Pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib (review of TA338)

12 October 2016

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Lead team: Iain D. Miller, Ph.D., David Chandler

Multiple myeloma

- Cancer arising from plasma cells in bone marrow and produces large quantities of abnormal antibody (paraprotein)
- Suppresses development of normal blood cells responsible for fighting infection (white blood cells), carrying oxygen (red blood cells), and clotting (platelets)
- In 2013 , 4,703 people were diagnosed with multiple myeloma in England
- 5-year survival rate in England is estimated to be 47%
- Main aims of therapy: prolong survival and maintain quality of life
- Definitions:
  - Relapse: Disease progression following a previously successful course of treatment
  - Refractory: No response to treatment whether initial treatment or treatment at relapse
  - Relapsed and refractory (RRMM): disease progression while on, or within 60 days after, a specific treatment

Glossary of abbreviations

- 2nd line – received at least 1 prior therapy
- 3rd line – received at least 2 prior therapies
- 4th line – received at least 3 prior therapies
- AEs – Adverse events
- BOR – Bortezomib
- BTD – Bendamustine + thalidomide + dexamethasone
- CI – Confidence interval
- CC – Conventional chemotherapy
- DEX – dexamethasone
- EoL – End-of-life criteria
- EQ-5D - EuroQol five dimensions questionnaire
- HRQoL – Health-related quality of life
- HiDEX – High-dose dexamethasone
- IPD – Individual patient level data
- IRAC – Independent review committee
- ITT – Intention-to-treat
- IV - Intravenous
- LEN – lenalidomide
- LoDEX – Low-dose dexamethasone
- MA – Marketing authorisation
- MM – multiple myeloma
- ORR – Objective response rate
- OS – Overall survival
- R/R – relapsed/refractory
- PANO+BOR+DEX – panobinostat, bortezomib and dexamethasone combination
- PAS - Patient Access Scheme
- PFS – Progression-free survival
- POM – Pomalidomide
- QoL – Quality of life
- QLQ-C30 – Quality of life questionnaire - cancer
- RPSFT – Rank preserving structural failure time model
- SCT – Stem cell transplant
- TA – technology appraisal
- TTF – Time to treatment failure
- TTP – Time to treatment progression
- THAL - thalidomide

NICE guidance (1)

First line	
TA311 (April 2014)	BOR recommended as an option, in combination with DEX, or with DEX and THAL, for the induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic SCT.
TA228 (July 2011)	THAL and BOR recommended as options for the first-line treatment of multiple myeloma in patients for whom high-dose chemotherapy with SCT is considered inappropriate.
Second line	
TA129 (October 2007)	BOR monotherapy recommended as an option for people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation.
Third line	
TA171 (June 2009)	LEN+DEX recommended as an option for people who have received two or more prior therapies
TA380 (January 2016)	PANO+BOR+DEX recommended as an option for treating adult patients with relapsed and/or refractory multiple myeloma who have received ≥2 prior regimens including BOR and an immunomodulatory agent

NICE guidance (2)

Fourth line	
*TA338 (February 2015)	POM +DEX is not recommended within its marketing authorisation for treating relapsed and refractory multiple myeloma in adults who have had at least 2 previous treatments, including LEN and BOR, and whose disease has progressed on the last therapy. *NICE have considered a review of TA338 more than 2 years earlier than originally anticipated, as the company has proposed a Patient Access Scheme for pomalidomide that may change the existing recommendations for this technology.

Patient Perspective - 1

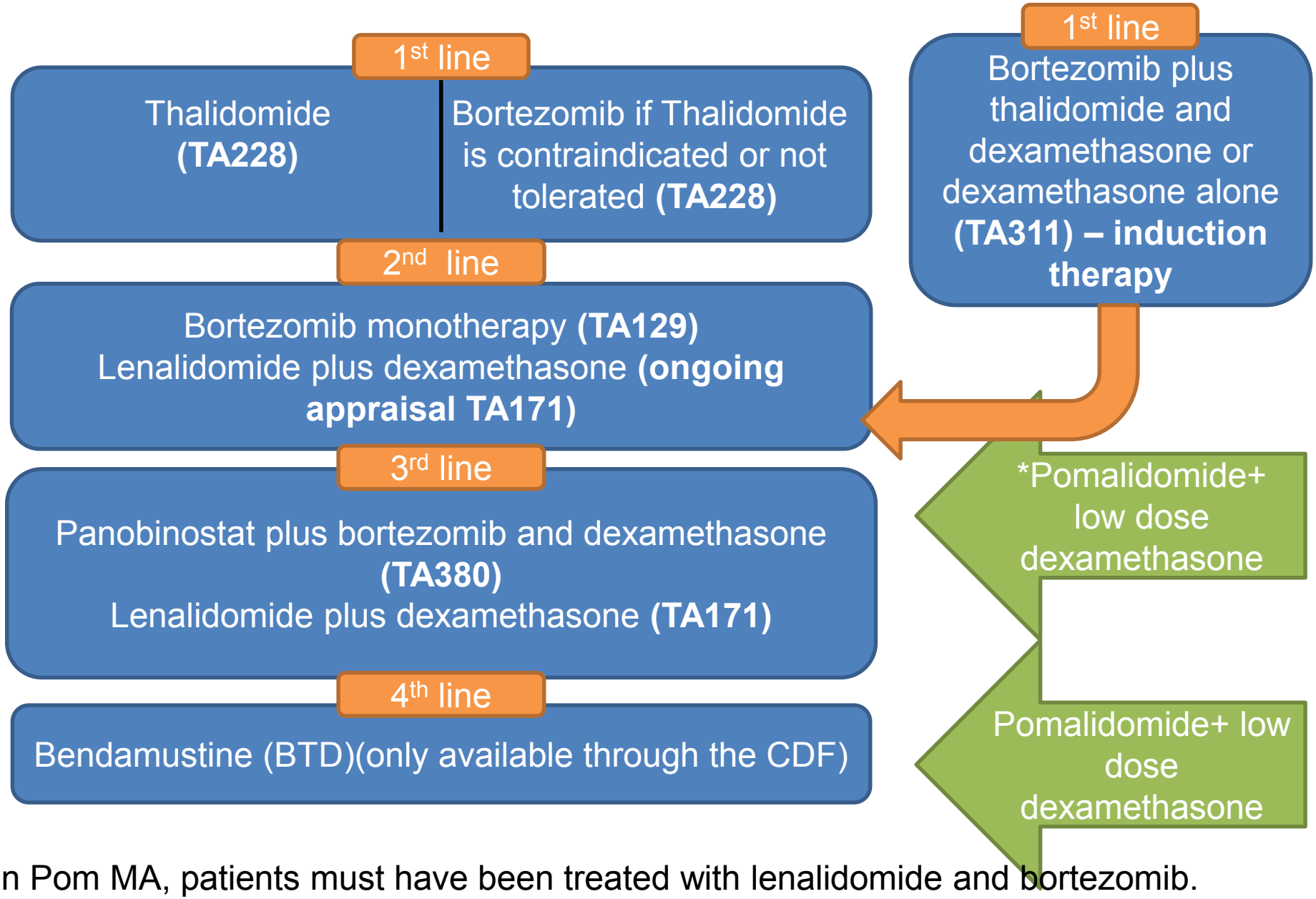
Living with multiple myeloma

- In the early stages, may not cause any symptoms
- Diagnosis is often late
- Eventually, problems include:
  - a persistent dull ache
  - tenderness in bones
  - weak bones that break easily
  - tiredness (from anaemia)
  - weakness and shortness of breath
  - repeated infections
- Significant impact on emotional and social well-being
  - Including family members and carers
- Relapse is also common
  - Adding further anxiety and emotional toll

Patient Perspective – 2
Treatments

- Patients value:
  - Length of life and quality of life benefits
  - Progression free survival (PFS)
  - Overall survival (OS)
  - Disease free remission periods
- Incremental gain as a ‘bridge’ for further down-the-line options
- Treatments with minimal impact on quality of life
- Few adverse events and low severity to reduce the need to stop
  - very important in heavily pre-treated population
- Oral treatment aids living a relatively normal life
- Further available option at third relapse
  - reducing the anxiety associated with relapse

NICE treatment pathway - multiple myeloma



*In Pom MA, patients must have been treated with lenalidomide and bortezomib. Since len+Dex is recommended 3rd line in NICE guidance, is Pom 4th line?

Decision problem

	Final scope issued by NICE	
Pop.	Adults with relapsed and refractory multiple myeloma (RRMM) who have had at least 2 prior treatment regimens, including both lenalidomide (LEN) and bortezomib (BOR), and whose disease progressed on the last therapy	
Int.	Pomalidomide (POM) in combination with dexamethasone (DEX)	
Com.	**2 prior therapies** (3rd line setting): • Panobinostat (PANO) in combination with BOR and DEX **3 or more prior therapies** (4th line setting and beyond): • PANO in combination with BOR and DEX • Bendamustine (BTD) (not appraised by NICE but funded via the Cancer Drugs Fund; does not currently have a marketing authorisation in the UK for this indication) • (*potentially*) Conventional chemotherapy regimens	
Out.	• Overall survival (OS) • Progression-free survival (PFS) • Response rates • Adverse effects of treatment • Health-related quality of life (HRQL)	The company also included 'time to treatment failure' as it informs the economic model

TA338 decision
(Published March 2015)

- Pomalidomide not recommended
- Substantial uncertainty about the relative effectiveness of pomalidomide compared with established clinical practice
  - No robust data on comparator treatments
  - Additional analyses did not reduce the uncertainty
- ICERs over £50,000 per QALY gained compared with bortezomib, and over £70,000 per QALY gained compared with bendamustine plus thalidomide and dexamethasone, and would further increase when a number of more realistic assumptions were included in the model
- End of Life criteria:
  - Population size and short life expectancy: both met
  - 3 month life extension: Committee not persuaded that the estimates of the extension to life were robust, objective or plausible

DETAILS OF THE TECHNOLOGY	
Technology	Pomalidomide (Imnovid)
Marketing authorisation	Pomalidomide in combination with dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy
Method of administration and dosage	The recommended starting dose of POM is 4 mg once daily taken orally on Days 1 to 21 of repeated 28-day cycles. The recommended dose of DEX is 40 mg orally once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle.
Acquisition cost (excluding VAT)	Cost per 21-tablet pack: 1mg, 2mg, 3mg and 4mg: £8,884 A PAS is in place which reduces the net price by [redacted]
Average cost of a course of treatment	£44,420 based upon the median time on treatment from MM-003 and assuming no dose interruptions; [redacted]

TA338 final guidance - MM-003 trial phase 3, open label, n=455

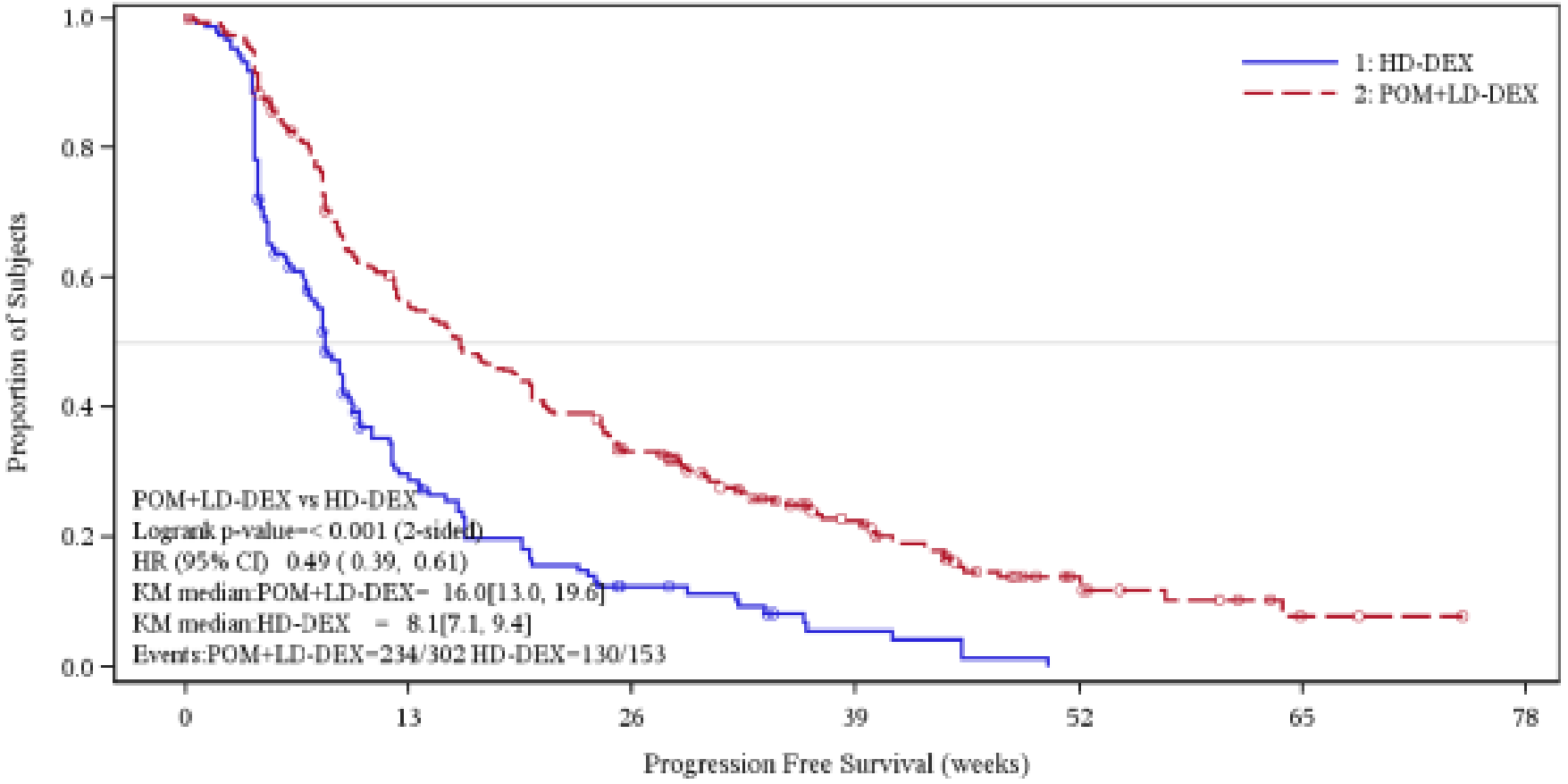
Participants	Patients with RRMM who have received at least two prior treatment regimens, including both LEN and BOR.
Intervention	POM (4 mg/day) plus LoDEX (40mg on Days 1, 8, 15 and 22 of a 28-day cycle)
Comparator	HiDEX (40mg on Days 1 through 4, 9 through 12 and 17 through 20 of a 28-day cycle)
Follow-up	Treatment was continued until progressive disease or unacceptable toxicity. Median follow up was 15.4 months at the latest follow-up.
Primary Outcome	Progression-free survival
Secondary Outcomes	Overall survival, Response rate, Time to progression, Time to response, Duration of response, Time to treatment failure, Health-related quality of life, Safety
Crossover	High proportion of patients crossed over to pomalidomide from the HiDEX group. Two methods of adjustment for treatment crossover for overall survival were presented, with the two-stage method preferred.

MM-003: summary of ITT results (as in TA338 final guidance)

Outcomes	Independent assessment (March 2013)		Investigator assessment (September 2013)	
	POM+LoDEX	HiDEX	POM+LoDEX	HiDEX
Follow-up, median	**10.0 months**		**15.4 months**	
PFS, median, months	3.7	1.9	4.0	1.9
HR	0.49 (95% CI: 0.39 to 0.61)		HR 0.50 (95% CI: 0.41 to 0.62)	
OS, median, months	12.5	8.1	13.1	8.1
HR	0.70 (95% CI: 0.54 to 0.92)		0.72 (95% CI: 0.56 to 0.92)	
ORR, %	**23.5**	**3.9**	**32**	**11**
OR	**7.53 (95% CI: 3.19 to 17.77)**		**3.79 (95% CI: 2.16 to 6.62)**	
TTP, median, months	4.6	2.1	4.7	2.1
HR	0.46 (95% CI: 0.36 to 0.59)		0.49 (95% CI: 0.38 to 0.61)	
TTF, median, months	2.9	1.8	2.9	1.8
HR	0.48 (95% CI: 0.39 to 0.60)		0.50 (95% CI: 0.40 to 0.61)	
DOR, median, months	8.1	6.5	7.5	5.1
HR	0.53 (95% CI: 0.19 to 1.51)		0.52 (95% CI: 0.29 to 0.95)	

All p values significant with exception of DOR independent assessment

MM-003 progression free survival (as in TA338 final guidance) (IRAC assessment, March 2013)



Number of subjects at risk:

1	153	37	13	4	0		
2	302	161	90	43	13	2	0

Source: Company submission, figure 8, page 71

MM-003: crossover adjusted results (as in TA338 final guidance) (impacts overall survival results only)

Median OS in months	POM+LoDEX	HiDEX	Difference
Intent-to-treat, median OS (independent assessment, earlier data cut)	12.7 (95% CI: 10.4,15.5)	8.1 (95% CI: 6.9, 10.8)	**4.6** (HR: 0.74; 95% CI: 0.56, 0.97)
Crossover adjustment, two-stage method	12.7 (95% CI: 10.4,15.5)	5.7 (95% CI: 4.2, 7.5)	**7.0** (HR: 0.52; 95% CI: 0.39, 0.68)
Crossover adjustment, RPSFTM method	12.7 (95% CI: 10.4,15.5)	6.7 (95% CI: 4.6, 10.5)	**6.0** (HR: 0.49; 95% CI: 0.33, 1.00)
Source: Company submission, table 24 (page 75)			

MM-003: Health-related quality of life (as in TA338 final guidance)

- HRQoL measured on day 1 of each treatment cycle and when treatment stopped using:
  - European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30)
  - Myeloma specific EORTC QLQ-MY20
  - EQ-5D

Domain	p-value
EQ-5D utility index	0.0050*
QLQ-MY20 Disease symptoms	0.2478
QLQ-MY20 Side effects of treatment	0.0253*
QLQ-C30 global health status	0.0451*
QLQ-C30 physical functioning	<0.0001*
QLQ-C30 emotional functioning	0.0003*
QLQ-C30 fatigue	0.0008*
QLQ-C30 pain	0.0049*
Key: * p<0.05; Model was adjusted for age group, RRMM type, and prior previous anti-myeloma therapies. Data cut-off: 1 March 2013. QLQ, Quality of life questionnaire	

Key supporting evidence
Data used in indirect comparisons

Study	Intervention	Comparator	Population	ITT results
MM-002, randomised open label, phase 2 trial *(as in TA338)*	POM+LoDEX (n=113)	POM (n=108)	Patients with RRMM with ≥2 lines of previous therapy (median 5 therapies) including LEN and BOR	Median PFS (unadjusted): **4.2 months** (12.6 to 19.8) Median OS (adjusted): **16.5 months** (3.7, 5.8)
MM-010 Single arm, open label phase 3b study *(new evidence – not in TA338)*	POM+LoDEX (n=682)	-	Patients with RRMM, refractory to last prior therapy, had received ≥2 prior therapies and had previous BOR and LEN treatment failure	Median PFS: **4.6 months** (95% CI: 3.9, 4.9) Median OS: **11.9 months** (95% CI: 10.6, 13.4) Similar OS and PFS results regardless of the number of prior lines of therapy

Indirect and mixed treatment comparisons (1) (updated since TA338)

- No direct comparative evidence with bendamustine (BTD), PANO+BOR+DEX or conventional chemotherapy
  - Company considers HiDEX data from MM-003 is proxy for conventional chemotherapy; considered reasonable because these patients receive HiDEX for a short time period (TTF = 1.8 months) with 60% going on to receive subsequent alternative active treatment
- Available evidence did not support a comparison of POM+LoDEX with BTD and with PANO+BOR+DEX in a conventional mixed treatment comparison
- The company selected individual treatment arms from the available studies and performed separate analyses comparing POM+LoDEX to each of the comparators independently

Indirect and mixed treatment comparisons (2)

Selection of studies (updated since TA338)

- **For POM+LoDEX**, MM-003, MM-002 and MM-010 studies included
  - MM-002 most comparable to available studies for BTD
  - Full trial dataset (MM-002, MM-003 and MM-010) most comparable to data for PANO+BOR+DEX; also presented as sensitivity analysis for comparison to BTD
- **For BTD**, only MUK-one trial available which compared two doses of BTD
  - Company obtained patient level data from MUK-one study (n=57)
  - Supplemented by patient level data on 21 patients from the Gooding and Tarant datasets
  - Company stated that these datasets are unlikely to have been influenced by patients receiving subsequent POM+LoDEX as the work was conducted before POM was commercially available
- **For PANO+BOR+DEX**, PANORAMA-2 trial identified – most comparable to POM population, but some differences in number of prior lines of treatment and lack of reporting of whether refractory to LEN limit validity of results

POM+LoDEX compared with BTD

	POM+LoDEX	BTD
Overall survival (median, months)		
IPD from MM-002, MUK-ONE, Gooding and Tarant	**16.5 months** (12.6 to 19.8)	**8.1 months** (5.3 to 13.5)
Unadjusted HR	**0.55** (95% CI 0.38 to 0.81)	
Covariate adjusted HR	**0.58** (95% CI 0.36 to 0.94)	
Inclusion of additional data for POM+LODEX from MM-003 and MM-010		
Unadjusted HR	**0.68** (95% CI 0.51 to 0.92)	
Covariate adjusted HR	**0.64** (95% CI 0.45 to 0.91)	
Progression-free survival (median, months)		
IPD from MM-002, MUK-ONE, Gooding and Tarant	**4.2 months** (3.7, 5.8)	**3.3 months** (2.5, 5.5)
Unadjusted HR	**0.76** (95% CI 0.56 to 1.05)	
Covariate adjusted HR	**0.79** (95% CI 0.52 to 1.22)	
Inclusion of additional data for POM+LODEX from MM-003 and MM-010 did not substantially change results		
Source: ERG report, table 4.27 (page 85)		

POM+LoDEX compared with PANO+BOR+DEX

- Individual patient data from MM-002, MM-003, MM-010 and aggregate data from PANORAMA-2
- Subgroup of patients (approximately 81%) in the POM+LoDEX trials (n=886) that were refractory to BOR but not primary refractory were included to align with PANORAMA-2 population (n=55)
- No patient level data available from PANORAMA-2, so covariate adjustment method not possible
- Matching adjusted indirect comparison (MAIC) used to adjust for the differences in patient characteristics between studies
  - reweights patient level data for POM+LoDEX to reflect a population of similar baseline characteristics to the PANO+BOR+DEX population

POM+LoDEX compared with PANO+BOR+DEX results

	POM+LoDEX	**PANO+BOR+DEX**
Overall survival (median, months)		
Unweighted Weighted	**12.4** (11.1 to 13.4) **13.4** (11.4 to 15.6)	**17.5** (10.8 to 22.22) NA
HR (95%CI) Unweighted Weighted		 **0.73** (0.52 to 1.02) **0.78** (0.56 to 1.09)
Progression-free survival (median, months)		
Unweighted Weighted	**4.1** (3.7 to 4.6) **4.2** (3.7 to 4.8)	**5.3** (3.9 to 6.6) NA
HR (95%CI) Unweighted Weighted		 **1.12** (0.85 to 1.48) **1.18** (0.89 to 1.56)
Source: ERG report, table 4.27 (page 85)		

ERG comments: MM-003

(as in TA338)

- Reasonably large, well conducted trial, appropriate population
- Comparator is no longer optimal in current practice, and is given at a lower dose mostly with palliative intent
  - Since HiDEX is no longer considered conventional chemotherapy there is no direct evidence comparing POM+LoDEX with any of the comparators listed in the NICE scope
- Over 50% of patients in the trial are aged 65 or under so may reflect a younger population than typically seen in practice
- Only 17 patients receiving two prior therapies thus the trial is not representative of POM as a third line therapy
  - Could be assumed that POM might perform better at third line in a less treated population but this is an assumption
- The trial was in a heavily treated population who had received a median of five therapies (range 2 to 17)
- Adverse event profile appears to be manageable with appropriate dose reductions and interruptions
  - However, slightly higher incidence of serious adverse events (grade 3 and 4) attributed to POM

ERG comments: POM+LoDEX compared with BTD

- Satisfied that approach to covariate selection was reasonable
- Magnitude of relative effect dependent on selection of data for inclusion in the analysis
- Assessment of comparability between studies was based primarily on the percentage of patients refractory to lenalidomide in each study but:
  - MM-002 study includes three to four times as many lenalidomide refractory patients as the BTD studies therefore
  - not clear that the gain in comparability justifies the exclusion of the MM-003 and MM-010 studies
- POM+LoDEX appears to improve both OS and PFS compared to BTD
  - But uncertainty surrounding the magnitude of improvement depending on the characteristics of patient population with regard to being refractory to lenalidomide and the number of lines of prior therapy
- Acknowledge that it is based on best evidence available

ERG comments: POM+LoDEX compared with PANO+BOR+DEX

- Small number of patients receiving PANO+BOR+DEX (n=55)
  - high degree of uncertainty surrounding the median OS on PANO+BOR+DEX
- Difference between the PANORAMA-2 study and the pomalidomide studies in terms of the number of lines of prior therapy
  - Patients in PANORAMA-2 received one fewer prior lines of therapy on average than in pomalidomide studies
- Modest differences in relative effects (hazard ratios) however median OS and median PFS are very similar for POM+LoDEX and PANO+BOR+DEX in both the unweighted results and in the MAIC

ERG comments: POM+LoDEX compared with conventional therapy

- Questioned whether conventional therapy is a comparator in UK clinical practice
- Company assumed HiDEX data as proxy for conventional therapy reporting evidence from the IFM 95-01 study to demonstrate similarity in outcomes between HiDEX and conventional chemotherapy. The ERG notes:
  - This study was for 1st line treatment
  - Results suggest that patients receiving DEX have a shorter time to progression than patients on other conventional chemotherapy regimens, so the effect of POM+LoDEX compared to HiDEX in the MM-003 trial may overestimate the true difference in PFS for POM+LoDEX compared to other conventional chemotherapy
  - OS measured from time of study entry was similar for patients receiving DEX compared to other conventional chemotherapy regimens; HiDEX arm of the MM-003 study may be a reasonable proxy for conventional chemotherapy when assessing OS

Innovation

(as in TA338)

- Pomalidomide is more potent than thalidomide and lenalidomide
- Pomalidomide is more effective in regards to:
  - anti-proliferative activity,
  - anti-inflammatory properties and
  - ability to stimulate Th1 cytokines and T and NK cells
- Pomalidomide is well tolerated and can be given continuously until disease progression
- Pomalidomide is an oral agent which can be self-administered at home which is anticipated to be more convenient, easier and less distressing for people
- Pomalidomide has shown to give a significant survival benefit when given with low dose dexamethasone in studies MM-003 and MM-002

PPRS payment mechanism

- PPRS is a voluntary agreement to control the prices of branded drugs sold to the NHS
  - 2014 PPRS scheme includes a payment mechanism in which the growth rate in sales of NHS branded medicines supplied by companies in the scheme is underwritten by those companies, above agreed levels
- NICE position statement concludes that 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines
- Company did not apply PPRS to its analyses
  - Does the company consider the PPRS 2014 Payment Mechanism has an impact on the effective price/cost of the technology to the NHS?
  - Has Committee heard anything that would change the conclusion in the NICE position statement?

https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/PPRS%202014%20-%20NICE%20Position%20Statement.pdf

Issues for consideration

- At what point in the pathway (3rd line, 4th line, 5th line, etc) is pomalidomide likely to be offered?
- Comparators:
  - Is conventional chemotherapy an appropriate comparator?
  - If so, is it appropriate to use HiDEX as a proxy for conventional chemotherapy?
- Is the population in the trial generalisable to the patient population who would be offered pomalidomide in clinical practice in England?:
  - Over 50% of patients in the trial are aged 65 or under. Is this a younger population than that typically seen in practice?
  - MM-003 population was heavily treated (median of 5 therapies received) with results for only 17 patients receiving 2 prior therapies. Is the trial representative of 3rd line myeloma treatment?
- What is the committee's view on the company's indirect comparisons?

Pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib (review of TA338)-STA

12 October 2016

1st Appraisal Committee meeting

Cost Effectiveness

Lead team: David Chandler, Rachel Elliott, Iain Miller

Company model: treatment comparisons

Population: patients with relapsed and refractory multiple myeloma (RRMM) who have previously been treated with lenalidomide and bortezomib and whose disease progressed during the last therapy

Intervention:

- Pomalidomide, POM, in combination with low-dose dexamethasone, LoDEX (POM-LoDEX)

Comparators:

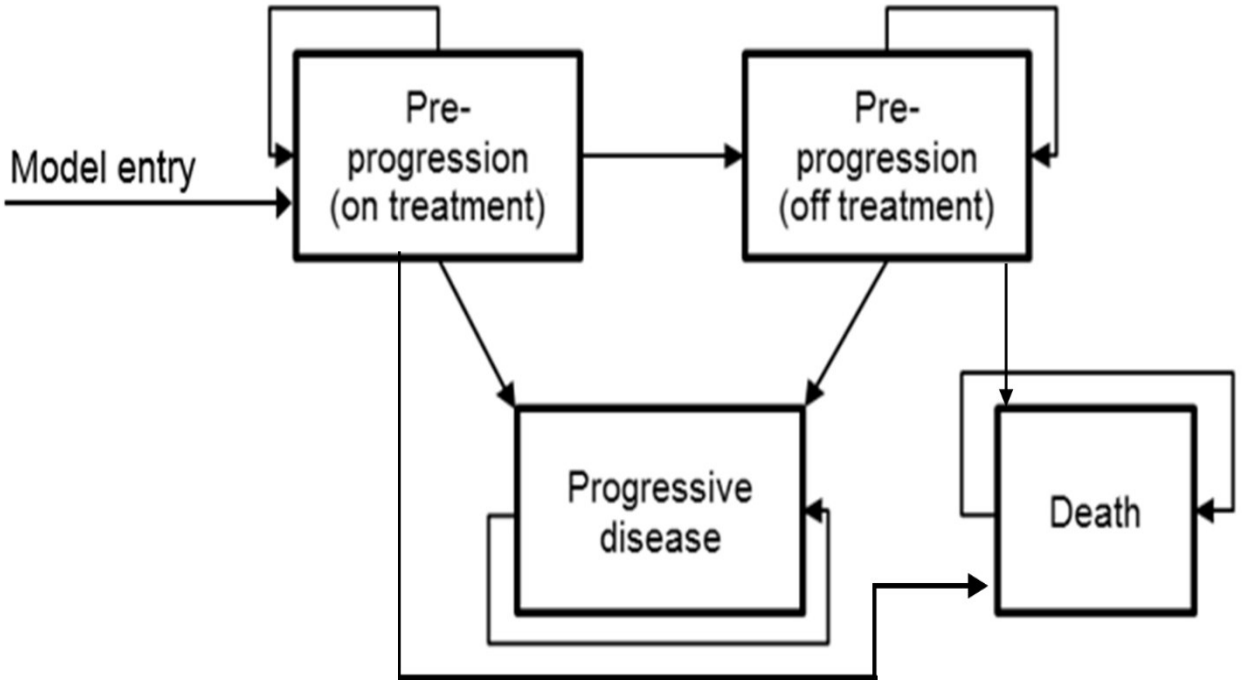
- Bendamustine+thalidomide+dexamethasone (BTD)
- Panobinostat + bortezomib + dexamethasone (PANO+BOR+DEX)
- Conventional chemotherapy (CC)

Review of TA338; the company has now proposed a Patient Access Scheme for pomalidomide

Company model (as in TA338)

Semi-Markov partitioned survival model

Population: Adults with RRMM previously treated with LEN and BOR



- Cycle length: 1 week
- Time horizon: Lifetime (15 years)
- Perspective: NHS
- Discount rate: 3.5%

Comparators

- POM + Lo-DEX
- BTD
- PANO+BOR+DEX
- CC

RRMM: relapsed and refractory multiple myeloma; LEN: lenalidomide; BOR: bortezomib

Company model: treatment effect (*base case sources of data and covariates, updated since TA338*)

	POM+LoDEX vs BTD	POM+LoDEX vs PANO+BOR+DEX	Conventional chemotherapy
Data Source	MM-002 Gooding et al. Tarant et al. MUK-One	MM-003 MM-002 MM-010 PANORAMA-2	MM-003 (HiDEX data used as a proxy)
Covariates	Age Prior lines of therapy Refractory to LEN Receipt of prior THAL	Age Prior lines of therapy Receipt of prior THAL ECOG stage	Not required – within trial comparison

LEN: lenalidomide, THAL: thalidomide, ECOG: Eastern Cooperative Oncology Group

Covariate adjusted comparisons implemented within model using corrected group prognosis (CGP) method in base-case analysis, and mean of covariates method in a scenario analysis.

Company model: base case survival curves

	POM+LODEX vs BTD	POM+LODEX vs PANO+BOR+DEX	Conventional chemotherapy
OS	Exponential curve was used to extrapolate using unadjusted Kaplan Meier data taken from MM-003, MM-002 and MM-010	Generalised gamma curve considered most appropriate model using unadjusted Kaplan Meier data (taken from MM-003, MM-002 and MM-010) and pseudo patient level data taken from PANORAMA-2	Exponential curve adjusted using the two stage Weibull approach provided best fit for the OS data (taken from MM-003)
PFS	Generalised gamma curve was used to extrapolate using unadjusted Kaplan Meier data from MM-003, MM-002 and MM-010	Generalised gamma curve considered most appropriate model using unadjusted Kaplan Meier data (taken from MM-003, MM-002 and MM-010) and pseudo patient level data taken from PANORAMA-2	Generalised gamma curve considered most appropriate using KM data taken from MM-003
TTF	Generalised gamma with unadjusted Kaplan Meier	Unstratified parametric survival curves (taken from MM-003, MM-002 and MM-010)	Extreme value curve
Source: Company submission, section 5.3.8 to 5.3.14 (page 174 to 185)			

Company model: comparison of clinical outcomes with base case model outcomes

	POM+LoDEX (MM-002)		POM+LoDEX (MM-003,-002, -010)		BTD		PANO+BOR+ DEX		CC	
	Trial	Model	Trial	Model	Trial unadjusted	Model adjusted	Trial	Model	Trial	Model
Median OS	16.5	14.26	13.1 (MM-003) 16.5 (MM-002) 11.9 (MM-010)	13.11	8.2 (MUK-One)	8.97	17.5	16.79	5.7	6.21
Median PFS	4.2	4.83	4.0 (MM-003) 4.2 (MM-002) 4.6 (MM-010)	4.37	3.3 (MUK-One)	3.68	5.4	3.68	1.9	1.84

Company model: Utility

- Utilities for each health state were found using a regression model (also used in TA338)
- The regression model based on EQ-5D data collected as part of MM-003
- While many covariates were assumed to be the same between treatments, treatment specific utilities were obtained by using treatment specific values for the following covariates: disease progression, best overall response, hospitalisations and adverse events
- Utility decrement of 0.025 in the base-case for patients receiving IV or SC therapy

Health status			MM-003: EQ-5D method
Best overall response	Within PD health state?	Hospitalisation or adverse event?	
Response	x	X	0.76
Response	X	Adverse event	0.68
Stable disease	x	X	0.66
Stable disease	X	Adverse event	0.59
Progressive disease	x	X	0.62
Progressive disease	X	Adverse event	0.54
Stable disease	x	Hospitalisation	0.53
Response	✓	X	0.72
Response	✓	Adverse event	0.65
Stable disease	✓	X	0.63
Stable disease	✓	Adverse event	0.55
Progressive disease	✓	X	0.58
Progressive disease	✓	Adverse event	0.51
Stable disease	✓	Hospitalisation	0.49

Company model: resource use and costs

- See table 56, page 224-225 for company submission costs
- The model assumed that a treatment interruption < 28 days would not lead to cost savings, as it is unlikely that the remaining drugs could be recovered by the NHS
- Interruptions > 28 days it was assumed that costs could be saved as less medication is dispensed
- Costs associated with IV/SC administration visits were obtained BOR first-line appraisal (TA311) and uplifted to 2014/15 costs
- Monitoring, concomitant medication and adverse event costs: information from a questionnaire filled in by six clinical specialists was used
- End-of-life costs were estimated using a UK study among 40 cancer patients during the last eight weeks of their life
- In the base case, no subsequent therapies included following discontinuation, due to uncertainty of treatments used beyond the POM setting. However, this assumption is explored in a scenario analysis.

Company base case results from corrected model and based on POM PAS price and PANO list price

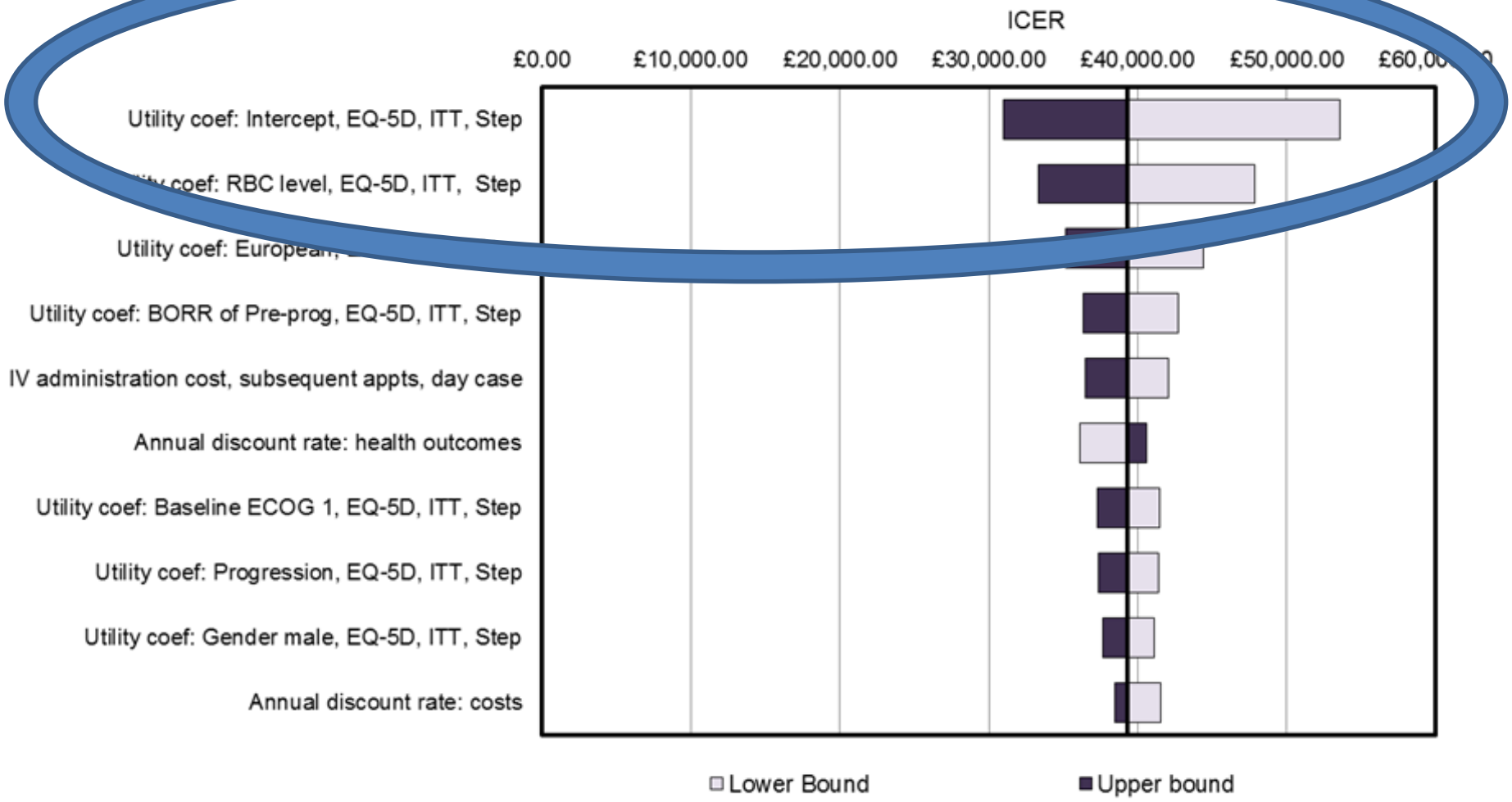
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
POM+LoDEX vs BTD							
BTD	[redacted]	1.14	[redacted]	[redacted]	-	-	-
POM+LoDEX	[redacted]	1.81	[redacted]	[redacted]	0.67	[redacted]	£39,665
POM+LoDEX vs PANO+BOR+DEX							
PANO+BOR+DEX	[redacted]	2.25	[redacted]	[redacted]	-	-	-
POM+LoDEX	[redacted]	1.71	[redacted]	[redacted]	-0.53	[redacted]	£141,793 (SW)
POM+LoDEX vs conventional chemotherapy (CC)							
CC	[redacted]	0.78	[redacted]	[redacted]	-	-	-
POM+LoDEX	[redacted]	1.45	[redacted]	[redacted]	0.68	[redacted]	£44,811

Source: ERG report, tables 5.16, 5.17 and 5.18 (page 131)

Company's probabilistic sensitivity analyses *using updated base case results from corrected model*

POM+DEX vs BTD
Mean incremental QALYs [redacted]
Mean incremental costs [redacted]
Probabilistic ICER **£39,317** (deterministic base-case ICER **£39,665**)
POM+DEX vs PANO+BOR+DEX
Mean incremental QALYs [redacted]
Mean incremental costs [redacted]
Probabilistic ICER **£134,379** (deterministic base-case ICER **£141,793**) SW Quadrant
POM+DEX vs conventional chemotherapy (CC)
Mean incremental QALYs [redacted]
Mean incremental costs [redacted]
Probabilistic ICER **£45,831** (deterministic, base-case ICER **£44,811**)

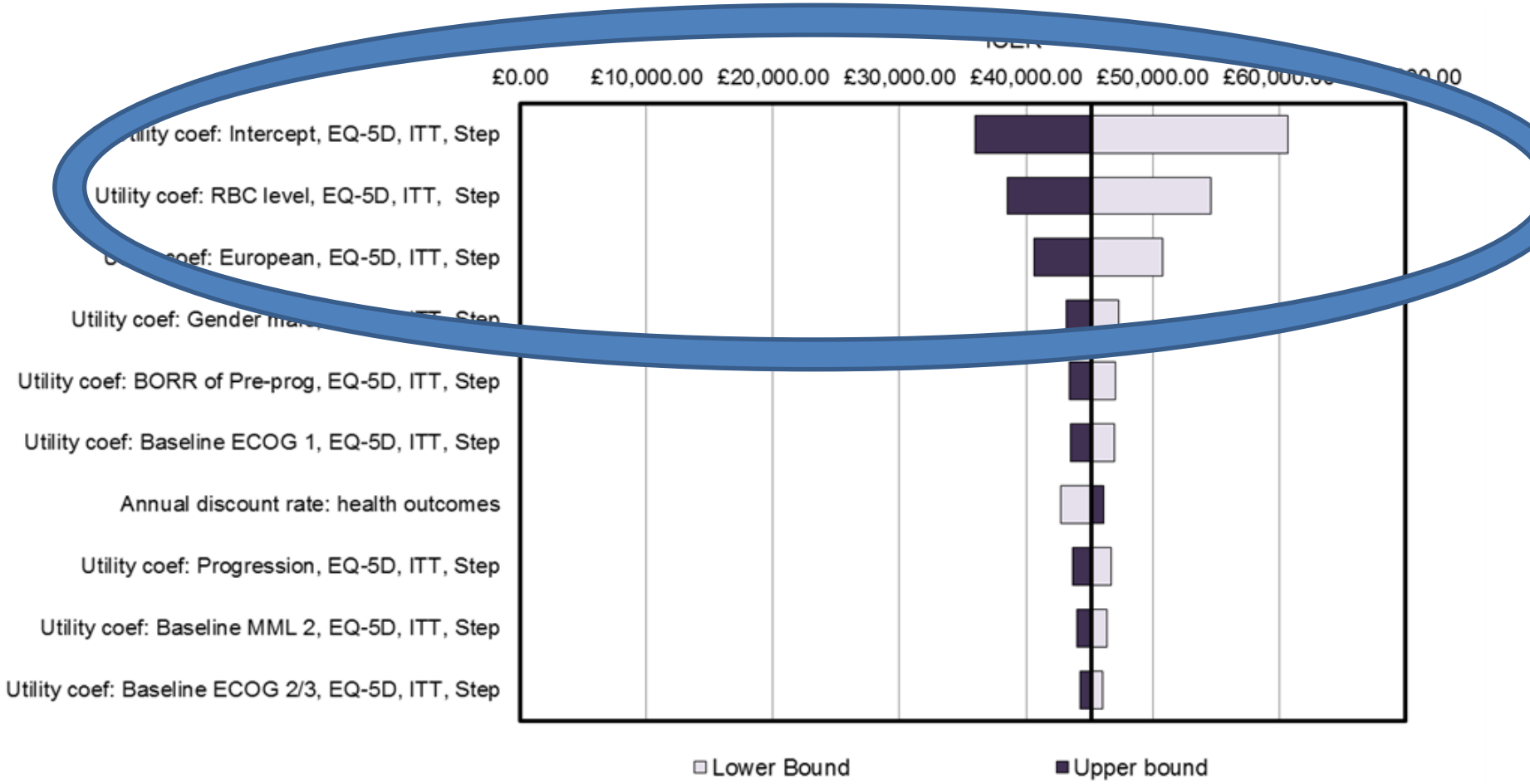
Company's deterministic sensitivity analyses - BTD



Company's deterministic sensitivity analyses - PANO+BOR+DEX

- Parameters showing the largest impact on the ICER were:
  - the hazard ratios (HRs) used to model comparative effectiveness (overall survival (OS) and progression-free survival (PFS) HRs)
  - Besides those parameters, the model showed relatively insensitivity to variations of other inputs

Company's deterministic sensitivity analyses - POM+DEX vs conventional chemotherapy



Summary of sensitivity analyses

Key areas of uncertainty in the model:

- the magnitude of survival benefit compared to PANO+BOR+DEX - when the HR for PFS is also used for OS in comparison to PANO+BOR+DEX (in an attempt to correct for potential imbalances in subsequent therapy use due to the PANORAMA trial being at an earlier line of therapy) POM+LoDEX is dominant
- uncertainty surrounding parameter estimates in the regression equation used for utilities
  - use of utilities estimated using the disease specific measure or published information reduced ICERs in all comparisons
  - vs BTD the ICER ranged between £31,000 and £54,000
  - vs CC the ICER ranged between £36,000 and £61,000
- The trial data used for comparison to BTD
  - however POM+LoDEX remained cost-effective even when data from more refractory patients in the MM-003 and MM-010 studies was included in the analysis

Company's scenario analyses - BTD

Scenario	Incremental Costs	Incremental QALYs	ICER
Base case	[redacted]	[redacted]	£46,206
POM+LoDEX data from all 3 trials	[redacted]	[redacted]	£46,206
Cost of subsequent therapy included using resource use questionnaires	[redacted]	[redacted]	£44,451
Administration costs of IV/SC treatments from NHS reference costs	[redacted]	[redacted]	£44,200
AEs based on relative tolerability profiles	[redacted]	[redacted]	£43,585
Gompertz (PFS curve choice)	[redacted]	[redacted]	£42,177
5 year time horizon	[redacted]	[redacted]	£41,605
Exponential	[redacted]	[redacted]	£41,306

Company's scenario analyses - PANO+BOR+DEX

Scenario	Incremental Costs	Incremental QALYs	ICER
Base case	[redacted]	[redacted]	*£141,793*
5 year time horizon	[redacted]	[redacted]	*£195,354*
Weibull (OS curve choice)	[redacted]	[redacted]	*£178,883*
Gompertz (OS curve choice)	[redacted]	[redacted]	*£176,308*
Exponential (OS curve choice)	[redacted]	[redacted]	*£158,863*
Mean covariate method used	[redacted]	[redacted]	*£152,848*
Weibull (PFS curve choice)	[redacted]	[redacted]	*£152,051*
Exponential	[redacted]	[redacted]	*£146,139*

All ICERs in SW quadrant – cost saving per QALY lost

Company's scenario analyses - CC

Scenario	Incremental Costs	Incremental QALYs	ICER
Base case	[redacted]	[redacted]	£44,811
Gompertz - TS weibull (OS curve choice)	[redacted]	[redacted]	£137,761
Gompertz – RPSFTM (OS curve choice)	[redacted]	[redacted]	£90,588
Generalised gamma – RPSFTM (OS curve choice)	[redacted]	[redacted]	£81,927
Generalised gamma - TS weibull	[redacted]	[redacted]	£61,667
Log-logistic (TTF curve choice)	[redacted]	[redacted]	£53,550
Log-normal (TTF curve choice)	[redacted]	[redacted]	£52,098
Generalised gamma (TTF curve choice)	[redacted]	[redacted]	£52,009

ERG comments – cost effectiveness (1)

- Model structure appropriate
- Inconsistency: in the base-case calculations it was assumed that the mean number of prior lines of therapy was 6.5, whereas in the utility calculations it was assumed that the mean number of prior lines of therapy was 3.7
- Comparators not stratified into third line and fourth and later lines
- Fully incremental results should be considered rather than pairwise comparisons
- Concerns related to the implementation of AEs.
- Approach taken by the company to include HRQoL is largely the same as the approach used for TA338 – considered appropriate

ERG comments – cost effectiveness (2)

- Error in the model on the transformation of yearly resource use for monitoring to weekly number that underestimates costs: affects the ICERs
- Input parameters derived from the resource use questionnaire should be considered with care
- Model allows for a decrease in treatment costs based on treatment interruptions lasting longer than 28 days
- The ERG does not agree with the base case choice to not include subsequent treatment costs
  - They are incorporated into the OS results and therefore costs should be included for consistency
  - In the scenario analyses it was found that these costs do affect the ICER

ERG comments on company sensitivity analyses

- Base case ICER is reasonably certain with regards to the structural assumptions of the base case model for all comparisons

- However, when the HR for PFS is also used for OS in comparison to PANO+BOR+DEX, POM+LoDEX becomes dominant

- Also, reducing the time horizon results in an increase of the ICERs for all 3 comparisons (important survival benefits are unlikely to be captured with short time horizon)

- Important structural uncertainty: choice of parametric curve for OS, PFS and TTF
  - Changing the distribution of the parametric curves can lead to both upward and downward changes in the ICER

ERG correction of errors

- After the clarification letter was send to the company, additional programming errors were found

- Additional errors in company model:

1) Half cycle correction was wrongly implemented
2) The model did not use the CGP results that were obtained from the provided VBA macro
3) The weekly numbers for resource use were calculated incorrectly and wrong unit costs were used for some of the resource use elements for some of the comparators.

- In the first part of the ERG exploratory analyses, the additional programming errors above are corrected, and the base case analysis of the company is repeated with these corrections

ERG correction of errors in company base case: results

POM+LoDEX vs BTD							
Technologies	Total costs (£)	Total LYG (undiscounted)	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£) versus baseline (QALYs)
BTD	[redacted]	1.12	[redacted]	[redacted]	-	-	-
POM+ LoDEX	[redacted]	1.80	[redacted]	[redacted]	0.67	[redacted]	£45,082
Source: ERG report, Table 5.36 (page 150)							

POM+LoDEX vs PANO+BOR+DEX							
Technologies	Total costs (£)	Total LYG (undiscounted)	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£) versus baseline (QALYs)
PANO+BOR+ DEX	[redacted]	2.05	[redacted]	[redacted]	-	-	-
POM+ LoDEX	[redacted]	1.55	[redacted]	[redacted]	-0.49	[redacted]	£142,930 (SW)
Source: ERG report, Table 5.37 (page 150)							

POM+LoDEX vs conventional chemotherapy (CC)							
Technologies	Total costs (£)	Total LYG (undiscounted)	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£) versus baseline (QALYs)
Conventional chemotherap y	[redacted]	0.76	[redacted]	[redacted]	-	-	-
POM+ LoDEX	[redacted]	1.43	[redacted]	[redacted]	0.68	[redacted]	£48,673
Source: ERG report, Table 5.38 (page 151)							

ERG full incremental analysis

- ERG provided a full incremental analysis including all comparators
- The pooled dataset including MM-002, MM-003 and MM-010 trials and all BTD trials were used
- ERG presented results exploring different methods for estimating parametric curves and obtaining hazard ratios
  - The preferred method included the mean covariate adjustment method and 2-stage HR adjustment instead of ITT HR for CC

Using 2-stage HRs from MM-003 for CC OS/PFS and TTF curves and mean covariate adjustment method is used for covariate adjustments			
	Incr Costs	**Incr QALYs**	**ICER**
PANO+BOR+DEX	[redacted]	[redacted]	£146,307
POM+LoDEX	[redacted]	[redacted]	£59,104
BTD	[redacted]	[redacted]	Extendedly dominated by POM+LoDEX
CC	[redacted]	[redacted]	-
Source: ERG report, table 5.42 (page 153)			

Summary of results

	POM+LoDEX vs. BTD			POM+LoDEX vs. PANO+BOR+DEX			POM+LoDEX vs. CC		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Updated company base case	[redacted]	[redacted]	£39,665	[redacted]	[redacted]	£141,793 (SW)	[redacted]	[redacted]	£44,811
ERG correction programming errors	[redacted]	[redacted]	£45,082	[redacted]	[redacted]	£142,930 (SW)	[redacted]	[redacted]	£48,673
Using pooled data set (MM-002, MM-003 and MM-010), ITT HR from MM-003, CGP	[redacted]	[redacted]	£54,428	[redacted]	[redacted]	£142,930 (SW)	[redacted]	[redacted]	£81,209
Using pooled data set (MM-002, MM-003 and MM-010), 2-stage HR from MM-003, CGP	[redacted]	[redacted]	£54,428	[redacted]	[redacted]	£142,930 (SW)	[redacted]	[redacted]	£57,288
ERG preferred: using pooled data set (MM-002, MM-003 and MM-010), 2-stage HR from MM-003, Mean Covariate	[redacted]	[redacted]	£55,974	[redacted]	[redacted]	£146,307 (SW)	[redacted]	[redacted]	£59,104

ERG exploratory analyses

The ERG explored the impact of including the following amendments in it's preferred model based on the mean covariate adjustment method and 2-stage HR adjustment instead of ITT HR for CC. These included:

- Dose interruptions applied for all arms assuming equal proportion of packs are skipped among comparators
- Including subsequent treatment cost using resource use questionnaire
- Including subsequent treatment cost based on Hemateologic Cancer Research Center in York
- No wastage of drugs
- Equal BORR, AE discontinuation and hospitalization rates for all 4 treatments (all same as POM+ LoDEX) for estimating utilities
- No disutility due to IV administration
- AE rates of the comparators are the same as POM+LoDEX.
- Utility weights are from Quinn et al

Pairwise results are presented and demonstrate that the ICER results do not change much and are more or less similar across the analyses

End of life

Criterion	Company submission	ERG comments
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	• Median OS is 3-9 months	• agrees that the patient group, being at least at third line of treatment for relapsed and refractory multiple myeloma (RRMS), have a short life expectancy
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	• Versus conventional chemotherapy: based on use of HiDEX outcomes as a proxy > 5 months benefit in median OS demonstrated in the MM-003 trial • Versus BTD: 6.1 months benefit in median OS demonstrated via unadjusted comparison, 8.4 months via adjusted comparison • Versus PANO+BOR+DEX no significant difference in survival	• POM + LoDEX vs HiDEX or BTD (meets 3 months extension criteria) • POM + LoDEX vs PANO + BOR + DEX (does not meet 3 months extension criteria) • POM+LoDEX will lead to a decrease in life expectancy of 6 months compared to PANO+BOR+DEX
EoL was not met in TA338, has anything changed since then?		

Equality issues

- No equality issues were raised

Key issues for consideration (1)

- Cost effectiveness analyses were not stratified into third line and fourth and later lines. Is this appropriate?
- Baseline covariates: efforts were made to correct for differences in baseline covariates between data sets, there are some unmeasured confounders. What is the committee's view on this uncertainty?
- Data used: a different dataset is used for each of the three comparisons a pairwise approach implies a slightly different population for each comparison. Does the committee consider that the results are sufficiently robust?
- Implementation of AE: AE rates observed for POM+LoDEX were also used for the comparators, though multiplied by correction factors. Is this approach appropriate, have they been derived correctly?

Key issues for consideration (2)

- Does the committee agree with the changes that make up the ERG's preferred base case results?
- What does the committee consider to be the most plausible ICER?
- Does the committee consider that EOL criteria are met?
- Does the committee have any comments on Innovation / Equality / PPRS?