumab vs pano+bort+dex	1.186	(0.733; 1.919)

Comparison	Hazard ratios	95% confidence interval
11 characteristics adjusted for daratumumab vs pom+dex (company's base case)	**0.57**	**(0.41, 0.81)**
5 characteristics adjusted for daratumumab vs pano+bort+dex (company's base case)	**0.84**	**(0.52, 1.37)**
28 characteristics adjusted for daratumumab vs pom+dex (ERG's preferred approach)	**0.88**	**(0.44, 1.77)**
16 characteristics adjusted for daratumumab vs pom+dex 28 characteristics adjusted for daratumumab vs. pano+bort+dex (ERG's preferred approach)	**0.61**	**(0.25, 1.45)**

Table 66, page 222

(integrated population, company's base case)		
11 characteristics adjusted for daratumumab vs pom+dex (MMY2002 population, company's scenario analysis)	1.540	(0.964; 2.463)
5 characteristics adjusted for daratumumab vs pano+bort+dex (MMY2002 population, company's scenario analysis)	1.089	(0.863; 1.802)
28 characteristics adjusted for daratumumab vs pom+dex (ERG's preferred approach)	1.136	(0.565; 2.273)
16 characteristics adjusted for daratumumab vs pano+bort+dex (ERG's preferred approach)	1.639	(0.690; 4.000)

Page 254:

"1. Given that the ERG's preferred methodological approach is not available as a modelling option in the company's Excel model, the ERG explored the impact of using fully adjusted HRs for PFS. This means using PFS HRs of 0.88 for pom+dex and of 1.18 for pano+bort+dex (instead of 0.935 and 0.83, respectively, in the company's scenario analysis for MMY2002);"

Page 254:

Comparison	Hazard ratios	95% confidence interval
11 characteristics adjusted for daratumumab vs pom+dex (integrated population, company's base case)	**0.57**	**(0.41, 0.81)**
5 characteristics adjusted for daratumumab vs pano+bort+dex (integrated population, company's base case)	**0.84**	**(0.52, 1.37)**
13 characteristics adjusted for daratumumab vs pom+dex (MMY2002 population, company's scenario analysis)	**0.65**	**(0.41, 1.04)**
8 characteristics adjusted for daratumumab vs pano+bort+dex (MMY2002 population, company's scenario analysis)	**0.92**	**(0.56, 1.52)**
28 characteristics adjusted for daratumumab vs pom+dex (ERG's	**0.88**	**(0.44, 1.77)**

"3. The ERG explored the impact of using fully adjusted HRs for OS. This means using OS HRs of 1.14 for pom+dex and of 1.64 for pano+bort+dex (instead of 1.54 and 1.09, respectively, in the company's scenario analysis for MMY2002)." Page 255: "the company's HRs for PFS in the MMY2002 population are 0.94 for pom+dex and 0.83 for pano+bort+dex. Therefore, when the ERG replaces these for the fully-adjusted HRs (0.88 for pom+dex and of 1.18 for pano+bort+dex)" Page 255: "When the HRs for OS are changed from the company's analysis of MMY2002 (1.54 for pom+dex and of 1.09 for pano+bort+dex) to the fully-adjusted HRs (1.14 for pom+dex and of 1.64 for pano+bort+dex)" This factually inaccurate	<table><tr><td>preferred approach)</td><td></td><td></td></tr><tr><td>16 characteristics adjusted for daratumumab vs pano+bort+dex (ERG's preferred approach)</td><td>0.61</td><td>(0.25, 1.45)</td></tr></table> Page 254: "1. Given that the ERG's preferred methodological approach is not available as a modelling option in the company's Excel model, the ERG explored the impact of using fully adjusted HRs for PFS. This means using PFS HRs of **1.14** for pom+dex and of **0.85** for pano+bort+dex (instead of **0.95** and **1.20**, respectively, in the company's scenario analysis for MMY2002);" Page 254: "3. The ERG explored the impact of using fully adjusted HRs for OS. This means using OS HRs of **0.88** for pom+dex and of **0.61** for pano+bort+dex (instead of **0.65** and **0.92**, respectively, in the company's scenario analysis for MMY2002)." Page 255: "the company's HRs for PFS in the MMY2002 population are **0.95** for pom+dex and **1.20** for pano+bort+dex. Therefore, when the ERG replaces these for the fully-adjusted HRs (**1.14** for pom+dex and of **0.85** for pano+bort+dex)" Page 255:		

	"When the HRs for OS are changed from the company's analysis of MMY2002 (**0.65** for pom+dex and of **0.92** for pano+bort+dex) to the fully-adjusted HRs (**0.88** for pom+dex and of **0.61** for pano+bort+dex)"		

Issue 4 ERG exploratory curve fitting

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 29 of the ERG report it is stated that: "The ERG is also concerned with the validity of the curve fitting exercise undertaken by the company for OS data, as some of the OS extrapolated curves by the company differ considerably from the ones obtained by the ERG." Also on page 195 "During the curve fitting exercise the ERG discovered more worrying issues, such as the fact that some of the OS fitted and extrapolated curves by the company differ very considerably from the ones obtained by the	Janssen request that the ERG removes these statements, and other similar statements, as they are based on an erroneous analysis carried out by the ERG.	Upon inspection of Figures 37 and 38 of the ERG report compared with Figures 39 and 40 of the ERG report, it would seem that the ERG is comparing the curve fits obtained via their R analyses using MMY2002 data with curve fits derived by Janssen using integrated MMY2002/GEN501. This is obvious when considering the K-M data across the Figures. Unless, the ERG did a very poor job of digitising the daratumumab integrated data, it seems that the comparison made in this section of the report is factually inaccurate.	Not a factual error. The data used by the ERG are the integrated dataset and not the MMY2002 (for which the last data point available is at around month 20). Small differences in the KM curves in Figure 37 and Figure 38 compared with Figure 39 and Figure 40 are due to different time scales across the graphs and related with the ERG using the company's data and the numbers at risk provided in the pivotal trials through the Guyot *et al.* method. This simulates the pseudo-individual patient-level data, using the algorithm in the

ERG” On page 204: “The ERG is also concerned with the validity of the curve fitting exercise undertaken by the company for OS data as some of the OS extrapolated curves by the company seem to differ considerably from the ones obtained by the ERG” On page 217 of the ERG report it is stated that: “After assessing the PH assumption in OS data, the ERG undertook a curve fitting exercise with the digitised data in R statistical package. The ERG is extremely concerned with the fact that some of the OS fitted and extrapolated curves by the company differ considerably from the ones obtained by the ERG. In Table 65 the ERG reports the AIC and BIC statistics obtained by the ERG compared with the ones reported by the company. The ERG also reproduces the curves fitted by the company (Figure 39 and Figure 40) to aid the visual comparison of the curves fitted by the ERG (Figure 37 and Figure 38). While the lognormal and log-logistic curves seem to have a			*survHE R* package. The main difference across the graphs is the fitted curves and not the KM data.

relatively similar positioning across the ERG estimated and company estimated curves, other curves, in particular the Gompertz and the gamma seem to be radically different. The AIC and BIC statistics estimated by the ERG suggest that the gamma, Gompertz and Weibull distributions would all be possible model candidates. All of these functions would be more flexible than the exponential distribution as they do not assume a constant baseline hazard. As the ERG's curve fitting exercise was carried as exploratory analysis, and there was insufficient time to fully validate the analysis undertaken, and the ERG did not use these curves in the company's model. The ERG would recommend an additional validation exercise of the curves, to be performed by the company, to explain the difference between the company and the ERG estimated survival curves." The ERG also states on pages 29, 204/205 and 265: "The ERG is also concerned with the validity of the curve fitting exercise undertaken by the company for OS data, as some of the OS extrapolated curves by			

the company differ considerably from the ones obtained by the ERG." Given that the ERG mistrust of the OS extrapolations results from an erroneous analysis carried out by the ERG. These statements are incorrect			

Issue 5 Pom-naïve MAIC-adjusted HRs for OS and PFS

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 189 of the ERG report it is stated that: "the ERG notes that the HRs for the pom-naïve subgroup analysis ran by the company (reported in Table 56 below) show that daratumumab compared with pom+dex is less effective in the pom-naïve population than in the overall trial population (albeit not statistically significant for PFS)" This factually inaccurate	Janssen request that the ERG corrects this statement as follows: "the ERG notes that the HRs for the pom-naïve subgroup analysis ran by the company (reported in Table 56 below) show that daratumumab compared with pom+dex is **more** effective in the pom-naïve population than in the overall trial population (albeit not statistically significant for PFS)"	Factually inaccurate	Not a factual error. Please see reply to issue 3 raised by the company.

Issue 6 Description of treatments available in clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 16 of the ERG report it is stated that: "However, other therapies given prior to daratumumab in MMY2002 and GEN501 included carfilzomib and pomalidomide, neither of which, at the time of writing, will have been used as a treatment for rrMM in England: carfilzomib is not an available treatment option and pomalidomide was recommended as an option in rrMM by NICE on 11 January 2017" Also on page 25 of the ERG report it is stated that: "In MMY2002 and GEN501 Part 2, some of the therapies people had received prior to trial entry are not available treatment options within the UK (carfilzomib, and, until January 2017, pomalidomide)" And on page 57 of the ERG report: "Other therapies given prior to daratumumab in MMY2002 and	Janssen request that these statements and any similar statements are corrected to state the availability of pomalidomide through the Cancer drugs fund until September 2015	It is not factually accurate to state that pomalidomide will not have been used as a treatment for rrMM in England.	The ERG thanks the company for highlighting this error. After consultation with clinical experts, the ERG has amended the text to read (or something similar): However, other therapies given prior to daratumumab in MMY2002 and GEN501 included carfilzomib and pomalidomide, both of which will have had limited use in UK clinical practice as a treatment for rrMM: carfilzomib has never been an available treatment option outside of clinical trials and a compassionate use scheme, and pomalidomide was available for treatment of rrMM through the Cancer Drugs Fund for a limited period between April 2013 and September 2015, when it was de-listed.

GEN501 included carfilzomib and pomalidomide, neither of which, at the time of writing, will have been used as a treatment for rrMM in England: …. pomalidomide was recommended as an option by NICE on 11 January 2017” And on page 73 of the ERG report: "the ERG notes that some treatments received before enrolment are not (carfilzomib), or were not until January 2017 (pomalidomide), available treatment options in UK clinical practice" And on page 79 of the ERG report: “As noted in Section 3.1, some of the prior treatments people had received at enrolment are not, or were not until recently, available treatment options in UK clinical practice, that is, carfilzomib and pomalidomide” And on page 81 of the ERG report: “Importantly, in the context of the decision problem, no person in the UK who would likely be eligible for treatment with daratumumab will have received pomalidomide as a prior treatment at the time of writing”			

And on page 86 of the ERG report: "In MMY2002 and GEN501 Part 2, some of the therapies people had received prior to trial entry are not available treatment options within the UK (carfilzomib, and, until January 2017, pomalidomide)" These statements are not factually accurate since pomalidomide was available through the Cancer drugs fund until September 2015			

Issue 7 Impact of subsequent treatment with carfilzomib, lenalidomide and bortezomib

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On pages 19, 26 and 97 of the ERG report it is stated that: "Carfilzomib, lenalidomide and bortezomib are likely to be associated with prolonged OS compared with other treatment options available in the UK setting for the population of interest." Also on page 28 of the ERG report it is stated that: "treatment with carfilzomib and retreatment with lenalidomide and bortezomib are …likely to considerably increase overall survival as subsequent therapies for rrMM patients"	Janssen request that the ERG removes these statements, and other similar statements	There is no evidence to support the claim that subsequent treatment with carfilzomib would result in better OS compared to treatments available at 5th line and beyond in the UK. Similarly, there is no evidence to support the claim that subsequent treatment with lenalidomide or bortezomib would result in better outcomes than UK clinical practice. These statements are not evidence based and may mislead the reader on the impact of differences in subsequent treatment between the daratumumab (and pom+dex) trials and clinical practice.	Not a factual error.

Also on page 101/102 of the ERG report it is stated that: “Compared with subsequent therapies received in MM-003 and PANORAMA 2, the ERG considers that carfilzomib, lenalidomide and bortezomib are likely to be associated with prolonged OS” Also on page 128 of the ERG report it is stated that: “Carfilzomib, lenalidomide and bortezomib are likely to be associated with prolonged OS compared with other treatment options available in the UK setting for the population of interest” Also on page 191 of the ERG report it is stated that: “As daratumumab patients received several non-NICE approved subsequent treatments which have been shown to be associated with a large improvement in the daratumumab OS estimate (see Section 5.5.7.2), the ERG considers that the true effectiveness of daratumumab monotherapy is greatly overestimated in the economic analysis” There is no evidence to support this claim. The ERG has used post-hoc			

subgroup analyses provided in response to clarification questions. This is statistically inappropriate, since these post-hoc analyses contain data for patients treated with a variety of subsequent treatments and it is not possible to disentangle the effect of one particular subsequent treatment. Furthermore, there is trial evidence against this claim from the FOCUS trial of carfilzomib in heavily pre-treated rrMM patients, carfilzomib failed to show an overall survival benefit over low-dose dexamethasone with or without cyclophosphamide.			

Issue 8 Use of individual patient level data from the IMF chart review

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 72 of the ERG report it is stated that: "The company commissioned two retrospective chart reviews, one with the International Myeloma Foundation (IMF) and one with the Haematological Malignancy Research Network (HMRN), which may contribute evidence on bendamustine for an ITC"	Janssen request that these statements are expanded to include the fact that the individual patient level data from the IMF chart review were synthesised in multivariate regression analysis to provide evidence of the relative effectiveness of daratumumab versus pomalidomide.	The ERG have neglected to mention that individual patient level data from the IMF chart review have been used alongside individual patient level data from the daratumumab trials to provide estimates of relative treatment effect of daratumumab monotherapy versus pomalidomide plus dexamethasone (CS, Section 4.10.4).	Not a factual error. The ERG thanks the company for the comment. The ERG decided against reporting the results of the multivariate regression analysis for daratumumab versus pomalidomide because an equivalent analysis for daratumumab versus

Also on page 140 of the ERG report it states: "the company used real-world data sources to provide efficacy estimates for bendamustine"		This is an important omission, as given the limitations of the MAIC, Janssen sought to provide as much evidence of relative treatment effect as possible.	panobinostat was not available.

Issue 9 Description of daratumumab trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On pages 15, 17, 18, 25, 55, 85, 87, 131, 261 and 262 of the ERG report, MMY2002 and GEN501 are described as 'observational studies. This is factually inaccurate; MMY2002 and GEN501 are Phase I/II non-randomised interventional studies.	Janssen request that the ERG amend these statements to accurately describe the MMY2002 and GEN501 trials	Factually inaccurate	Not a factual error. The ERG considers that when the highlighted sentences are read in the context of the full text it is clear that the ERG is referring to a specific stage of the study and that stage is observational, in that the effects of an intervention are being observed in a single cohort. In the highlighted sentences, the ERG used the term observational for brevity. The design and conduct of MMY2002 and GEN501 Part 2 are discussed in detail in various sections of the ERG's report. The ERG did not consider it appropriate to

			describe both MMY2002 and GEN501 as Phase I/II non-randomised interventional studies, as, in contrast to GEN501, MMY2002 is solely a Phase II study and has a randomised component.

Issue 10 Contradiction in the ERG's assessment of survival benefit versus pano+bort+dex

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 30 of the ERG report it is stated that: "the 5-characteristic-adjusted OS curve for daratumumab vs pano+bort+dex seems to underestimate the survival benefit for daratumumab when compared with the fully adjusted, 16-characteristic-adjusted OS curve" The ERG then state (also on page 30) that: "The company's base case approach …. is also likely to overestimate the survival benefit compared with pano+bort+dex" This is a contradiction and factually inaccurate.	Janssen request that the incorrect statement that "the company's base case approach….is also likely to overestimate the survival benefit compared with pano+bort+dex" is removed.	Factually inaccurate.	The ERG agrees with the company. The sentence "The company's base case approach … is also likely to overestimate the survival benefit compared with pano+bort+dex" on page 29 has been replaced with "The company's base case approach …. underestimates the survival benefit compared with pano+bort+dex"

Issue 11 Inaccurate statement on impact of daratumumab safety profile

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 139 of the ERG report it is stated that: "the company states that the unique mechanism of action associated with daratumumab monotherapy appears to change the natural course of disease in rrMM as its favourable safety profile is potentially associated with a disease reset. This culminates in an improved health status of patients, allowing them to receive further active treatments (and retreatment with drugs received previously) to re-stabilise their disease" This is factually inaccurate	Janssen request that the statement be corrected as follows: "the company states that the unique mechanism of action associated with daratumumab monotherapy appears to change the natural course of disease in rrMM **and** is potentially associated with a disease reset. This, **along with its favourable safety profile** culminates in an improved health status of patients, allowing them to receive further active treatments (and retreatment with drugs received previously) to re-stabilise their disease"	Factually inaccurate. Janssen do not claim that daratumumab's favourable safety profile is associated with disease reset, rather that daratumumab's new MoA is associated with disease reset and that this, in conjunction with its favourable safety profile results in an improved health status (Cs, pgs 17 and 160).	The ERG thanks the company for clarifying and has replaced the sentence as proposed by the company.

Issue 12 Description of trial safety results

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On pages 20 and 129 of the ERG report it is stated that: "According to the company, IRRs were managed with pre- and post-infusion medications that included antihistamines, corticosteroids and	Janssen request that "According to the company" is replaced with "As reported in the CSRs".	Stating that the management of IRRs is a company claim rather than an observation based on the data reported in the CSRs is factually inaccurate	Not a factual error. The points highlighted by the company relating to management of IRRs are reported in the company's submission and are thus also

paracetamol/ acetaminophen” This is factually inaccurate, that IRRs were managed with pre- and post-infusion medications that included antihistamines, corticosteroids and paracetamol/ acetaminophen is provided in the CSRs and as such is a fact rather than a company claim.			statements made by the company.
On page119 of the ERG report it is stated that: “According to the company, daratumumab was well tolerated and resulted in no patient death or treatment discontinuation due to drug toxicity” This is factually inaccurate, that daratumumab was well tolerated and resulted in no patient death or treatment discontinuation due to drug toxicity is provided in the CSRs and as such is a fact rather than a company claim.	Janssen request that “According to the company” is replaced with “As reported in the CSRs”.	Stating that the daratumumab’s safety profile is a company claim rather than an observation based on the data reported in the CSRs is factually inaccurate.	Not a factual error. The points highlighted by the company relating to adverse effects are reported in the company’s submission and are thus also statements made by the company.

Issue 13 Information provided on time to treatment discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On pages 36 and 213 of the ERG report it is stated that:	Janssen request that this incorrect statement is removed	Factually inaccurate.	Not a factual error.

"Time to treatment discontinuation was not a pre-specified outcome in the MMY2002 and GEN501 trials but instead resulted from a post-hoc analysis of patient level data. Therefore the ERG has little to no information on this clinical outcome" This is factually inaccurate, the ERG have been provided with all information on time to treatment discontinuation, including: • How TTD was analysed • K-M data • Parametric extrapolations			
On pages 147 and 213 of ERG report it states: "Time to treatment discontinuation is used by the company to model treatment costs for daratumumab and pom+dex. This is done by subtracting the PFS curve from the TTD curve for each treatment, to obtain time on treatment for daratumumab and pom+dex patients (TOT = P(PFS)-P(TTD))." This in incorrect	Please correct as follows: "Time to treatment discontinuation is used by the company to model treatment costs for daratumumab and pom+dex. This is done by **using the TTD curve to calculate treatment costs**. **The TTD** curve **is subtracted** from the **PFS** curve for each treatment, to obtain **PFS (off Tx)** for daratumumab and pom+dex patients (**PFSOT** = P(PFS)-P(TTD))."	Factually inaccurate As stated on pg 140 of the ERG report, PFS (off Tx) is calculated by subtracting TTD from PFS.	The ERG thanks the company for pointing this out. The ERG agrees with the company suggestion and has made the necessary changes to the report.

Issue 14 Description of data from different data cuts

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 75 Patient disposition data from the CSR are reported. These data are from the primary data cut-off in January 2015. "*Over the duration of the study, 90 people (85%) discontinued treatment with daratumumab. The most common reason for discontinuation was disease progression (82 people [77%]). Five people (5%) discontinued daratumumab because of AEs not related to treatment, and three people (3%) withdrew due to symptoms related to disease progression.*"	More recent data are available from the December 2015 data cut and the ERG may wish to report these instead. These were presented in Table 10 of the CS; 100 (94.3%) of patients discontinued the study. In 92 (86.8%) patients this was due to disease progression, in 5 (4.7%) patients this was due to adverse events and in 3 (2.8%) patients this was due to withdrawal of consent	The ERG may prefer to present the most recent data	The ERG thanks the company for the comment. The ERG has updated the text to include the most recent data.
Page 76 The ERG report lists outcomes assessed at the primary data cut-off in January 2015, but omits one (clinical benefit rate). *"At the primary analysis data cut-off in January 2015, outcomes assessed were ORR, DoR, PFS, OS, TTR, and safety."*	Clinical benefit rate was also assessed at this data point as described in Table 9 of company submission. Clinical benefit rate is defined as MR plus ORR.	Full transparency	Not a factual error.

Issue 15 ERG critique of cost-effectiveness SLR

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 135 of the ERG report it is stated that: "the ERG disagrees with the company's approach of limiting the cost-effectiveness search to a specific intervention (daratumumab), as this led the company to exclude relevant sources of data unnecessarily" Limiting the cost-effectiveness search to daratumumab follows NICE methods guide (Section 3.3.9) and as such it is incorrect to claim this is the company's approach. The ERG incorrectly states that relevant quality of life data was missed as a result of the design of the economic SLRs. On page 135 of the ERG report it states: "the company did not identify the TA submission for pomalidomide to the SMC which included a more recent publication of the analysis of EQ-5D data from the MM-003 trial" Also on pages 156,184 and 185	Janssen request that the ERG removes these statements, and other similar statements, as they do not present a balanced case of the review process, and mislead the reader regarding the robustness of the economic literature review.	The current statements suggest that the economic SLR was conducted incorrectly, firstly through limiting the cost-effectiveness search by intervention and secondly through the incorrect assertion that quality of life papers were missed. **Justification for application of limitation to intervention within the cost-effectiveness search** The methodology of the cost-effectiveness SLR followed Section 3.3.9 of the NICE Guide to the methods of technology appraisal, which states: *3.3.9 "Evidence on cost effectiveness may be obtained from new analyses performed according to the NICE reference case; however, a systematic review of published, relevant evidence on the cost effectiveness of the technology should also be conducted."* It is therefore incorrect for the ERG to suggest that this design is the company's approach. **Evidence that papers would not be missed within the quality of life**	Not a factual error.

the ERG state: *"As the cost-effectiveness search was limited by the intervention (daratumumab) and the ERG is unware of how the company searched for TA submissions, it is difficult to predict why some relevant data on QoL (identified through the SMC pomalidomide submission) were missed by the company."* The paper that the ERG discuss as evidence of relevant information not being identified, on page 233 of the ERG report, Song et al, was in fact identified in the SLR and excluded as it does not report utility values usable in an economic model.		**search** The method used to search relevant HTA submissions is described on page 195 of the manufacturer's submission. *"In addition to the literature review described above, utility data and associated assumptions within key previous in rrMM NICE submissions (TA338 and TA380) were reviewed."* Relevant SMC submissions were not reviewed as these do not generally report the utility values used in economic evaluations. The paper reported in the SMC document identified by the ERG was identified in our database searches. The ERG states on page 231 (with reference to the Song paper which is asserted to have been missed): *"The ERG identified a more recent full publication by Song et al. reporting details of the longitudinal analysis of EQ-5D data from MM-003 using a mixed-effects model. According to Song et al. the quality of life of patients in the pom+loDEX arm of the MM-003 trial was statistically significantly better (p=0.05) compared to patients in the HiDEX arm in the first 10 treatment cycles. The analysis did not cover*	

		the period beyond 10 cycles due to a small sample size.(141) The ERG notes that the utility values of 0.61 prior to progression and 0.57 after progression reported in Palumbo et al. are for the whole dataset and not analysed separately by treatment arm, and are therefore confounded by the poorer quality of life experienced by patients receiving high doses of dexamethasone without pomalidomide. Thus, the utility estimates used in the base case analysis are likely to be an underestimate of patients' quality of life. However, the company applies the utility values from TA338 in a scenario analysis reported in Section 5.6.2.1." The paper identified by the ERG (Song et al) was in fact identified in the search for quality of life evidence. The paper was excluded as it did not report utility values which are usable in the economic model (instead reporting only values from baseline). This was a valid decision based on the inclusion/exclusion criteria stated in the SLR design which the ERG did not consider to be unreasonable (page 154 of ERG report).	

		The ERG is correct that this paper demonstrates that the utility values used in the base case from Palumbo et al underestimate the quality of life of patients receiving treatment with daratumumab; thus providing further evidence that a conservative approach to utility assumptions was taken. Unfortunately, data was not available within the daratumumab trials to enable us to show the value of the product. Analysing patient level data, instead of using literature proxies, is advantageous to regimens with good toxicity profiles and response rates such as daratumumab but was not possible with the phase II data available. Therefore, we were forced to use utility values reported in the literature, which as the ERG comment, underestimate the quality of life of patients receiving daratumumab.	

Issue 16 Factual inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 15 of the ERG report it is stated that: "Thus, the second stage of the study from which data are presented in support of the submission is observational in nature, not having a randomised component"	Amend to "Thus, the second stage of the **studies** from which data are presented in support of the submission is observational in nature, not having a randomised component"	Factually inaccurate	Not a factual error. No change required. The ERG considers that, when read in the context of the full paragraph, it is clear that the sentence is referring the second stage of each study. The text from page 15 reads: The clinical evidence presented in the company's submission (CS) is derived from two studies MMY2002 and GEN501 Part 2. MMY2002 and GEN501 are a Phase II and Phase I/II study, respectively, that were carried out in parallel. Both studies were carried out in two stages, with the first stage in each study involving investigation of different doses of daratumumab. Subsequent to identification of the optimum dose of daratumumab, the final stage in each study involved following a single cohort to evaluate clinical effectiveness and safety of daratumumab at the licensed dose (16.0 mg/kg). Thus, the second stage of the study from which data are presented in support of the submission is observational in nature, not having a randomised component.

On pages 19, 97 and 128 of the ERG report it is stated that: "The company reports that 71% of people (n=73) in MMY2002 went on to receive another intervention subsequent to treatment with daratumumab" This should be (n=75), as per CS, p86	Amend to n=75	Factually inaccurate	The ERG thanks the company for pointing out some discrepancies in the values reported by the ERG and the company. The ERG took the number of people of receiving subsequent treatment in MMY2002 from the company's response to clarification. The ERG acknowledges that this number should be marked as CiC and apologises for any inconvenience caused. The CSR for MMY2002 reports data to May 2015 and so the ERG is unclear whether the correct number of people receiving subsequent treatment is that reported in the CS or that in the response to clarification. For consistency within the ERG's report, the ERG has used the number reported in the response to clarification and marked the reported number of people receiving subsequent treatment as CiC.
On pages 20, 97/98 and 128 of the ERG report statements are made regarding the median OS of patients in MMY2002 and GEN501 receiving no subsequent treatment versus any subsequent treatment. These statements are only	Remove statements for GEN501	Factually inaccurate	The ERG thanks the company for highlighting the error. The ERG has amended the statements to make it clear the text relates to MMY2002.

correct for MMY2002			
On pages 20, 129 and 131 the ERG report states: "most IRRs (95.6%) occurring at first infusion".	Correct to 95.8%.	Factually inaccurate	The ERG thanks the company for highlighting the error. The ERG has amended the text as outlined by the company.
On pages 27, 189 and 263 of the ERG report it is stated that: "The ERG interprets this trend in the data as a possible consequence of the effect of daratumumab as a subsequent therapy"	Amend to "The ERG interprets this trend in the data as a possible consequence of the effect of **pomalidomide** as a subsequent therapy"	Factually inaccurate	The ERG agrees with the company. The suggested amendment has been implemented in the report.
On page 28 and page 231, Figure A and Figure 44 should be marked as CiC	Amend to CiC marking	Incorrect confidentiality marking	The figures mentioned by the company have been marked as CiC as suggested.
On page 34 of the ERG report, Figure I is incorrectly labelled with independent fit	Correct to dependent fit	Factually inaccurate	The ERG agrees with the company that Figure I has been incorrectly labelled. The ERG has replaced this with "ERG's preferred approach to OS curves".
On page 36 of the ERG report, Figure I is incorrectly labelled with independent fit	Correct to dependent fit	Factually inaccurate	The ERG agrees with the company that Figure K has been incorrectly labelled. The ERG has replaced this with "ERG's preferred approach to PFS curves".
On page 59 of the ERG report it is stated that:	Please amend to "The FDA approval **partly** aligns with the company's positioning of	Factually inaccurate The EMA license does not require patients	The ERG had added "partly" to the text as requested.

"The FDA approval aligns with the company's positioning of daratumumab as an alternative treatment at fourth-line and higher (Table 6), which is a narrowing of the population specified in the final scope "	daratumumab as an alternative treatment at fourth-line and higher (Table 6), which is a narrowing of the population specified in the final scope "	to be double refractory	
On page 185 of the ERG report it is stated that: "The company included all the comparators specified in the NICE scope" Not factually accurate	Correct to "The company included **most of** the comparators specified in the NICE scope"	Factually inaccurate	The ERG has amended the sentence on Table 54 as requested by the company.