NICE National Institute for Health and Care Excellence

For committee, company and experts:
Contains confidential information (ACIC)

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [ID3881] – CDF review of TA510

Lead team presentation

Chair: Charles Crawley
Committee B
Lead team: Tony Wootton (lay), Stuart Williams (clinical) and Henry Edwards, NICE (cost)
ERG: BMJ Technology Assessment Group (BMJ TAG)
Technical team: Jeremy Dietz, Michelle Green, Henry Edwards
Company: Janssen
20th January 2022

Abbreviations: Academic Commercial in Confidence (ACIC); Cancer Drugs Fund (CDF)

Summary of original appraisal TA510

FAD issued December 2017: “Daratumumab monotherapy is recommended for use within the Cancer Drugs Fund”

CDF - managed access agreement with further data collection:

1. MMY2002: longer-term overall survival (OS) data, progression-free survival (PFS) data, and time-to-discontinuation (TTD) data
2. Systematic Anti-Cancer Therapy (SACT):
   - OS data in daratumumab patients
   - 2nd-line treatments and beyond
   - treatment duration

Daratumumab (Darzalex®)

Janssen – Clinical practice has shifted from giving via intravenous infusion (in TA510) to primarily giving via subcutaneous injection

Marketing authorisation	Treatment of adult patients with rrMM, whose prior therapy included a PI and an IMiD and who have demonstrated disease progression on the last therapy
Mechanism of action	• Binds to CD38, causing cells to apoptose via antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, inhibition of mitochondrial transfer or antibody-dependent cellular phagocytosis
Administration & dose	• Recommended at a dose of 1,800 mg (15 ml, 120 mg per ml) via subcutaneous injection administered over approximately 3–5 minutes • Also available via intravenous infusion at a dose of 16 mg/kg (focus of original submission) Both methods administered according to the following dosing schedule: Weeks 1–8: weekly Weeks 9–24: every two weeks Weeks 25 onward until disease progression: every four weeks Subcutaneous injection is widely used in the UK due to its convenience and favourable tolerability profile. Non-inferiority demonstrated in COLUMBA
List price	• Per dose of 1,800mg solution for injection: £4,320.00 • Patient Access Scheme (PAS discount) approved by Department of Health

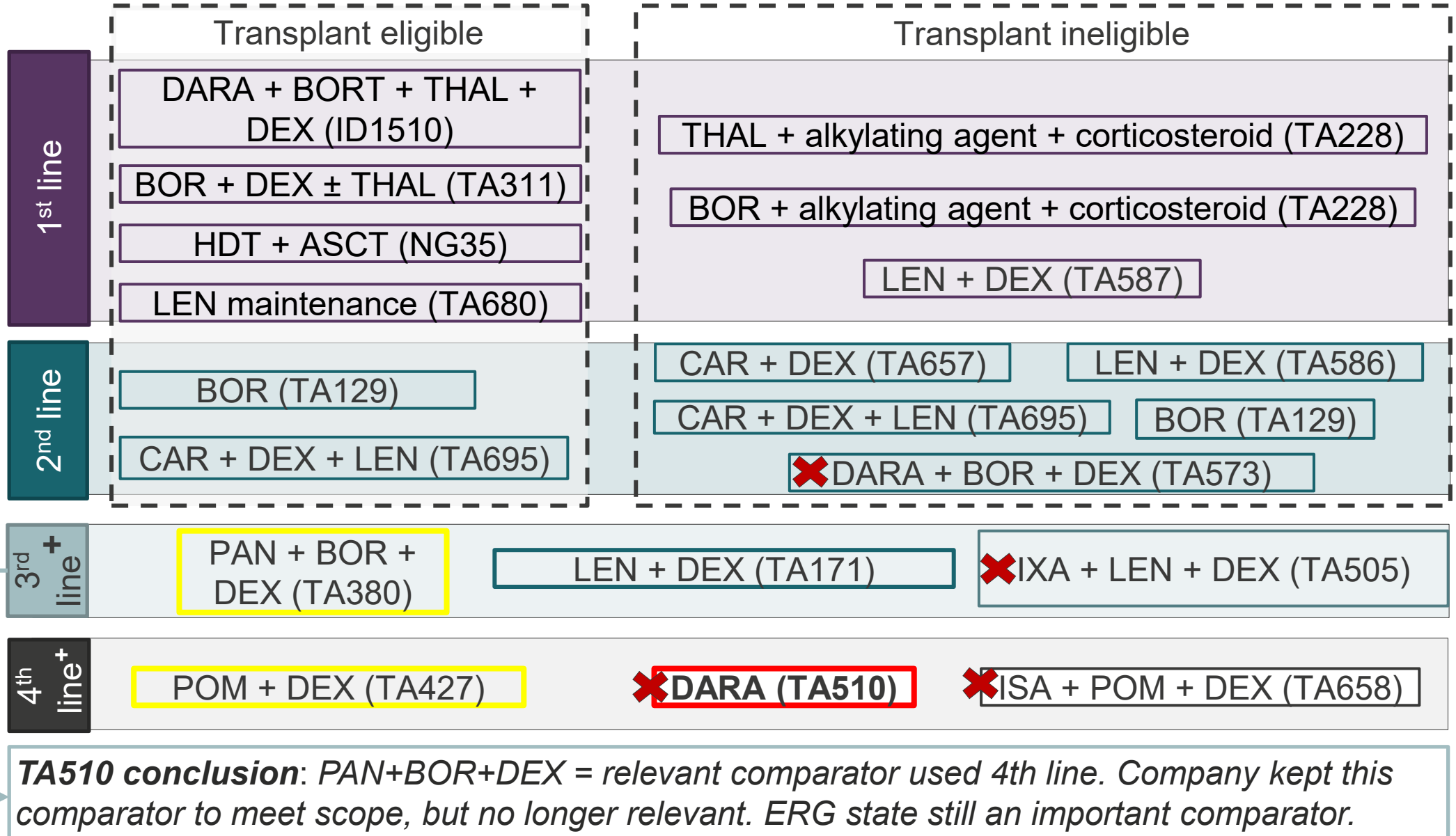
Abbreviations: Relapsed and refractor multiple myeloma (rrMM); Proteasome inhibitor (PI); Immunomodulator (ImiD); Patient access scheme (PAS)

Preview: Key issues

- **Uncertainty in clinical-effectiveness estimates**
  - Daratumumab has not been compared head-to-head with POM+DEX or PANO+BORT+DEX
  - MMY2002 and SACT dataset are non-comparative, therefore any indirect analyses are unanchored. Can the uncertainty associated with these comparisons be quantified?
- **Source of treatment effectiveness in the model**
  - What is the preferred source of data for the comparison of daratumumab with POM+DEX and the comparison with PANO+BORT+DEX?
- **Subsequent treatments**
  - Is there an impact from the choice of subsequent treatments that should be taken into consideration?
  - What is most reliable source of data for modelling subsequent treatments post daratumumab?

Abbreviations: Bortezomib (BORT); Cancer Drugs Fund (CDF); Dexamethasone (DEX); Overall survival (OS); Panobinostat (PANO); Pomalidomide (POM); Systemic anti-cancer therapy (SACT)

Multiple myeloma treatment pathway



TA510 conclusion: *PAN+BOR+DEX = relevant comparator used 4th line. Company kept this comparator to meet scope, but no longer relevant. ERG state still an important comparator.*

◉ *Does this reflect practice?*

ASCT: autologous stem cell transplantation; BOR: Bortezomib; CAR: Carfilzomib; DARA: Daratumumab; DEX: Dexamethasone: HDT: High dose therapy: ISA: Isatuximab; IXA: Ixazomib; LEN: Lenalidomide; PAN: Panobinostat; POM: Pomalidomide; THAL: Thalidomide

✖ Not routinely commissioned, available via the Cancer Drugs Fund only

Comparator in TA510

Patient and carer perspectives

- Being diagnosed with myeloma is extremely difficult, in particular the uncertainty around the possibility of a relapse. It affects peoples mental health and day-to-day activities

"The problem with myeloma is that you can set a goal, work towards it but then suddenly when you relapse it's dragged away again." Patient on 3rd line of treatment

"That uncertainty and thinking you might have come to the end of the road that is so worrying." Patient on 5th line treatment

- People value treatments that prolong their life and put their myeloma into remission for as long as possible.

"Only one benefit for this new treatment for me and that is staying alive for six months… if I could get maybe another drug trial, this and the panobinostat and pomalidomide then that is an extra two years instead of one year. Then maybe by that time something such as the CAR-T cells treatment will have progressed. However long I can extend my life then that is a positive, it is all about staying alive." Patient with high risk myeloma on 5th line treatment

- People value treatments that allow them to enjoy normal day-to-day life

"I have had a lot of treatment but I'm still up and about, walking and doing what I want to do. Overall, I would rate my quality of life highly." Patient at 5th line of treatment

UK Myeloma Forum perspective

- Daratumumab monotherapy via CDF has been associated with excellent responses and durations of response.
- Daratumumab is extremely well tolerated even when given to heavily pre-treated patients with fragile bone marrow
- Despite the access to daratumumab earlier in the treatment pathway and an alternative anti-CD38 monoclonal antibody at a similar time point in the pathway there remains a place for daratumumab monotherapy for less fit patients who are unable to tolerate immunomodulatory therapy (low blood counts or tendency to drop blood counts, prior class hypersensitivity, significant thrombosis, unable to take large capsules)
- Daratumumab monotherapy should continue to be an option for patients at 4th line and beyond to ensure therapy decisions are patients focused.

Abbreviations: Cancer Drugs Fund (CDF)

Decision problem

Scope from TA510 with optimised population

Population	Adults with relapsed or refractory multiple myeloma who have had 3 previous treatments (3 previous treatments not included in original scope) including a proteasome inhibitor and an immunomodulator
Intervention	Daratumumab monotherapy
Comparators	The company should present clinical and cost-effective evidence for daratumumab compared to pomalidomide plus dexamethasone (POM+DEX) – considered most appropriate comparator by company and ERG; and panobinostat plus bortezomib plus dexamethasone (PANO+BORT+DEX) – included by company, but not considered relevant. Judged relevant by ERG.
Outcomes	• progression-free survival • overall survival • time-to-discontinuation • adverse effects of treatment • health-related quality of life

TA510 – key committee recommendations

Area	Assumptions	Company	Discuss?
Generalisability of the trials (4.6 & 4.7)	Poor generalisability of the trial results to people who would have daratumumab in the NHS because of differences in prior and subsequent treatment and patients were fitter in the trial **Company should use SACT data to test the generalisability of the trial data.**	✓ Base-case: OS data from SACT consistent with observed OS data from MMY2002	Are the OS curves from the SACT data set and MMY2002 similar?
Relative effectiveness (4.12)	High degree of uncertainty in the relative effect estimates produced by the MAIC **Company should use SACT data to inform the matching in the MAIC and the generalisability of the results.**	✓ Scenario analysis: adjusted comparison of SACT data versus MMY2002; partially adjusted MAIC used in base case	What is the most appropriate MAIC to use in the model?
Subsequent treatments (4.13-4.15)	Absolute life expectancy seen in clinical trials was likely to overestimate the overall survival benefit of daratumumab were it used in the NHS. **Company should use SACT data to assess whether subsequent therapies are used in practice.**	✓ Base-case: Subsequent therapies informed by SACT data	What is the most appropriate source of data for subsequent therapies?

TA510 – key committee recommendations

Area	Assumptions	Company	Discuss?
Overall survival and progression-free survival (4.19-4.20)	Potential for daratumumab to be clinically effective but there are limitations in the evidence base **Company should use updated MMY2002 data in its new base case and perform scenario analyses using SACT data to validate long-term survival extrapolations.**	✓ Base-case	No
Proportional hazards (4.22)	**Company should test whether proportional hazards assumption holds.**	✓ Base-case	No
End of life (4.30)	Unable to conclude if the 3-month life extension criterion was **Uncertainty in clinical effectiveness underpinning the survival estimates**	✓ Base-case	Does daratumumab meet end of life criteria?

Updated clinical evidence after CDF

Post-CDF clinical evidence

1 single-arm trial, MMY2002 considered key trial by company and ERG

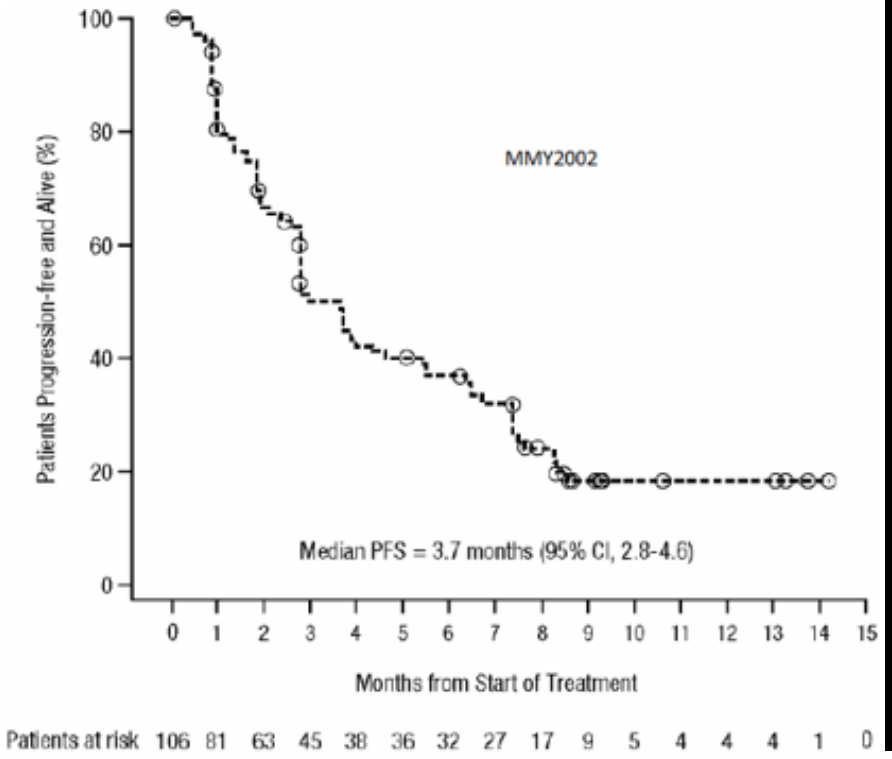
	MMY2002 Single-arm trial N=106	**Systemic Anti-Cancer Therapy (SACT) dataset N=2,301**
Period	Sep 2013 to May 2017	Jan 2018 to Nov 2020
Follow-up in months, median (range)	Update 36.7 (0.5 to 42.3) TA510 20.7 (0.5 to 26.3)	10.8 (5.0 to 36)
Age, median (range)	[redacted]	71 (NR to NR)
Comparator	None	None
Company use of data in model	• overall survival • progression-free survival • time to discontinuing treatment	• 2nd line treatments and beyond

GEN501 (single-arm daratumumab trial, n=42)
TA510 – data from GEN501 pooled with MMY2002 data by company. Committee disagreed with this approach and judged MMY2002 to more closely match marketing authorisation.
Company & ERG agree that MMY2002 more relevant study and is used in MAICs and modelling.
MM-003 (two-arm trial) comparing pomalidomide plus low-dose dexamethasone (n=302) versus high-dose dexamethasone. Low-dose used in company's MAIC as the source of POM+DEX data

Abbreviations: Evidence review group (ERG); Not recorded (NR); matched adjusted indirect comparisons (MAICs); Dexamethasone (DEX); Pomalidomide (POM);

Updated clinical evidence progression-free survival (PFS) – MMY2002

20.7 months follow-up



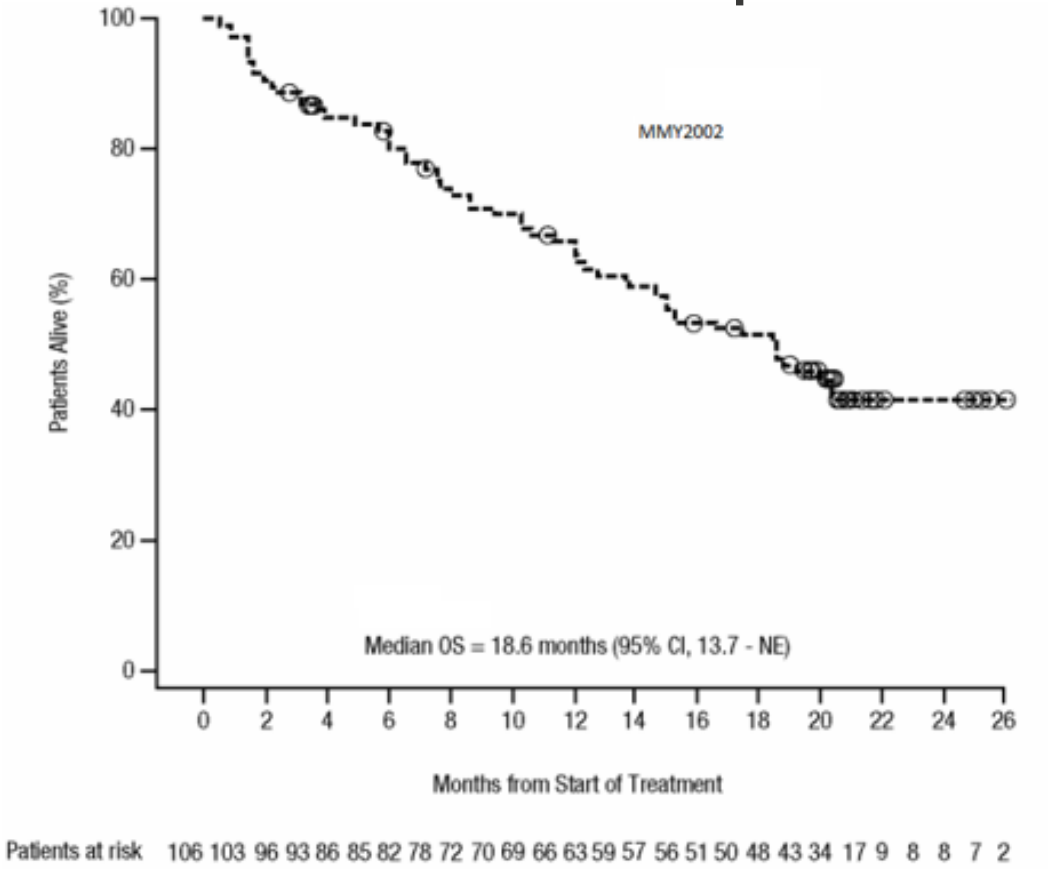
36.7 months follow-up

[redacted]

Treatment	Subjects	Number of events (%)	Median PFS (95% CI)
20.7 months follow-up			
Daratumumab	106	75 (70.8%)	3.7 months (2.8, 4.6)
36.7 month follow-up			
Daratumumab	106	[redacted]	[redacted]

Updated clinical evidence overall survival (OS) – MMY2002

20.7 months follow-up



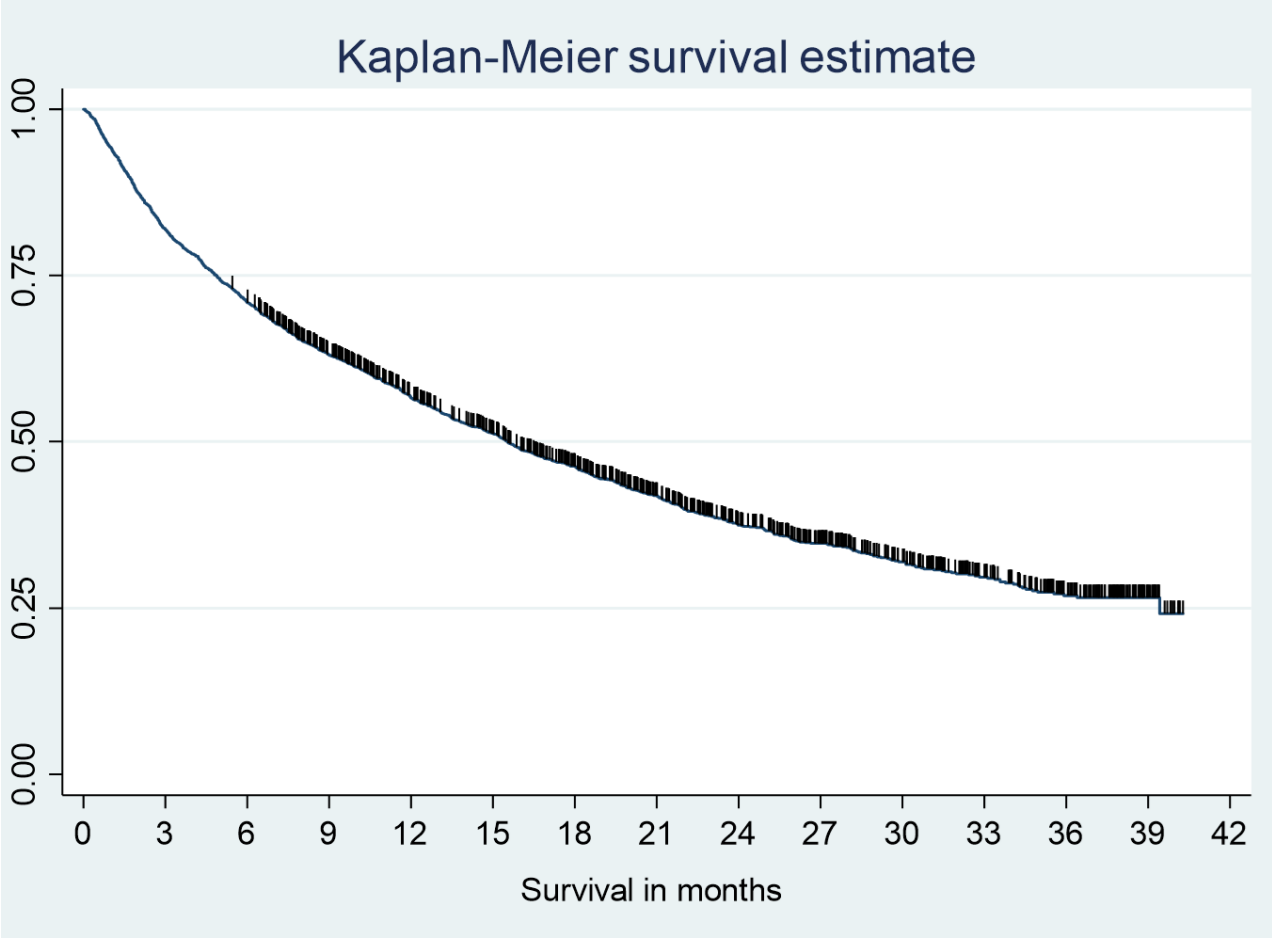
36.7 months follow-up

[redacted]

Treatment	Subjects	Number of events (%)	Median OS (95% CI)
20.7 months follow-up			
Daratumumab	106	57 (53.8)	18.6 months (13.7, NR)
36.7 month follow-up			
Daratumumab	106	[redacted]	[redacted]

Updated clinical evidence OS – SACT dataset

- **Median age**
  - SACT older than MMY2002 (71 vs [redacted] years).
- **ECOG**:
  - SACT had fewer with ECOG 0 than MMY2002 (20.3% vs [redacted]).
- **Previous stem cell transplant**:
  - SACT had fewer with a transplant than MMY2002 (44% vs [redacted])
- **Prior/subsequent treatments:**
  - SACT had fewer go on to subsequent therapy than MMY2002 (59.2% vs [redacted])
  - MMY2002 had people receive dexamethasone monotherapy or carfilzomib (not available on the NHS) and nobody received these in the SACT dataset



Treatment	Subjects	Events	Median OS (95% CI)
11.6 months median follow up			
Daratumumab	2,301	1,877 (82%)	15.5 months (14.5, 16.7)

Abbreviations: Overall survival (OS); Eastern cooperative oncology group (ECOG); Systemic anti-cancer therapy (SACT)

Updated clinical evidence time-to-discontinuation (TTD) – MMY2002

20.7 months follow-up

TTD from MMY2002 data was not presented in the TA510 submission.

36.7 months follow-up

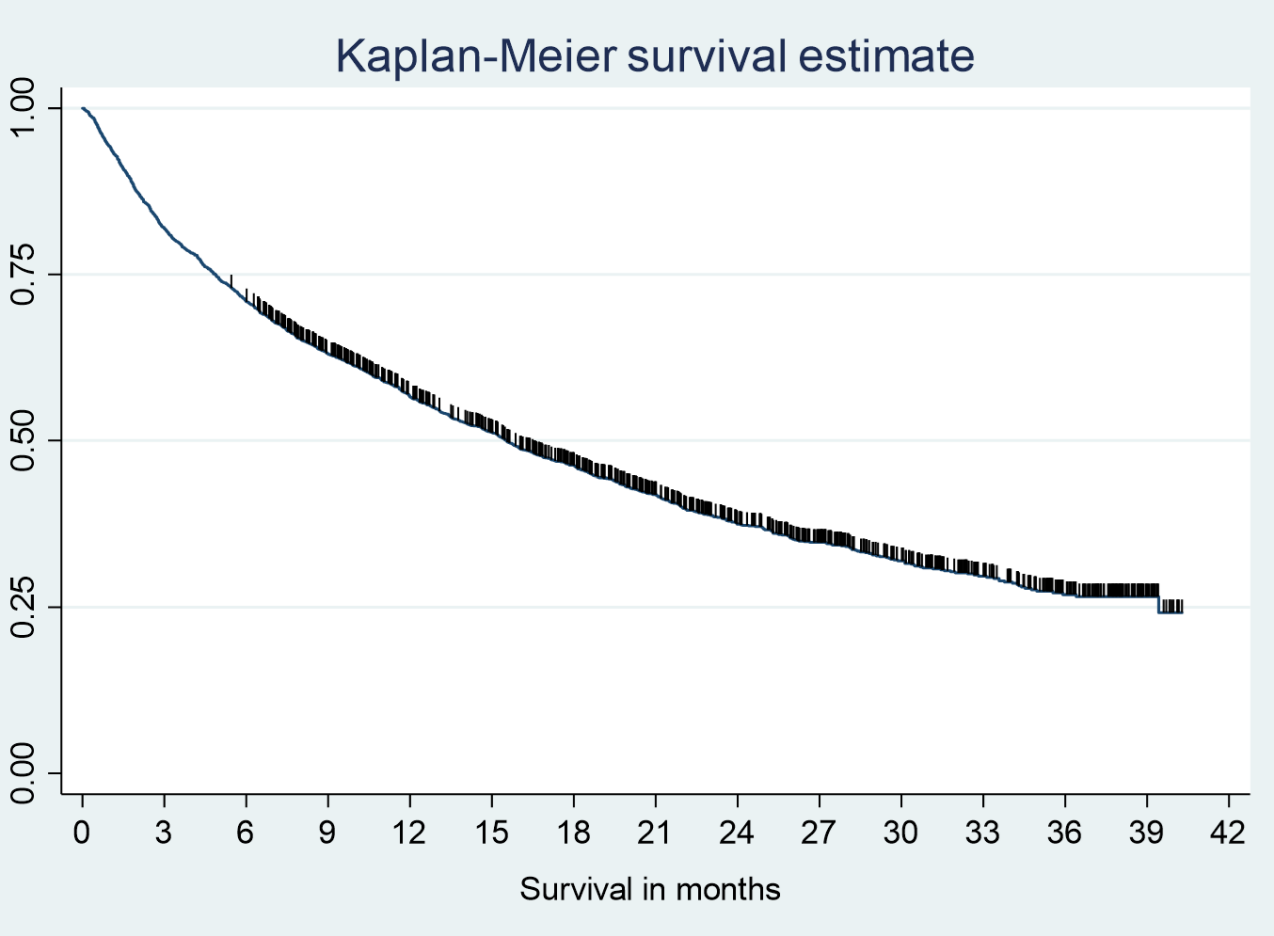
[redacted]

Treatment	Subjects	Number of events (%)	Median duration of treatment (range)
		20.7 months follow-up	
Daratumumab	106	100 (94.3%)	2.83 months (0.03-25.5)
		36.7 month follow-up	
Daratumumab	106	[redacted]	[redacted]

Updated clinical evidence TTD – SACT dataset

ERG uses TTD data as a proxy for PFS in their comparison

- **Median age**
  - SACT older than MMY2002 (71 vs [redacted] years).
- **ECOG**:
  - SACT had fewer with ECOG 0 than MMY2002 (20.3% vs [redacted]).
- **Previous stem cell transplant**:
  - SACT had fewer with a transplant than MMY2002 (44% vs [redacted])
- **Prior/subsequent treatments:**
  - SACT had fewer go on to subsequent therapy than MMY2002 (59.2% vs [redacted])
  - MMY2002 had people receive dexamethasone monotherapy or carfilzomib (not available on the NHS) and nobody received these in the SACT dataset



Treatment	Subjects	Events	Median treatment duration (95% CI)
4.3 months median follow up			
Daratumumab	2,301	1,877 (82%)	15.5 months (14.5, 16.7)

Abbreviations: time-to-discontinuation (TTD); Progression free survival (PFS); Eastern cooperative oncology group (ECOG)

How does SACT inform generalisability of MMY2002? What is the preferred data set, SACT or MMY2002?

Unanchored matched adjusted indirect comparison (MAIC) methods

Company

- In the absence of direct head-to-head evidence, company used a MAIC to calculate relative treatment effects to use in the model
- Company base case uses partially adjusted MAIC from MMY2002
  - Fully adjusted did not provide a large enough sample size to use
  - Clinical experts advised on key prognostic factors to match on: refractory status, number of prior treatments, ISS staging

ERG

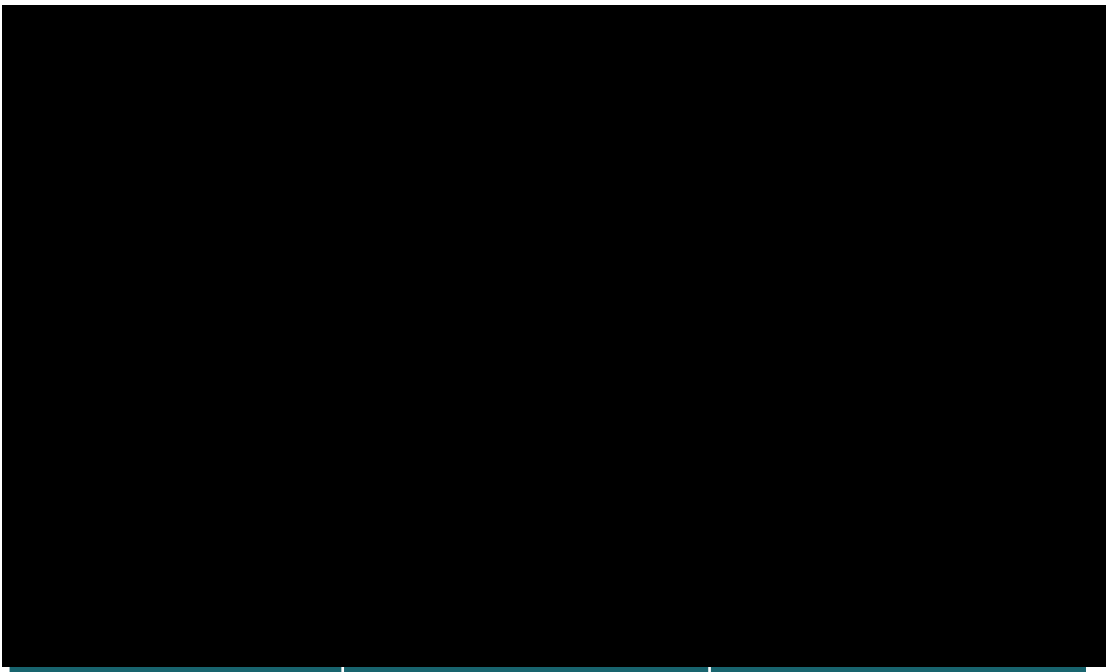
- MAIC is unanchored (to a common comparator) therefore the interactions are uncertain
- TSD 18 suggests unanchored MAIC should be fully adjusted
  - However, it produced implausible results (overall survival)
- Considered naïve comparison with SACT data a better source of comparison
  - Acknowledge that this has limitations
- Absence of head-to-head data or IPD data for SACT or comparator trials – limitations in what further analyses can be performed – uncertainty may be unresolvable given the data

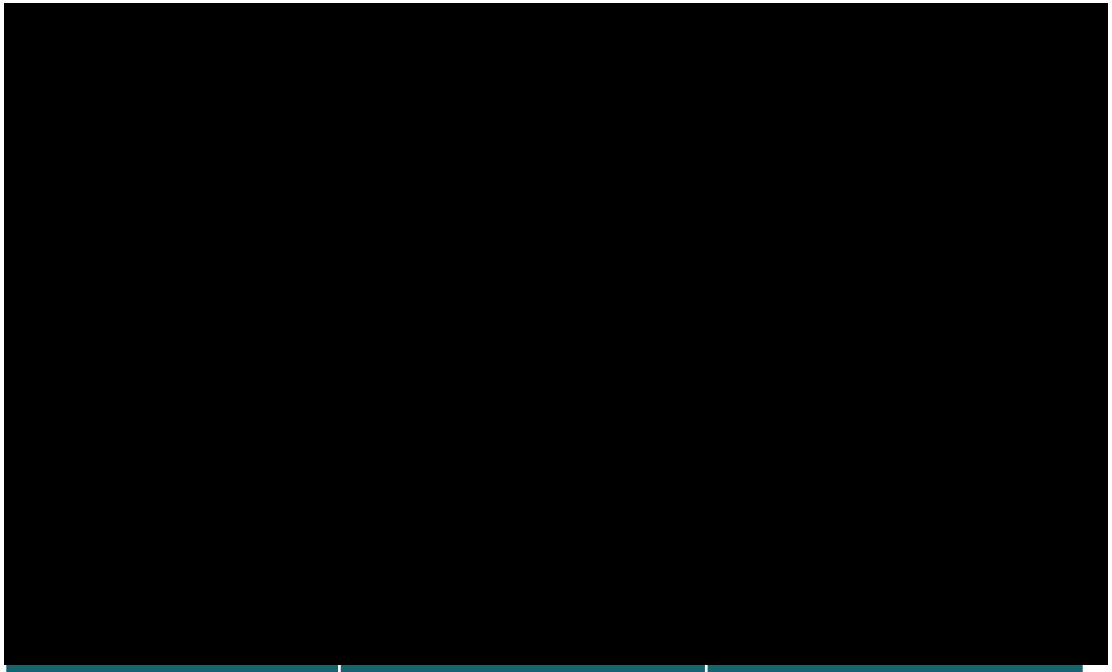
Abbreviations: International staging system (ISS); Matched adjusted indirect comparison (MAIC)

Unanchored MAIC: OS, daratumumab v POM+DEX

Fully adjusted unanchored MAIC produces implausible OS extrapolations for daratumumab

Green solid line – Daratumumab observed
Green dashed line – Daratumumab adjusted
Blue Solid line – POM+DEX





Treatment	Median, months (95% confidence interval)	HR (95% confidence interval)
Daratumumab adjusted (ESS=)		
POM+DEX (n=302)		

Treatment	Median, months (95% confidence interval)	HR (95% confidence interval)
Daratumumab adjusted (ESS=)		
POM+DEX (n=302)		

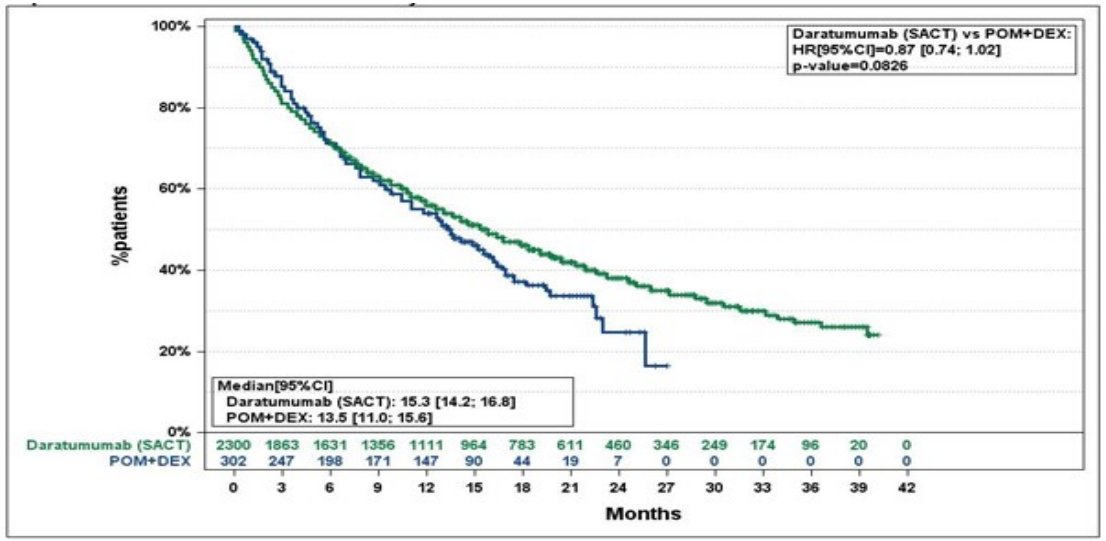
Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; POM+DEX, pomalidomide plus dexamethasone; ESS, effective sample size.

Daratumumab v POM+DEX, Overall survival

Green solid line – Daratumumab observed; Green dashed line – Daratumumab adjusted

Blue Solid line – POM+DEX

Naïve comparison with SACT (ERG)



Treatment	Median, months (95% confidence interval)	HR (95% confidence interval)
Daratumumab (n=2,300)	15.3 (14.2 to 16.8)	0.87 (0.74 to 1.02)
POM+DEX (n=302)	13.5 (11.0 to 15.6)	

Partially adjusted MAIC (Company)

[redacted]

Treatment	Median, months (95% CI)	HR (95% CI)
Daratumumab adjusted (ESS=[redacted])	[redacted]	[redacted]
POM+DEX (n=302)	[redacted]	

Which option for comparative OS data is preferred? What is the certainty that daratumumab has a survival benefit over pomalidomide?

Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; POM+DEX, pomalidomide plus dexamethasone; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone.

Unanchored MAIC results: OS, daratumumab versus PANO+BORT+DEX

Green solid line – Daratumumab observed
Green dashed line – Daratumumab adjusted
Blue Solid line – PONO+BORT+DEX

Treatment	Median, months (95% confidence interval)	HR (95% confidence interval)
Daratumumab adjusted (ESS=[redacted])	[redacted]	[redacted]
PANO+BORT+DEX (n=55)	[redacted]	

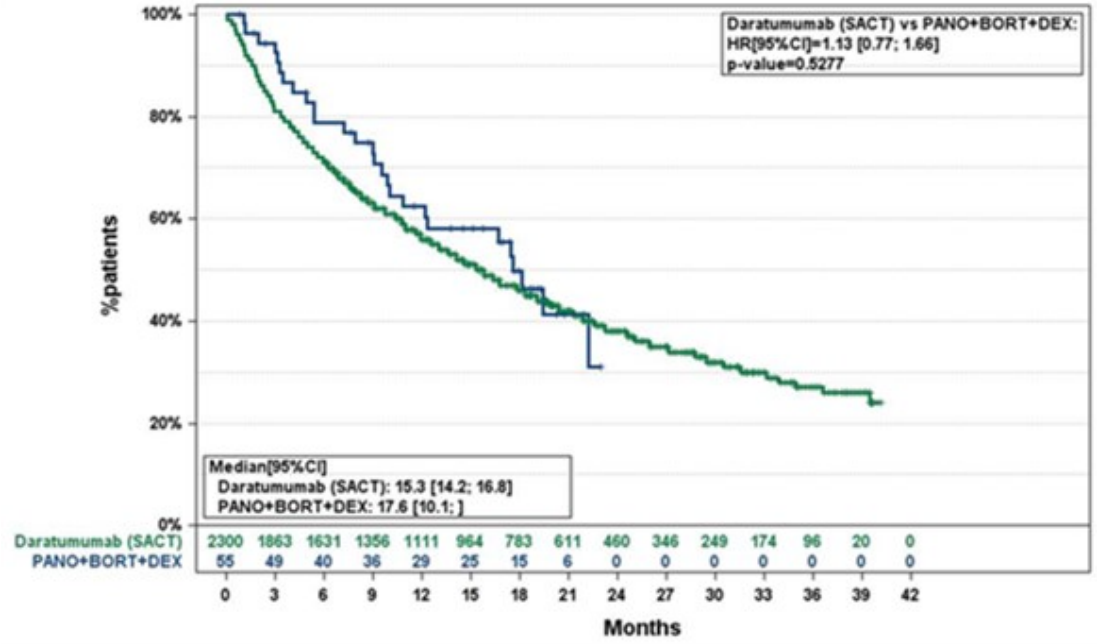
Treatment	Median, months (95% confidence interval)	HR (95% confidence interval)
Daratumumab adjusted (ESS=[redacted])	[redacted]	[redacted]
PANO+BORT+DEX (n=55)	[redacted]	

Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; ESS, effective sample size.

Daratumumab v PANO+BORT+DEX, Overall survival

Green solid line – Daratumumab observed
Green dashed line – Daratumumab adjusted
Blue Solid line – PAN+BORT+DEX

Naïve comparison with SACT (ERG)



[redacted]

Treatment	Median, months (95% confidence interval)	HR (95% confidence interval)
Daratumumab (n=2,300)	15.3 (14.2 to 16.8)	1.13 (0.77 to 1.66)
PANO+BORT+DEX (n=55)	17.6 (10.1 to not estimatable)	

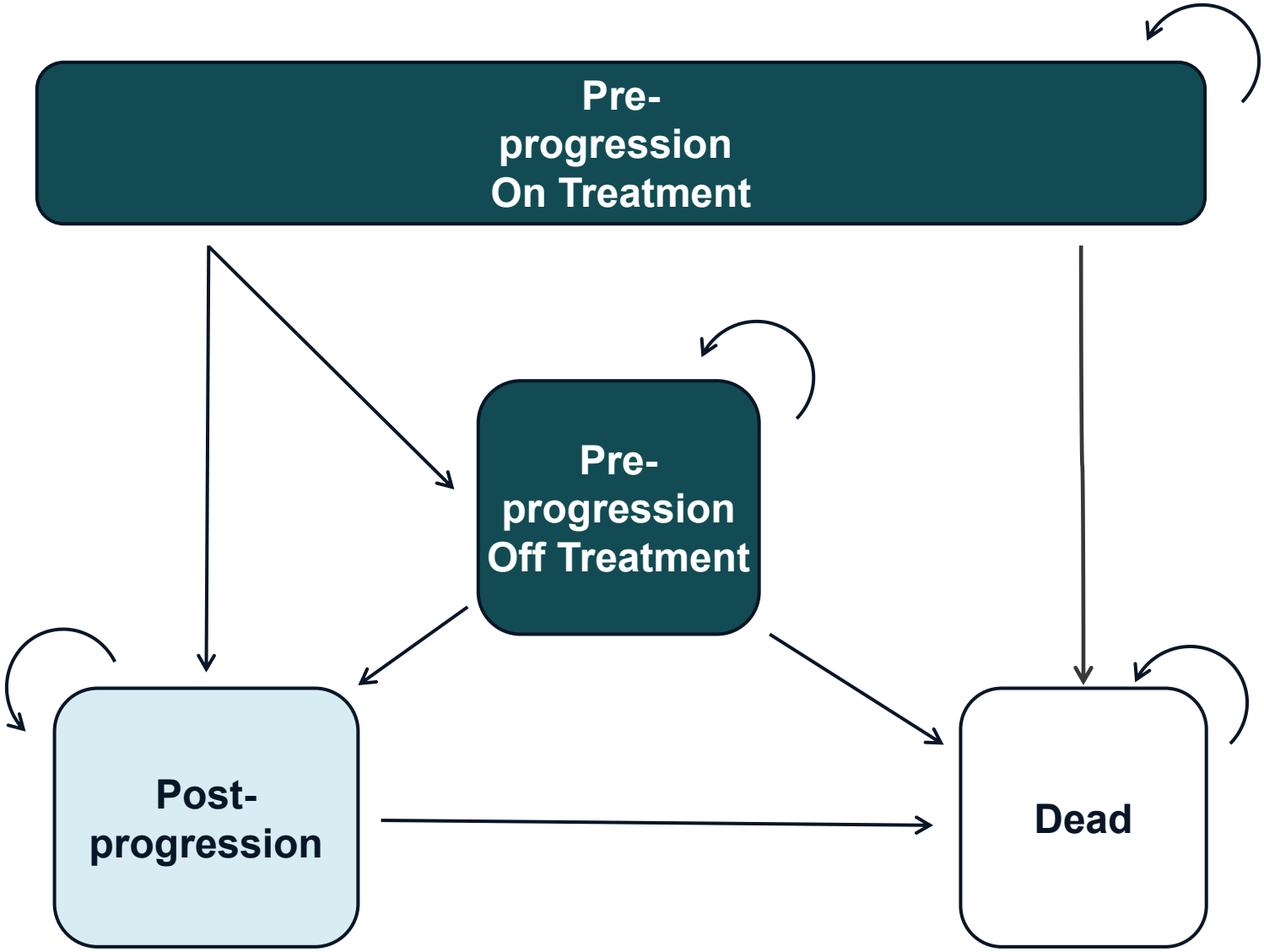
Treatment	Median, months (95% confidence interval)	HR (95% confidence interval)
Daratumumab adjusted (ESS=[redacted])	[redacted]	[redacted]
PANO+BORT+DEX (n=55)	[redacted]	

Which option for comparative OS data is preferred?

Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; POM+DEX, pomalidomide plus dexamethasone; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone.

Updated modelling and issues

Recap: company's state-transition model

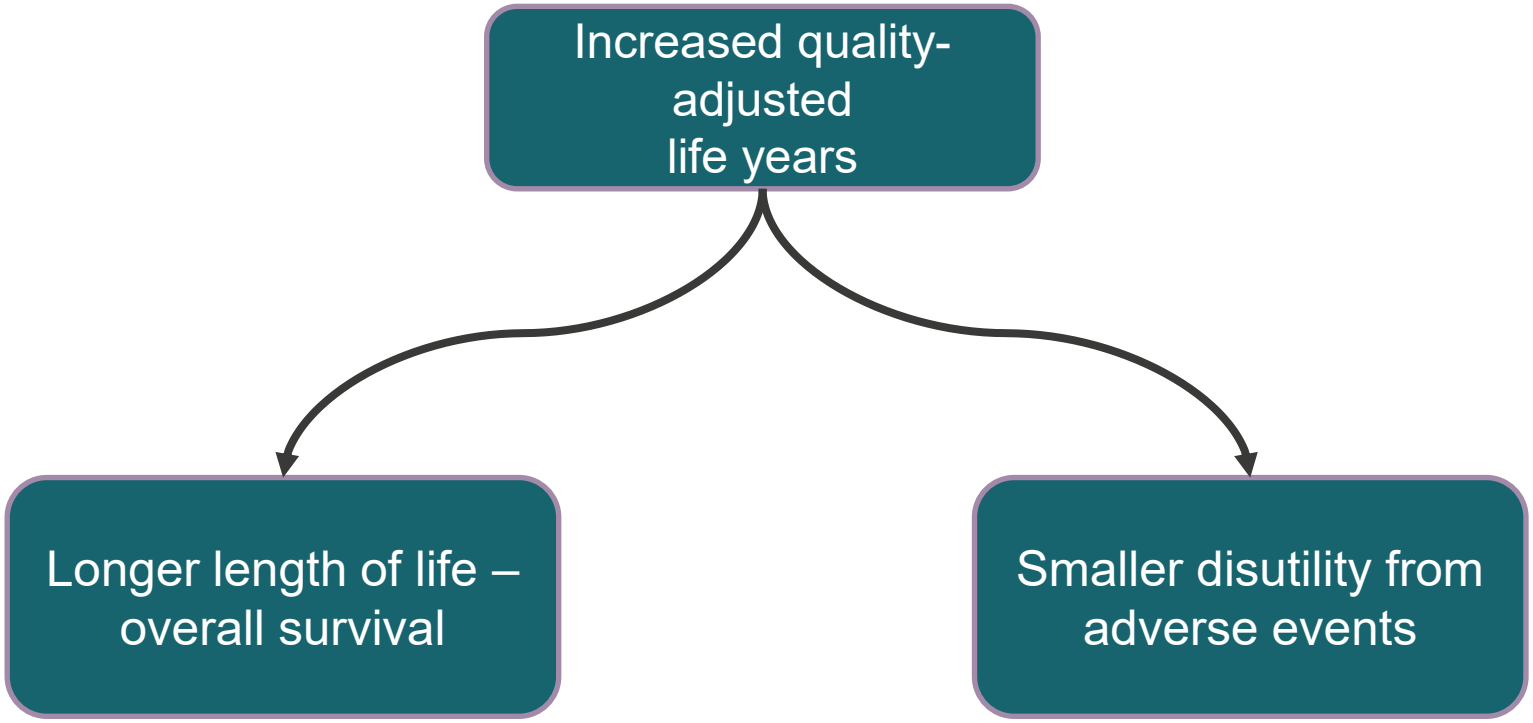


Model design	Partitioned survival analysis
Time horizon	15 years
Cycle length	7 days
Half cycle correction	No
Discount rate	3.5% per year
Perspective	NHS and PSS

Abbreviations: PSS: personal social services

Where do the QALY gains come from in the model?

Generating a survival benefit compared to POM+DEX and PANO+BORT+DEX



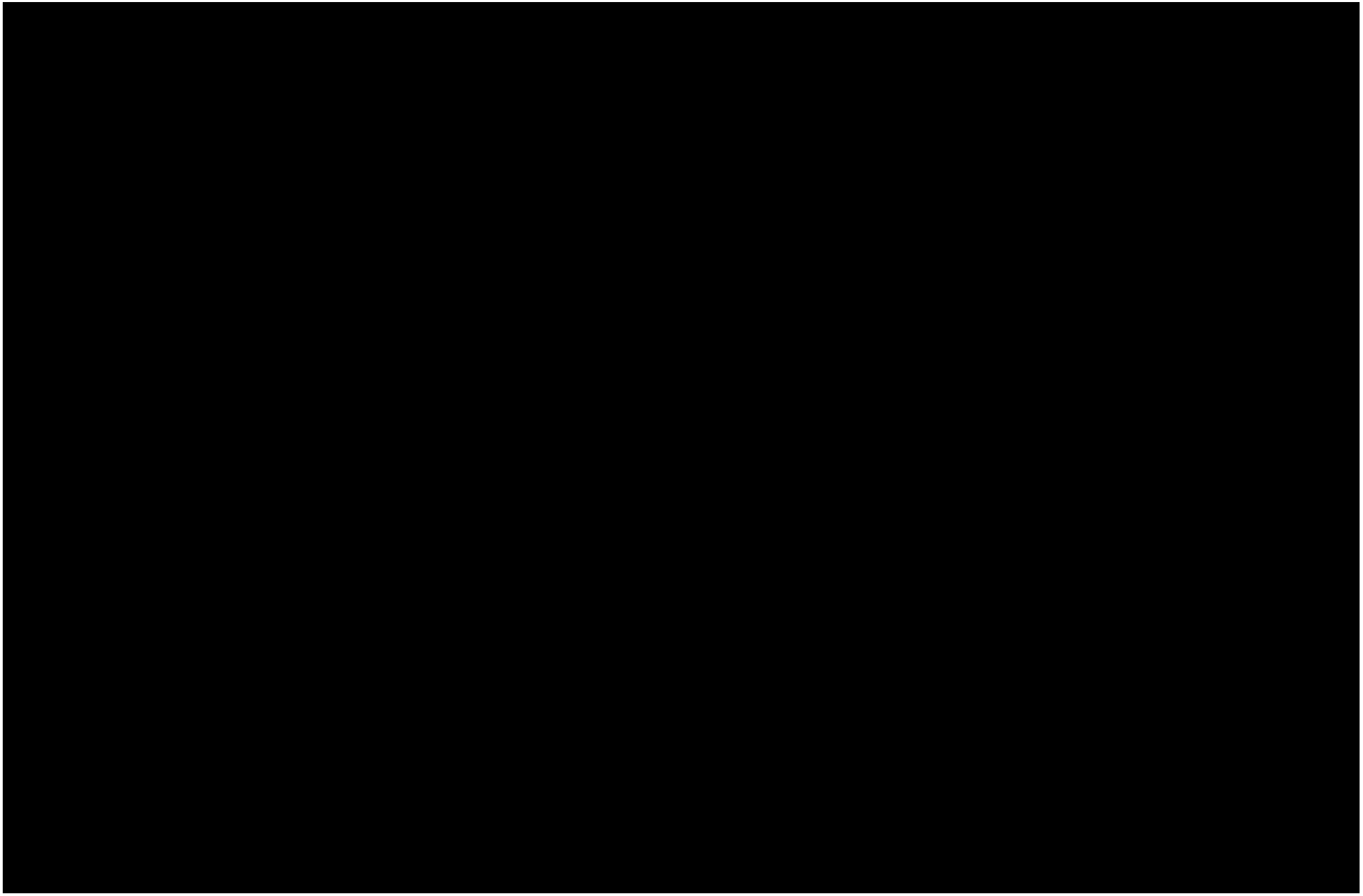
Abbreviations: QALY, quality-adjusted life year

Company model inputs

Model inputs	Company	ERG comment	Impact of ERG on ICER
Overall survival and progression-free survival	Partially adjusted MAIC using MMY2002 data	Concerns over fully adjusted MAIC MMY2002, alternatives explored including SACT	**Varies by scenario**
Time to treatment stopping	Daratumumab: MMY2002 POM+DEX: MM-003 PANO+BORT+DEX: aligned with PFS or max treatment duration	Generally agrees with approach	**N/A**
Survival distributions	OS: Weibull independent fit PFS: Log-normal independent fit TTD: Log-logistic	Agrees with approach, except for SACT comparison (gamma for PFS)	**N/A**
Adverse events	Subcutaneous arm of COLUMBA trial for daratumumab	Agrees with approach	**N/A**
Administration and dose	As per subcutaneous dosing schedule	Agrees with approach	**N/A**
Subsequent therapy costs	58% in all arms receive subsequent therapy. Drug informed by SACT.	Source of subsequent treatment should match clinical effectiveness source	**Varies by scenario**
General population mortality	Probability of death could not fall below that of the general population	Agrees with approach	**N/A**

OS curves for daratumumab versus POM+DEX

Modelled extrapolations overlaid with Kaplan-Meier survival data



Issue 3: Source of treatment effectiveness in model

Background:

- Company used the partially adjusted MAIC daratumumab data for the comparison with POM+DEX and PANO+BORT+DEX in its base case

Company:

- Adjusting for as many prognostic factors as possible results in a low ESS, which results in estimates becoming unstable and inferences depending heavily on just a small number of individuals
- Clinical experts advised on the key prognostic factors for MAIC
- In all 3 scenarios, daratumumab remains dominant (however, this is without discounts on any other drugs)

ERG:

- Fully adjusted MAIC, though methodologically superior, produces implausible OS curves for the comparison of daratumumab vs POM+DEX
- Naïve comparison of SACT data with POM+DEX is of relevance, whilst acknowledging it is also flawed methodologically
- ERG considers the fully adjusted MAIC the most methodologically robust source of effectiveness for the comparison of daratumumab with PANO+BORT+DEX

Abbreviations: BOR: Bortezomib; DEX: Dexamethasone; ESS: Effective sample sizes; PANO: Panobinostat; POM: Pomalidomide; TE: Technical engagement; IPD: Individual patient data; SACT: Systemic anti-cancer therapy; ERG: Evidence review group; OS: Overall survival; MAIC: Matching adjusted indirect comparison

What is the committee's preferred source of data?

Issue 4: Subsequent treatments

What best reflects clinical practice in the UK?

Therapy (numbers reported by drug are for first line only)	SACT (N=1,877) n (%)	MMY2002* (N=106) n (%)	MM-003 (%)
Total number of patients who received subsequent therapy	1,111 (59.2)	[redacted]	-
Dexamethasone	–	[redacted]	(29)
Pomalidomide	709 (37.8)	[redacted]	(0)
Cyclophosphamide	12 (0.6)	[redacted]	(21)
Carfilzomib	–	[redacted]	(2)
Bortezomib	7 (0.4)	[redacted]	(18)
Lenalidomide	30 (1.6)	[redacted]	(5)
Bortezomib + Panobinostat	147 (7.8)	[redacted]	-
Cyclophosphamide + pomalidomide	55 (2.9)	[redacted]	-
Trial	30 (1.6)	[redacted]	-
Melphalan	19 (1.0)	[redacted]	(8)
Etoposide	-	[redacted]	(3)
Bendamustine	16 (0.9)	[redacted]	(11)
Thalidomide	-	[redacted]	(7)
Bortezomib + panobinostat + thalidomide	15 (0.8)	[redacted]	-
Bendamustine + thalidomide	10 (0.5)	[redacted]	-

* first subsequent therapy data aggregated by single component [redacted]

MM-003 trial: POM+DEX in company's MAIC not used by the company to inform subsequent treatments after POM+DEX in its model, but is used by ERG

Issue 4: Subsequent treatments

Background

- The ERG was originally concerned with the possibility of OS outcomes for daratumumab being confounded by the impact of subsequent therapies received in MMY2002 (and not available in the UK NHS).

Company

- Provided the updated MMY2002 data on subsequent therapies and the survival curves
  - Does not consider it appropriate to conduct analysis on MMY2002 OS by subsequent therapy received
    - High levels of selection bias by selecting patients based on their outcome
    - Number of patients will be low (N=[redacted] for bortezomib) and therefore insufficient to inform KM curves
- Company considers OS curves in SACT and MMY2002 are similar

ERG

- A considerable separation in OS curves in SACT and MMY2002 between months 3-21
- SACT dataset does not include carfilzomib
- Differences in SACT and MMY2002 OS curves likely due to treatment with carfilzomib

Does subsequent treatment impact on survival? Which subsequent treatment should be costed?

Impact of subsequent treatments received

OS by subsequent therapy received (all lines), MMY2002

[redacted]

OS by subsequent therapy received (first-line only), MMY2002

[redacted]

Does the committee consider that subsequent treatment has an impact on survival?

Abbreviations: BORT: bortezomib; CARF: carfilzomib; ERG: Evidence review group; OS: Overall survival

Impact of subsequent treatments received

Company – OS curves from SACT and MMY2002 are similar

ERG – not similar and considerable separation between month 3 and 21

Abbreviations: ERG: Evidence review group; OS: Overall survival, HR: Hazard ratio; SACT: Systemic-Anti-Cancer Therapy

Impact of subsequent treatments received

ERG:

- Notes a considerable separation of the curves between month 3 and month 21
- Ad hoc analysis by company, demonstrates that people receiving carfilzomib had a survival advantage compared to people receiving any other subsequent treatment between approximately month 3 and month 19.
  - This corresponds to the separation in MMY2002 and the SACT OS curves between month 3 and month 21.
- Maintains original conclusion that the differences in OS curves seen in SACT and in MMY2002 are likely due to treatment with carfilzomib after in MMY2002
  - therefore reinforces the use of the SACT data as its preferred source of clinical effectiveness for daratumumab in the model

Is there a difference in OS and is this due to subsequent therapies?

Issue 5: Subsequent treatments modelled

Company base

- [redacted]% of people all arms receive subsequent therapy.
- Informed by SACT data – most reliable source, real world-estimates of subsequent therapy use in UK clinical practice

ERG

- Company base case is reliant on the assumption that that SACT and MMY2002 data have similar survival outcomes
- Unclear why subsequent treatment data for POM+DEX from MM-003* trial was not used to estimate subsequent treatments for POM+DEX
- The source of subsequent treatments post daratumumab in the model should match the source of clinical effectiveness for daratumumab in the analysis

- Company and ERG agree that the choice of subsequent treatments has a negligible impact on the final ICERs

*MM-003 trial used for POM+DEX in company's matching-adjusted indirect comparison

◉ **What source of subsequent treatment best reflects clinical practice?**

Abbreviations: DEX: Dexamethasone; POM: Pomalidomide; SACT: Systemic anti-cancer therapy; ERG: Evidence review group;

End of life

Conclusion in TA510

- *The committee concluded that it could not make an informed decision as to whether daratumumab meets the end-of-life*

Criteria	Company	ERG
Short life expectancy, normally <24 months	Median life expectancy: less than 24 months, and closer to 12 months.	Mean undiscounted total life-years: POM+DEX: 1.49 years PANO+BORT+DEX: 1.80 years
Extension to life, normally ≥ 3 months	Daratumumab extends life by [redacted] and [redacted] months versus POM+DEX and PANO+BORT+DEX respectively	ERG base case extends life by 0.77 years (9.24 months) Min extension to life of 0.46 years (5.52 months)

ERG

- Clinical effectiveness evidence underpinning this assessment to be extremely uncertain and recommends caution in drawing conclusion on the end of life criterion from only these findings

- *the Appraisal Committees will need to be satisfied that: the estimates of the extension to life are robust and can be shown or reasonably inferred from either progression-free survival or overall survival …and the assumptions used in the reference case economic modelling are plausible, objective and robust (NICE methods guide, section 6.2.10)*

NICE

Has the end of life criteria been met?

Innovation and Equality

Innovation

- TA510 - considered daratumumab a major change in managing myeloma
- TA510 - but no evidence of demonstrable and distinctive benefits of a substantial nature not captured in the quality-adjusted life year
- No considerations regarding innovation were raised by the company in this submission

Equality

- Equalities considerations were not applicable in the original appraisal (TA510)
- No equalities considerations were raised by the company in this submission

Company and ERG modelling

Assumption	Company	ERG
Source of treatment effectiveness for overall-survival	Partially adjusted MAIC	Naïve comparison of SACT data with POM+DEX
Source of treatment effectiveness for progression-free survival	Partially adjusted MAIC	Naïve comparison of SACT TTD data with POM+DEX PFS data using a gamma distribution
Source of subsequent treatments	SACT data for both daratumumab and POM+DEX	SACT data for daratumumab and MM-003 data for POM+DEX (subsequent treatment source aligned with clinical data source)

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential PAS discounts

Key committee considerations

Which source of comparative OS data should be used, considering:

- No head-to-head data
- Methodological robustness of unanchored matched indirect adjusted comparisons
- Plausibility of curves and extrapolations

How should treatments after daratumumab be costed, considering:

- Generalisability to clinical practice
- Impact on survival

Are end of life criteria met, considering:

- Uncertainty

Back up slides

MAIC results: PFS, daratumumab versus POM+DEX

Fully adjusted inc sex

Treatment	Median, months (95% confidence interval)	HR (95% confidence interval)
Daratumumab adjusted (ESS=[redacted])	[redacted]	[redacted]
POM+DEX (n=302)	[redacted]	

Partially adjusted

Treatment	Median, months (95% confidence interval)	HR (95% confidence interval)
Daratumumab adjusted (ESS=[redacted])	[redacted]	[redacted]
POM+DEX (n=302)	[redacted]	

Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival; POM+DEX, pomalidomide plus dexamethasone; ESS, effective sample size.

MAIC results: PFS, daratumumab versus PANO+BORT+DEX

Fully adjusted inc sex

Treatment	Median, months (95% confidence interval)	HR (95% confidence interval)
Daratumumab adjusted (ESS=[redacted])	[redacted]	[redacted]
PANO+BORT+DEX (n=55)	[redacted]	

Partially adjusted

Treatment	Median, months (95% confidence interval)	HR (95% confidence interval)
Daratumumab adjusted (ESS=[redacted])	[redacted]	[redacted]
PANO+BORT+DEX (n=55)	[redacted]	

Abbreviations: CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival; PANO+BORT+DEX, panobinostat plus bortezomib and dexamethasone; ESS, effective sample size.