NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib (review of TA338) [ID985]

Committee papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib (review of TA338) [ID985]

Contents:

Premeeting briefing

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

This slide set is the premeeting 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.

Decision problem

	Final scope issued by NICE	Company submission
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: • Panobinostat (PANO) in combination with BOR and DEX 3 or more prior therapies: • 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) • Conventional chemotherapy regimens	
Out.	• Overall survival (OS) • Progression-free survival (PFS) • Response rates • Adverse effects of treatment • Health-related quality of life (HRQL)	• Time to treatment failure (included as it informs the economic model)

Premeeting briefing 2

The relevance of conventional chemotherapy regimens as appropriate comparators was questioned in the clinical expert statement submitted on behalf of UK Myeloma Forum /Guys and St. Thomas' NHS Foundation Trust which states that '*Cyclophosphamide, melphalan, high dose dexamethasone and thalidomide would generally be considered as a palliative approach rather than an active approach (in comparison to the treatments outlined above). These are NOT appropriate comparators. There is no evidence to support these agents at this stage of therapy in the modern era of myeloma therapy (other than as palliative treatments).*'

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
- 43% of people diagnosed are aged 75 years and over
- 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: disease progression while on, or within 60 days after, a specific treatment

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	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]

NICE guidance (1)

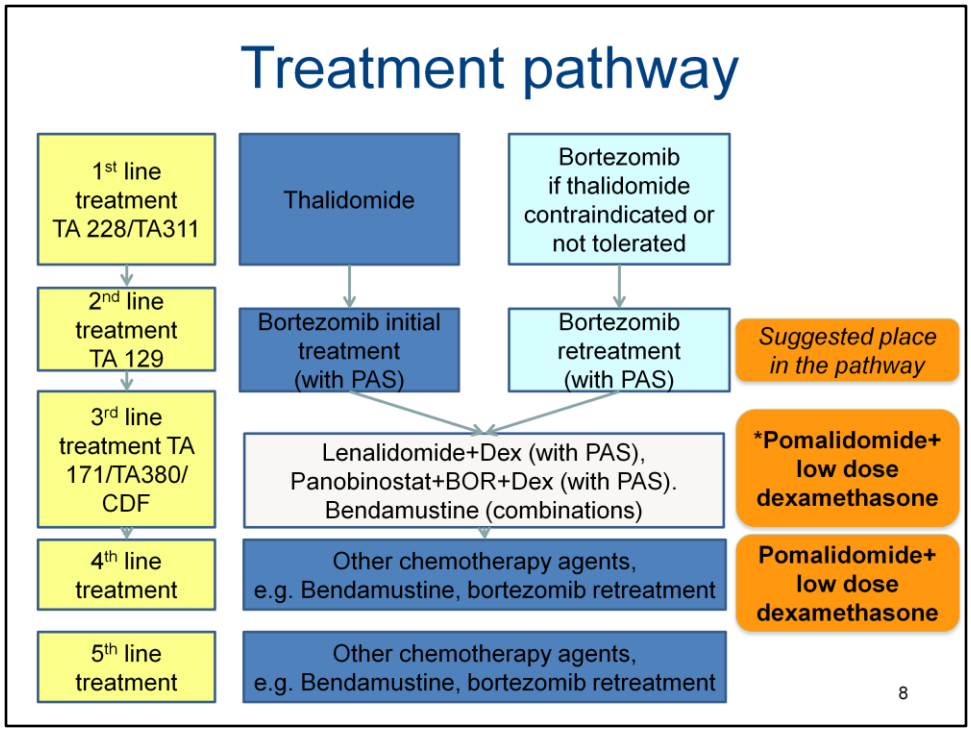
First line	
TA311 (April 2014)	BOR recommended as an option, in combination with DEX, or with DEX and THAL, for the induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic SCT.
TA228 (July 2011)	THAL and BOR recommended 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.

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



*But patients must have been treated with lenalidomide and bortezomib according to the marketing authorisation of pomalidomide. Since lenalidomide+Dex is recommended 3rd line in NICE guidance, it could be considered that pomalidomide is meant for 4th line treatment.

Patient Perspective (1)

- Very ill population
  - most experience number of relapses and/or quickly become refractory to available treatments
  - Substantial impact on emotional well-being
  - Treatment side-effects and frequent hospital visits have social and financial impact
- Introduction of novel drugs such as thalidomide, bortezomib and lenalidomide have improved survival and quality of life
  - But mortality rates remain high and continual need for new treatments
- Patients experience an increased incidence of:
  - Bone pain, bone fractures, tiredness (from anaemia), infections, hypercalcaemia and kidney problems

Patient Perspective (2)

- Most important outcomes:
  - PFS and OS
  - Even small gains in survival seen as bridge to treatments further down the line
  - Increase in remission (i.e. disease free periods) for the longest possible time
  - Side effect profile important in heavily pre-treated population
- Oral treatment allows living a relatively normal life
- Another treatment option at third relapse will reduce the anxiety associated with relapse for both patients and their families
- Side effects experienced on POM: Shortness of breath and muscle pain

Clinical effectiveness evidence

company submission chapter 4

Overview of evidence

The company identified:

- 4 RCTs, of which MM-003 key trial
- 9 non-RCTs
- a retrospective real world data collection project to compare BTD, BOR and POM+LoDEX at third line
- 2 ongoing trials, MM-008 and MM-013 (details provided for information only)

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.

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The ERG noted that patients in MM-003 had received a median number of five prior treatments (range 2 to 17). The ERG asked the company to clarify the comparability of the patients in MM-003 to the total population in this appraisal. The company acknowledged that '*MM-003 has been conducted in an advanced and highly refractory population likely to have a poor prognosis, with a reduced ability to benefit from subsequent treatment*'

The ERG asked the company to provide results for all outcomes specified in the scope for patients who had had exactly two prior therapies. They provided results for 17 patients (25 are listed in the baseline characteristics) but stated that '*Due to the small numbers of patients….these results cannot be credibly interpreted.*

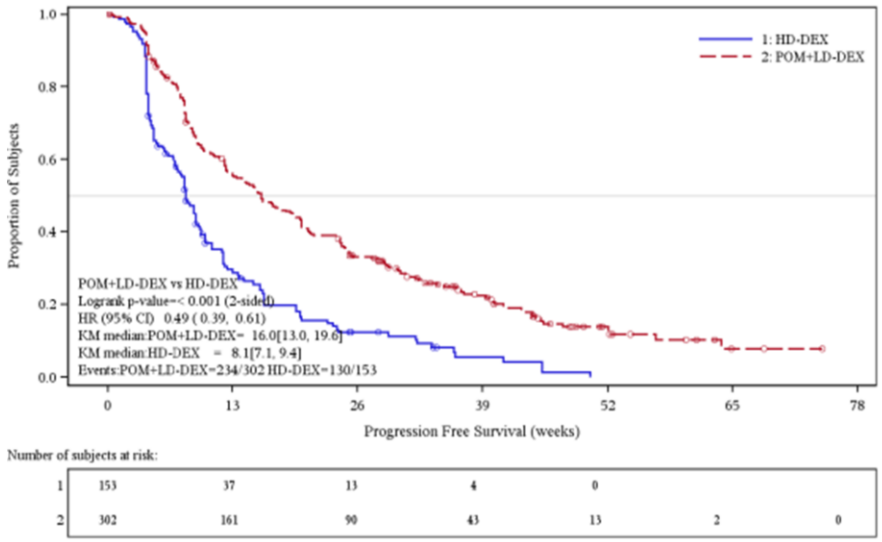
MM-003: summary of ITT results

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 [p-value]	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 [p-value]	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 [p-value]	**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 [p-value]	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 [p-value]	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 [p-value]	0.53 (95% CI: 0.19 to 1.51)		0.52 (95% CI: 0.29 to 0.95)	

ERG commented that investigator-derived results are at greater risk of bias in an open-label trial for subjective outcomes.

MM-003 progression free survival

(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
(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)			

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56% (85/153) of patients on the HiDEX arm received subsequent therapy with POM

11 patients (7.2%) entered MM-003 companion study and received POM as they progressed on HiDEX

The remaining 74 patients (48.4%) received POM (with or without LoDEX) at the final analysis for PFS and the interim analysis for OS based on the IDMC recommendation that people in the HiDEX group who had not progressed should have the option to receive POM.

MM-003: subsequent anti-myeloma treatment

Patients in both treatment groups in MM-003 went on to receive a range of other therapies

Subsequent therapy, n (%)[a]	POM+LoDEX (N = 302)	HiDEX (N = 153)
≥1 subsequent anti-myeloma drug	134 (44.4)	92 (60.1)
Pomalidomide	1 (0.3)	74 (48.4)[b]
Dexamethasone	88 (29.1)	36 (23.5)
Cyclophosphamide	64 (21.2)	17 (11.1)
Bortezomib	54 (17.9)	24 (15.7)
Bendamustine	34 (11.3)	13 (8.5)

Source: Company submission, table 28 (page 84)

Note:

a. Patients may have received more than one of the subsequent treatments listed therefore numbers listed for individual drugs do not necessarily correlate with the total number of patients receiving ≥1 subsequent anti-myeloma drug.

b. An additional 11 patients crossed over to the POM+DEX arm during the study after IDMC review

MM-003: Health-related quality of life

- HRQoL was reported from the 01 March 2013 data cut (433 patients of 455)
  - Song 2015 publication for a cross-sectional analysis and a longitudinal analysis
  - Wiesel 2015 publication for a logistic regression analysis and an assessment of minimally important difference (MID)
- 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

Results

- In a longitudinal analysis, using repeated measure mixed-effect models, significant ($p<0.05$) overall treatment differences between POM+LoDEX and HiDEX over the course of treatment in seven of the eight pre-selected clinically relevant domains
- In repeated-measures logistic regression analyses five out of eight domains demonstrated a trend or statistically significant improvement in OR favouring POM+LoDEX versus HiDEX
- A mixed-model analysis of the EQ-5D utility index score showed that there was a significant effect for treatment ($p=0.005$) on utility

MM-003: Adverse effects of treatment

- Discontinuation of POM+LoDEX because of an AE was uncommon (8.6% versus 10.5% in the HiDEX group)
- There were 11 (4%) treatment-related deaths in the POM+LoDEX arm:
  - eight cases of infections and infestations
  - two cases of multi-organ failure or sudden death
  - one nervous system disorder:
- There were seven deaths (5%) in the HiDEX arm due to infections and infestations
- Patients experiencing ≥1 adverse reaction similar between pomalidomide (99.0%) and dexamethasone (99.3%)
- Grade 3 or 4 adverse reactions reported in 86.3% and 84.7% of patients taking pomalidomide or dexamethasone
- 183 (61.0%) patients in the POM+LoDEX arm and 80 (53.3%) patients in the HiDEX arm experienced at least one serious AE
- Dose interruptions more common than dose reductions in pomalidomide group (67.0% compared with 27.3%)
- Dose reductions more common than dose interruptions in HiDEX group (32.7% compared to 30%)
- Company presented additional safety data from MM-010 STRATUS and MM-001 studies.

MM-003: Subgroup analyses

based on age, disease population and number of prior therapies

Results of PFS analysis by subgroup:

- Consistent with ITT population, PFS subgroup results showed statistically significant benefit for POM+LoDEX versus HiDEX in the majority of subgroups
- POM+LoDEX significantly improved PFS irrespective of whether refractory to previous therapies
- Irrespective of previous exposure to anti-myeloma therapies, POM+LoDEX significantly improved PFS based on IMWG criteria

Results of OS analysis by subgroup:

- OS subgroup analysis was also generally consistent with the overall ITT population
- Patients who received 2 prior anti-myeloma therapies demonstrated lower OS for both the POM+LoDEX and HiDEX groups compared with the overall ITT population, however, the company highlighted that patient pool is small (n=25)

Results of response analysis by subgroup:

- Across the range of subgroups, POM+LoDEX produced higher response rates compared with HiDEX

ERG comments: MM-003

- 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

Overview of supporting RCTs

Study	Intervention	Comparator	Population
MM-002, open label, phase 2	POM+LoDEX (n=113) Data used in indirect comparison	POM (n=108)	Patients with RRMM with ≥2 lines of previous therapy (median 5 therapies) including LEN and BOR
IFM 2009-02: Leleu et al., 2013	POM (21/28 day)+LoDEX (n=43)	POM (28/28 day)+LoDEX (n=41)	Relapsed MM ≥1 previous therapy *n.b. population under appraisal RRMM ≥2 previous therapies*
Baz et al., 2016 Phase 2	POM+LoDEX (n=36)	POM+DEX+ cyclophosphamide (n=34)	Patients with RRMM with ≥2 prior therapies and LEN refractory *n.b. Only 75% were also refractory to bortezomib*
Source: ERG report, table 4.2 (page 38)			

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Overview of supporting non-RCTs

- 9 non-RCTs, but only MM-010 used to inform indirect comparison and model
- MM-010: n=682, open label, single arm, phase 3b study
  - POM+LoDEX in patients with RRMM, refractory to last prior therapy, had received ≥2 prior therapies and had previous BOR and LEN treatment failure

Results of supporting non-RCTs (MM-010) (1)
overall survival and progression-free survival – ITT population

Outcomes	ITT population	Patients refractory to LEN	Patients refractory to BOR	Patients refractory to LEN and BOR	ITT population ≤3 prior lines	ITT population >3 prior lines
PFS, median, months	4.6	4.6	4.2	4.2	3.9	4.6
	(95% CI: 3.9, 4.9)	(95% CI: 3.8, 4.9)	(95% CI: 3.8, 4.8)	(95% CI: 3.8, 4.7).	[95% CI: 3.7, 5.1];	[95% CI: 4.0, 5.3]).
OS, median, months	11.9	11.9 months (95% CI: 10.6, 13.4)			12.8	11.9
	(95% CI: 10.6, 13.4)				(95% CI: 8.9, 18.4)	(95% CI: 10.6, 13.0)
Source: Company submission, page 127 and 128						

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The company concluded that:

- MM-010 study is the largest study conducted to date with POM+LoDEX in a heavily pre-treated RRMM patient population
- Result support the previous studies with POM+LoDEX in demonstrating that the combination is an effective treatment for heavily pre-treated patients with RRMM who have exhausted currently available treatment options
- In the 80% of patients who were refractory to both LEN and BOR clinical benefits were similar to the overall population, supporting the sequential use of these treatment regimens

The ERG noted:

- The trial relates to 4th line
- 93.4% of the patients in this trial had received over 2 therapies
- Results are presented by the company for ≤ 3 therapies and > 3 therapies but not for ≤ 2 therapies presumably due to the small numbers.

Real world evidence
aim to increase comparator evidence

- Retrospective data collection (n=150)
- All patients must have received at least 2 prior treatments
  - ≥ 2 consecutive cycles of LEN and BOR (alone or in combination)
  - Adequate prior alkylator treatment (SCT or ≥6 cycles or PD after ≥2 cycles)
- All patients must have progressed on BOR and LEN
- All patient should have been prescribed and progressed on one of the following at 3rd line onwards
  - BTD
  - BOR (retreatment)
  - POM+LoDEX
- Company stated that substantial protocol deviation occurred and there were major differences between treatment groups re. age, median number of prior treatments and amount of subsequent treatment received
  - results not considered to be informative

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The ERG agrees that the data from the UK RWE study are not comparable to the data from the pomalidomide RCTs and therefore could not be used to provide additional evidence for the comparator treatments.

Indirect and mixed treatment comparisons (1)

- No direct comparative evidence with 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

- 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

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MUK-one study which compared 60 mg/m^2 bendamustine with 100 mg/m^2 bendamustine in patients with RRMM. All patients in both arms received oral thalidomide 100 mg on days 1-28 and oral dexamethasone 20 mg on days 1, 8, 15 and 22 of each 28 day cycle

The company also included data from a subset of RRMM patients in the Gooding study who were refractory to both bortezomib and lenalidomide and who had received BTDdamustine+thalidomide+dexamethasone (BTD).

Furthermore, data were included from the Tarant study in patients who had progressive disease or were intolerant after having sequentially received thalidomide based, bortezomib based and lenalidomide based combination therapy.

Individual patient data (IPD) were obtained from each of the MUK-one, Gooding and Tarant studies. Patient data were selected for inclusion in the analysis if they had received bendamustine base

The PANORAMA-2 study was a '*two-stage, single-arm, open-label multicentre study of oral panobinostat in combination with bortezomib and dexamethasone*' in '*adult patients>18 years of age with relapsed and bortezomib-refractory MM (progressed on or within 60 days of the last bortezomib-containing regimen) who had received at least 2 prior lines of therapy and had been exposed to an IMiD* [immunomodulatory drug]d treatment, were refractory to prior bortezomib and lenalidomide and reported data for all of a set of key prognostic factors (Section 4.10.2 of the CS)

POM+LoDEX compared with BTD

- Base case: individual patient data from MM-002, MUK-one, Gooding and Tarant studies
  - sensitivity analysis including data from all three POM+LoDEX studies (MM-002, MM-003, MM-010) reported but results considered conservative
- Series of patient level parametric survival regression models were fitted to the data, adjusting for potential prognostic factors
  - presented adjusted and unadjusted results for both OS and PFS
- Overall survival results
  - 16.5 months (12.6, 19.8) vs 8.1 months (5.3, 13.5)
  - Unadjusted hazard ratio (HR) was 0.55 (95% CI 0.38 to 0.81) compared to 0.58 (95% CI 0.36 to 0.94) in the covariate adjusted analysis
  - inclusion of additional POM+LoDEX data from MM-003 and MM-010 reduced BTD benefit: unadjusted HR 0.68 (95% CI 0.51 to 0.92), adjusted HR 0.64 (95% CI 0.45 to 0.91);
- PFS results
  - 4.2 months (3.7, 5.8) vs 3.3 months (2.5, 5.5)
  - unadjusted HR 0.76 (95% CI 0.56 to 1.05) compared to 0.79 (0.52 to 1.22) in the adjusted analysis
  - inclusion of MM-003, MM-010 data did not substantially alter results

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Following the selection process the CS reported that the following covariates were included in the final analysis:

'Treatment arm [POM+LoDEX/BTD]

Age at the start of treatment [continuous]

Number of prior lines of therapy [continuous]

Receipt of prior THAL [Yes/No]

Refractory to LEN [Yes/No]

ISS stage [1/2/3]'

The MM-002 trial alone was selected for use for POM+LoDEX within the base case analysis due to the lower levels of refractoriness exhibited within this trial (78%) compared to the remainder of the POM+LoDEX data (95%). This lower level of refractoriness was considered more comparable to the BTD data (18-25%) across sources. As this covariate was identified as most prognostically important by clinicians and is difficult to adjust for with the current datasets (given that the overlap between datasets is low) it was considered more important to select the more comparable dataset for analysis than to retain the maximum number of patients for analysis in the POM+LoDEX arm.

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

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Additionally, the company acknowledged the following limitations (see page 112 of company submission)

• This approach of modelling data arising from several data sources breaks randomisation

• There is a notable amount of heterogeneity observed between studies in terms of patient demographics and study design (combination of observational, Phase II and III trial data).

• MM-003 – documented OS time for two patients was shorter than their recorded PFS time, due to withdrawal of consent. In this case, these patients' OS time was substituted with their PFS time.

• It is possible that not all influential prognostic factors were captured, for example, ISS stage is not recorded in MM-002 or Gooding, meaning that additional sensitivity analyses are required to attempt to tease out the covariate effect versus removal of data sources.

• Subsequent therapy information was not captured within either the MUK-One or Tarant datasets meaning that any differences in subsequent therapy use could not be assessed.

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: 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

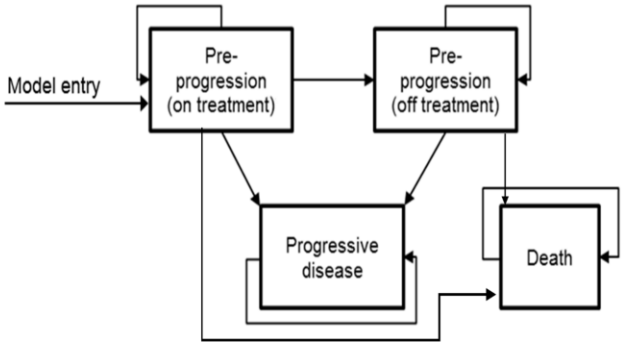
Cost effectiveness evidence

company submission chapter 5

Company model

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%

Compared with TA338, incorporates the more recent datasets from MM-003, MM-002, MM-010, MUK-One and PANORAMA-2

Disease progression was based on the Independent Response Adjudication Committee (IRAC) review by International Myeloma Working Group (IMWG) criteria.

The proportion of patients on treatment is calculated using time to treatment failure (TTF) rates.

TTF is defined as the earliest of progression, death, treatment discontinuation or withdrawal.

	Issues in TA338	How current submission addresses this
Comparative effectiveness data	Very few data identified for current care	Updated data included
Assumptions regarding equivalence of comparators	Disagreed with assumption of equal effectiveness	Comparator specific data for 2 comparators now available
Relative benefit of current care vs HiDEX	Concerns that predictions for current care estimated lower survival than for HiDEX, which was considered sub-optimal treatment	This unexpected result is no longer seen with the new evidence identified for BTD
Adjustment of trials to provide comparable estimates	Differences in patient characteristics meant that the populations in the studies included for analysis were not considered comparable	Adjustment for differences in patient characteristics has been conducted based upon a thorough covariate selection process ability to adjust is still limited
AEs	The Committee considered the cut-off point to include disutility values only for AEs that occurred in more than 2% of patients on the POM+LoDEX arm to be arbitrary.	The 2% cut off is considered for the MM-003 trial as this is the most granular and consistent data available. A 2% cut-off was selected for clinical trial reporting (and therefore also for modelling).
Dosing	Assumption that unused tablets of POM+LoDEX due to non-protocol interruptions were fully recovered by the NHS was not justified properly and it may not hold in clinical practice	It is now assumed that unused tablets are not recovered by the NHS. Only dose interruptions that would result in an entire pack not being used are assumed not to incur costs

Company model: base case sources of data and covariates

	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

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. CGP estimates OS for every possible combination of covariates found in the dataset and calculates a weighted OS curve using the proportion of patients with each combination of covariates.

MM-002 baseline is more in line with the bendamustine trials.

*The ERG highlighted that the matched adjusted indirect comparison (MAIC) HR was conducted on the MM-003, MM-002, MM-010 and PANORAMA trial dataset but this HR is applied on the POM+LoDEX curve that was based on MM-002, MM-003, MM-010 and all bendamustine trials data.

Company model: base case survival curves

	POM+LODEX vs BEN	POM+LODEX vs PANO+BOR+DEX	Conventional chemotherapy
OS	Exponential curve with baseline characteristics as covariates used to extrapolate using unadjusted KM data taken from MM-002, MUK-ONE, Gooding and Tarant	Generalised gamma curve considered most appropriate for POM+LoDEX using unadjusted KM data (taken from MM-003, MM-002, MM-010, MUK-ONE, Gooding and Tarant). Then HR based on MAIC is applied on POM+LoDEX OS (MAIC uses a subset of patient level data taken from MM-003, MM-002 and MM-010 and pseudo patient level data from PANORAMA-2)	Exponential curve adjusted using two stage Weibull approach provided best fit for OS data (taken from MM-003)
PFS	Generalised gamma curve with baseline characteristics as covariates used to extrapolate using unadjusted KM data taken from MM-002, MUK-ONE, Gooding and Tarant	Generalised gamma curve considered most appropriate model for POM+LoDEX using unadjusted KM data (taken from MM-003, MM-002, MM-010, MUK-ONE, Gooding and Tarant). Then HR based on MAIC is applied on POM+LoDEX PFS (MAIC uses a subset of patient level data taken from MM-003, MM-002 and MM-010 and pseudo patient level data from PANORAMA-2)	Generalised gamma curve considered most appropriate using KM data taken from MM-003
TTF	A common treatment effect based on MM-002 and BTD trials applied to PFS (hence generalised gamma)	A common treatment effect based on MM-002, MM-003 and MM-010 and BTD trials was applied to PFS (hence generalised gamma), only for POM+LoDEX.	Extreme value curve

Six parametric distributions (exponential, log-normal, log-logistic, Gompertz, gamma and Weibull) were examined for each clinical outcome (OS, PFS and TTF). The fit of each parametric model to the covariate adjusted survival data was explored using visual inspection, LCHPs, Q-Q plots, Akaike information criterion (AIC) and Bayesian information criterion (BIC) goodness of fit statistics and clinical plausibility.

Source: Company submission, section 5.3.8 to 5.3.14 (page 174 to 185)

Key assumptions

Patients receive the fixed dose regimen associated with PANO+BOR+DEX
Prior to response being modelled at 12 weeks, all patients are in the pre-progression health state and have a stable disease relative to response
Utility benefit associated with response is maintained for the duration of the model
AE rates are proportional to the relative proportion of patients discontinuing from treatment due to an AE
Quality of life impact associated with AEs is captured within the original utility regression estimated using MM-003 data
Only whole packs can be recovered and that only whole packs can be used
No vial sharing for BOR
Hospitalisation rates of the comparators are equal to the HiDEX arm of the MM-003 trial
Resource use associated with conventional chemotherapies is the same as that for BTD
The only difference in concomitant medication use is in G-CSF use
No subsequent therapies following discontinuation of treatment

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Along with the above, the company also made the following assumptions:

- that the differences in patient characteristics across trials when comparing to BTD and PANO+BOR+DEX can be at least partially accounted for via covariate adjustment
- that the efficacy and safety results observed in the MM-003 study for POM+LODEX versus HiDEX are equivalent for comparison to conventional chemotherapy regimens
- that the proportional hazards assumption allows for reasonable comparison for BTD and PANO+BOR+DEX compared with POM+LoDEX

Adverse events

- Treatment emergent adverse events (TEAEs) Grade 3/4 were included in the economic analysis if they occurred in at least 2% of POM+LoDEX and Hi-DEX patients in the MM-003 trial dataset.
- In the base case, the AE rates observed for POM+LoDEX were also used for the comparators, though multiplied by correction factors. These correction factors were based on the ratio of the TEAE discontinuation rate for each comparator and the TEAE discontinuation rate of POM+LoDEX in the MM-003 study.
  - Assumes that AE rates are proportional to the relative proportion of patients discontinuing from treatment due to an AE
- In a scenario analysis, relative safety scores provided by an advisory board were applied to the POM+LoDEX data sourced from MM-003

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

Resource and costs

- The model assumed that a treatment interruption of less than 28 days would not lead to cost savings, as it is unlikely that the remaining drugs could be recovered by the NHS
- However, for interruptions longer than 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
- For the monitoring costs, concomitant medication costs, 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.

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See table 56, page 223 in company submission for costs

*The ERG noted that there was variation in terms of the frequency of tests in relation to monitoring costs, concomitant medication costs, and adverse event costs.

Comparison of the clinical outcomes with the 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

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*This overall survival result is after adjustment from MM-003

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The ERG states that there are some remarkable differences between trial outcomes and model outcomes, especially in the PFS results of BTD and PANO+BOR+DEX. However, it should also be noted that the model estimates of PANO+BOR+DEX PFS, were based on the baseline covariate adjustments according to a dataset that consists of POM+LoDEX (MM-002, MM-003 and MM-010) and BTD trials. For a better reflection, it would have been more informative if the trial results were compared with the model results which were based on covariate adjustments according to the baseline characteristics of that trial.

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

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
POM+DEX vs BTD							
BTD	[redacted]	1.14	[redacted]	-	-	-	-
POM+LoDEX	[redacted]	1.81	[redacted]	[redacted]	0.67	[redacted]	£39,665
POM+DEX vs PANO+BOR+DEX							
PANO+BOR+DEX	[redacted]	2.05	[redacted]	-	-	-	-
POM+LoDEX	[redacted]	1.55	[redacted]	[redacted]	-0.49	[redacted]	[redacted]
POM+DEX vs conventional chemotherapy (CC)							
CC	[redacted]	0.78	[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). For POM+DEX vs PANO+BOR+DEX: ERG confidential appendix, table 3 (page 6)

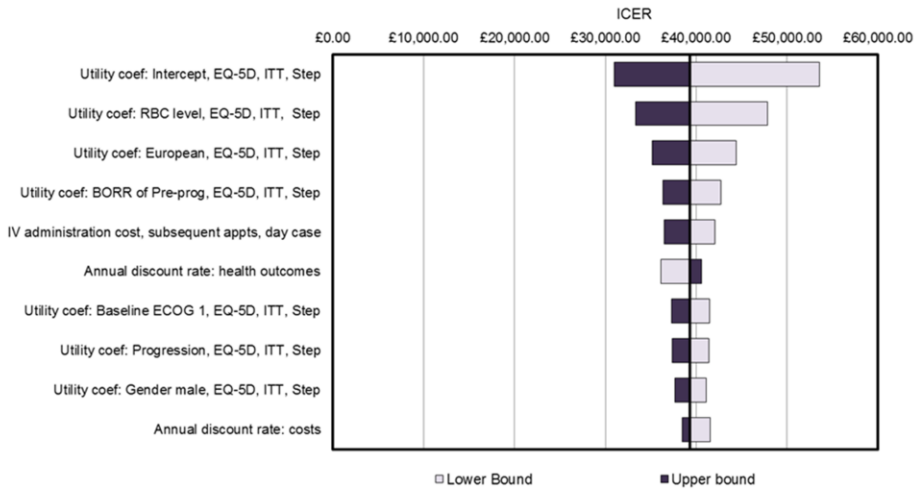
At the clarification stage the ERG identified programming errors and the company presented updated results which are in the table above. These results are presented above. However, the ERG subsequently identified further errors and further updated the company's results to reflect these corrections. These results are presented in the ERG section.

Please note that the POM+DEX vs PANO+BOR+DEX comparison is based on confidential PAS's for both pomalidomide and panobinostat.

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 [redacted] (deterministic base-case ICER **£39,665**)
POM+DEX vs PANO+BOR+DEX
Mean incremental QALYs [redacted]
Mean incremental costs [redacted]
Probabilistic ICER was [redacted](deterministic base-case ICER [redacted])
POM+DEX vs conventional chemotherapy (CC)
Mean incremental QALYs [redacted]
Mean incremental costs [redacted]
Probabilistic ICER was [redacted] (deterministic, base-case ICER of **£44,811**)

Company's deterministic sensitivity analyses - BTD

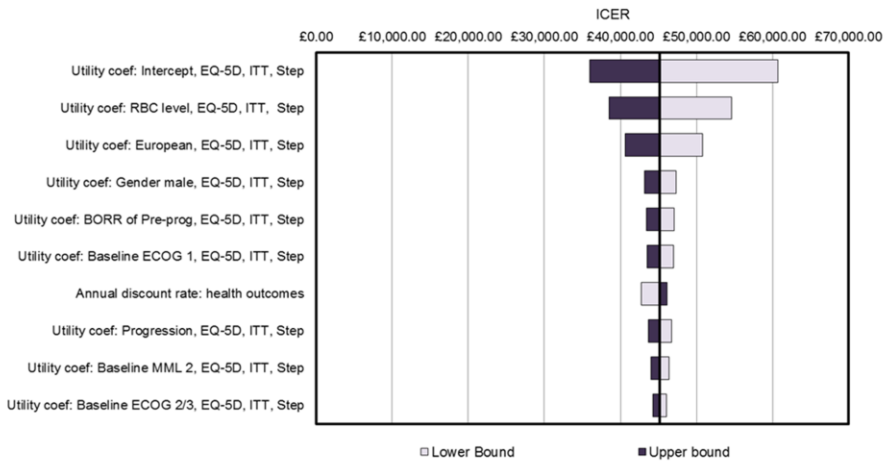


Company's deterministic sensitivity analyses - PANO+BOR+DEX

- 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

Please note, this figure (taken from the ERG confidential comparator PAS appendix, page 4) is commercial in confidence (CiC)

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



Company's scenario analyses - BTD

Scenario	Incremental Costs	Incremental QALYs	ICER
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

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Source: ERG report, table 5.32 (page 143)

The scenarios above had the greatest effect on the ICER. For full details of the scenario analyses please see section 5.8.3 of the company submission.

Company's scenario analyses - PANO+BOR+DEX

Scenario	Incremental Costs	Incremental QALYs	ICER
5 year time horizon	[redacted]	[redacted]	[redacted]
Weibull (OS curve choice)	[redacted]	[redacted]	[redacted]
Gompertz (OS curve choice)	[redacted]	[redacted]	[redacted]
Exponential (OS curve choice)	[redacted]	[redacted]	[redacted]
Weibull (PFS curve choice)	[redacted]	[redacted]	[redacted]
Mean covariate method used	[redacted]	[redacted]	[redacted]
Exponential (PFS curve choice)	[redacted]	[redacted]	[redacted]

Source: ERG confidential comparator PAS appendix, table 2 (page 5)

The scenarios above had the greatest effect on the ICER. For full details of the scenario analyses please see section 1.2.4 of the ERG confidential appendix.

Company's scenario analyses - CC

Scenario	Incremental Costs	Incremental QALYs	ICER
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

Source: ERG report, table 5.34 (page 146)

The scenarios above had the greatest effect on the ICER. For full details of the scenario analyses please see section 5.8.3 of the company submission.

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

- 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

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

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Some of the parameters in the model delivered after clarification were not included in the sensitivity analyses (e.g. PFS/ OS and TTF HRs for CC, which were derived from MM-003) or the administration costs of the IV chemotherapy drugs. The ERG considers that not incorporating these variables in the probabilistic sensitivity analysis will lead to an underrepresentation of uncertainty in the model.

ERG comments – cost effectiveness (1)

- Model structure appropriate
- In the model, proportion of lenalidomide refractory patients, proportion of patients that received thalidomide and previous number of therapy lines are used in OS/PFS calculations
  - 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
  - considered acceptable, as data would be lacking for such stratification
- Fully incremental results should be considered rather than pairwise comparisons

ERG comments – cost effectiveness (2)

- Even though efforts were made to correct for differences in baseline covariates between data sets, there can be still some unmeasured confounders that add uncertainty to the effectiveness results
- A different dataset is used for each of the three comparisons. This implies a slightly different population for each comparison, without being able to clearly define these sub populations
- Concerns related to the implementation of AEs.
  - The TEAE discontinuation probabilities for each comparator were derived from disconnected parallel trials without any adjustments for baseline characteristic differences
  - Mirrors the frequency order of the AEs of POM+LoDEX for each of the comparators, in the same magnitude.
- Approach taken by the company to include HRQL is largely the same as the approach used for TA338 - appropriate
  - However, data about the exploratory variables (i.e. BORR, hospitalization and adverse events) has its limitations which might cause bias in the estimation of utilities

ERG comments – cost effectiveness (3)

- Current submission has re-estimated various types of resource use compared to TA338
  - error in the model on the transformation of yearly resource use for monitoring to weekly number that underestimates monitoring costs which also affects the ICERs
- Input parameters derived from the resource use questionnaire should be considered with care
  - difficult to fill in, and only six clinical experts completed it
- Model allows for a decrease in treatment costs based on treatment interruptions lasting longer than 28 days
  - However, only done for POM+LoDEX and not available for the other comparators creating an inconsistency (this was amended by the company providing a new model)
- 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 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]	-	-	-	-
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]	[redacted]
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]	-	-	-	-
POM+ LoDEX	[redacted]	1.43	[redacted]	[redacted]	0.68	[redacted]	£48,673
Source: ERG report, Table 5.38 (page 151) and ERG confidential PAS appendix, table 3 (page 6)							

ERG's confidential comparator PAS appendix (page 7).

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]	[redacted]
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) and ERG confidential appendix, table 6 (page 8)

See ERG report pages 151-153 for results using alternative methods.

See ERG confidential comparator PAS appendix, table 7 (page 9)

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

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]	[redacted]	[redacted]	[redacted]	£44,811
ERG correction programming errors	[redacted]	[redacted]	£45,082	[redacted]	[redacted]	[redacted]	[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]	[redacted]	[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]	[redacted]	[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]	[redacted]	[redacted]	[redacted]	£59,104

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

Equality issues

- No equality issues were raised

Innovation

- 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

Issues for consideration

Clinical effectiveness

- 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?
- What is the committee's view on the adverse event profile of pomalidomide?

Issues for consideration

Cost effectiveness

- 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?
- Estimation of resource use: taken from an extensive questionnaire filled in by six clinical experts. Is this sufficiently representative?
- Should subsequent treatment costs be included?
- Decrease in treatment costs: the model allows a decrease based on based on treatment interruptions lasting longer than 28 days. Data were available for POM+LoDEX and PAN but not BOR, BTD and CC. Is this approach appropriate?
- What are the committee's preferred methods for estimating parametric curves and obtaining hazard ratios?

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of pomalidomide within its marketing authorisation for treating relapsed and refractory multiple myeloma previously treated with both lenalidomide and bortezomib.

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[1]. Forty-three percent of people diagnosed are aged 75 years and over[1]. 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[1]. The 5-year survival rate for adults with multiple myeloma in England is estimated to be 47%[2]. The main aims of therapy are to prolong survival and maintain a good quality of life by controlling the disease and relieving symptoms.

For initial treatment:

- NICE technology appraisal guidance 311 recommends bortezomib as an option, in combination with dexamethasone or with dexamethasone and thalidomide, for the induction treatment of adults with untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

- When stem-cell transplantation is not suitable, NICE technology appraisal guidance 228 recommends thalidomide or bortezomib (only if the person is unable to tolerate or has contraindications to thalidomide)

as an option, in combination with an alkylating agent (melphalan or cyclophosphamide) and a corticosteroid (prednisolone or dexamethasone).

Following initial treatment, the choice of subsequent therapy is influenced by previous treatment and response to it, duration of remission, comorbidities and patient preference. For people whose disease is relapsed or refractory after at least 1 prior therapy:

- NICE technology appraisal guidance 129 recommends bortezomib monotherapy as an option for treating progressive multiple myeloma in people who are at first relapse and who have undergone, or are unsuitable for, bone marrow transplantation.

- An ongoing NICE technology appraisal is assessing lenalidomide for treating multiple myeloma after 1 prior treatment with bortezomib.

For people who have had at least 2 prior therapies:

- NICE technology appraisal guidance 171 recommends lenalidomide in combination with dexamethasone as a treatment option.

- NICE technology appraisal guidance 380 recommends panobinostat in combination with bortezomib and dexamethasone as a treatment option for people with relapsed and refractory multiple myeloma who have received at least 2 prior therapies 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 conventional chemotherapy regimens (for example, alkylating agents such as melphalan and cyclophosphamide).

NICE technology appraisal guidance 338 does not recommend pomalidomide within its marketing authorisation for treating relapsed and refractory multiple myeloma. NICE has decided to review technology appraisal 338 because:

- new clinical evidence is available
- the company is proposing a patient access scheme for pomalidomide.

The technology

Pomalidomide (Imnovid, Celgene) is an oral immunomodulatory drug analogue of thalidomide that directly inhibits myeloma growth.

Pomalidomide in combination with dexamethasone has a marketing authorisation in the UK for ‘the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 2 prior treatment

regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on last therapy'.

Intervention(s)	Pomalidomide in combination with dexamethasone
Population(s)	Adults with relapsed and refractory multiple myeloma who have had at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and whose disease progressed on the last therapy
Comparators	For people who have had 2 prior therapies: • panobinostat in combination with bortezomib and dexamethasone For people who have had 3 or more prior therapies: • panobinostat in combination with bortezomib and dexamethasone • 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) • conventional chemotherapy regimens (for example, melphalan and cyclophosphamide)
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • 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. When appropriate, validation of the economic model may use comparators included in the clinical trial that are not listed in the 'Comparators' section above.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Panobinostat for treating multiple myeloma after at least 2 previous treatments' (2016). NICE Technology Appraisal 380. Review date January 2019. 'Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib' (2015). NICE Technology Appraisal 338. 'Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation' (2014). NICE Technology Appraisal 311. Review date February 2017. 'Bortezomib and thalidomide for the first-line treatment of multiple myeloma' (2011). NICE Technology Appraisal 228. Guidance on static list. 'Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy' (2009). NICE Technology Appraisal 171. Guidance on static list. 'Bortezomib monotherapy for relapsed multiple myeloma' (2007). NICE Technology Appraisal 129.

	Guidance on Static list. Appraisals in development: 'Carfilzomib for previously treated multiple myeloma' NICE technology appraisal [ID934]. Publication date April 2017. 'Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma' NICE technology appraisal [ID807]. Publication date January 2017. 'Lenalidomide for treating multiple myeloma after 1 prior treatment with bortezomib (part-review of TA171)' NICE technology appraisal [ID667]. Publication date to be confirmed. Clinical guidelines: 'Myeloma: diagnosis and management of myeloma' (2016). NICE guideline 35. Related NICE Pathways: NICE pathway: Myeloma (2016) http://pathways.nice.org.uk/pathways/myeloma
Related National Policy	NHS England (2015) 'Cancer Drugs Fund list v6.1' NHS England Manual for prescribed specialised services 2013/2014. Blood and marrow transplantation services (all ages) [section 29, page 78–79]: http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1, 4–5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

References

1. Cancer Research UK (2013). Multiple myeloma incidence statistics. Accessed February 2016.

2. Cancer Research UK (2011). Multiple myeloma survival statistics. Accessed February 2016.

APPENDIX C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Final matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
<u>Company</u> • Celgene (pomalidomide) <u>Patient/carer groups</u> • Black Health Agency • Bloodwise • Cancer Black Care • Cancer Equality • Cancer52 • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Leukaemia Cancer Society • Leukaemia CARE • Lymphoma Association • 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 <u>Professional groups</u> • 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 • Royal College of Nursing • Royal College of Pathologists	<u>General</u> • 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 <u>Comparator manufacturers</u> • Aspen (melphalan) • Baxter (cyclophosphamide) • Napp pharmaceuticals (bendamustine) • Novartis Pharmaceuticals (panobinostat) • Pfizer (cyclophosphamide) <u>Relevant research groups</u> • Clinical Trials Research Unit • Cochrane Haematological Malignancies Group • Elimination of Leukaemia Fund • Institute of Cancer Research • Leuka • Leukaemia Busters • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network

• Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • UK Clinical Pharmacy Association • UK Health Forum • UK Myeloma Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS England • NHS North Staffordshire CCG • NHS Redbridge CCG • Welsh Government	• National Collaborating Centre for Cancer • 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 not. 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 experts 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 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;; 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 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

Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib (review of TA338) [ID985]

Company evidence submission

8 July 2016

File name	Version	Contains confidential information	Date
IMNOVID NICE 08July16 Final CIC		Yes	8 July 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.

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Abbreviations

AE	Adverse event
AF	Acceleration factor
AFT	Accelerated failure time
AIC	Akaike information criterion
APC	Antigen-presenting cell
ASCT	Autologous stem cell transplant
ATE	Arterial thrombotic event
AWMSG	All Wales Medicines Strategy Group
BCSH	British Committee for Standards in Haematology
BEN	Bendamustine
BIC	Bayesian information criterion
BOR	Bortezomib
BORR	Best overall response rate
BSA	Body surface area
BTD	Bendamustine + thalidomide + dexamethasone
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curves
CFZ	Carfilzomib
CGP	Corrected group prognosis
CI	Confidence interval
cm	Centimetre
CR	Complete response
CrCl	Creatinine clearance
CSR	Clinical study report
CTD	Cyclophosphamide + thalidomide + dexamethasone
CYC	Cyclophosphamide
Del	Chromosomal deletion
Den	Denominator
DEX	Dexamethasone
Df	Degrees of freedom
DOR	Duration of response
DSU	Decision Support Unit
EBMT	European Society for Blood and Marrow Transplantation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	drugs and pharmaceutical electronic market information

EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European public assessment report
EQ-5D	EuroQoL five dimensions
ERG	Evidence review group
EU	European union
FAD	Final appraisal determination
FDA	Food and Drug Administration
G-CSF	Granulocyte colony stimulating factor
GEE	Generalised estimating equation
GFR	Glomerular filtration rate
HiDEX (HD-Dex)	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
IDMC	Independent data monitoring committee
IFN	interferon alpha
IMiDs®	Immunomodulatory drugs
IMWG	International Myeloma Working Group
IPD	Individual patient data
IRAC	Independent response adjudication committee
ISS	International Staging System
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
KM	Kaplan-Meier
LCHP	Log cumulative hazard plot
LDH	Lactate dehydrogenase
LEN	Lenalidomide
LoDEX (LD-Dex)	Low-dose dexamethasone
MAIC	Matched adjusted indirect comparison
MedDRA	Medical Dictionary for Regulatory Activities
MEL	Melphalan
MGUS	Monoclonal gammopathy of undetermined significance
MHRA	Medicines and Healthcare Products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
ml	millilitre
MP	Melphalan + prednisone

MPT	Melphalan + prednisone + thalidomide
MR	Minimal response
MTC	Mixed treatment comparison
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCT	National clinical trial
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NK	Natural killer
NMB	Net monetary benefit
NR	Not reported
ONS	Office of National Statistics
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAMT	Prior anti-myeloma therapy
PANO	Panobinostat
PAS	Patient access scheme
PD	Progressive disease
PFD	Progression-free disease;
PFS	Progression-free survival
PI	Protease inhibitor
PK	Pharmacokinetic
POM	Pomalidomide
PPP	Pregnancy prevention programme
PPS	Post-progression survival
PR	Partial response
PRED	Prednisone
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
QALY	Quality-adjusted life year
QLQ	Quality of life questionnaire
QoL	Quality of life
RANKL	Receptor activator for nuclear factor kB ligand
RBC	Red blood cell
RCT	Randomised controlled trial
RDI	Relative dose intensity
RPSFTM	Rank preserving structure failure time model

RRMM	Relapsed and refractory multiple myeloma
RWE	Real world evidence
SC	Subcutaneous
sCR	Stringent complete response
SCT	Stem cell transplantation
SD	Standard deviation
StD	Stable disease
SF-36	Short form 36
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SPM	Second primary malignancies
STA	Single technology appraisal
TA	Technology appraisal
TEAEs	Treatment-emergent adverse events
THAL	Thalidomide
TNF	Tumour necrosis factor
Trt Phase Dis	Treatment phase discontinuation visit
TS	Two stage method
TSG	Tumour suppressor gene
TTF	Time to failure
TTP	Time to progression
TTR	Time to response
VEGF	Vascular endothelial growth factor
VGPR	Very good partial response
VTE	Venous thromboembolism
WTP	Willingness to pay

1 Executive summary

1.1 Statement of decision problem

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	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	As defined in scope	N/A
Intervention	Pomalidomide (POM) in combination with dexamethasone (DEX)	As defined in scope	N/A
Comparator(s)	For people who have had 2 prior therapies: • Panobinostat (PANO) in combination with BOR and DEX For people who have had 3 or more prior therapies: • PANO in combination with BOR and DEX • Bendamustine (BEN) (not appraised by NICE but funded via the Cancer Drugs Fund; does not currently have a marketing authorisation in the UK for this indication) • Conventional chemotherapy regimens (for example, melphalan and cyclophosphamide)	As defined in scope: • PANO+BOR+DEX • BEN ± THAL retreatment ± steroid • Conventional chemotherapy (including cyclophosphamide & melphalan) ± THAL retreatment ± steroid	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • Overall survival (OS) • Progression-free survival (PFS) • Response rates • Adverse effects of treatment • Health-related quality of life (HRQL)	As defined in scope with the addition of time to treatment failure (TTF)	Time to treatment failure added as this is used to inform the economic model
Economic analysis	Reference case	As per reference case	N/A
Subgroups to be considered	None specified in final scope	N/A	N/A
Special considerations including issues related to equity or equality	None specified in final scope	N/A	N/A

Key: BEN, bendamustine; BOR, bortezomib; DEX, dexamethasone; HRQL, health-related quality of life; LEN, lenalidomide; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; POM, pomalidomide; RRMM, relapsed and refractory multiple myeloma; THAL, thalidomide; TTF, time to treatment failure.

Source: NICE, 2016.[1]

1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Pomalidomide (IMNOVID®▼)
Marketing authorisation/CE mark status	POM was granted EMA marketing authorisation on 05 August 2013. The EMA granted POM accelerated approval for the indication under appraisal citing its ability to prolong survival.[2, 3] POM received an orphan designation on 08 October 2009 for the indication "Treatment of Multiple Myeloma". The product is registered on the EU register of orphan drugs (EU number EU/3/09/672).
Indications and any restriction(s) as described in the summary of product characteristics	POM has a UK marketing authorisation for the following indication: POM in combination with DEX for the treatment of adult patients with RRMM who have received at least two prior treatment regimens, including both LEN and BOR, and have demonstrated disease progression on the last therapy.[4] POM treatment must not be initiated if the Absolute Neutrophil Count is <1.0 x 10^9/L, and/or platelet counts are <50 x 10^9/L.[4] The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.[4]
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.[4] The recommended dose of DEX is 40 mg orally once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle.
Key: BOR, bortezomib; DEX, dexamethasone; EMA, European Medicines Agency; LEN, lenalidomide; POM, pomalidomide; RRMM, relapsed and refractory multiple myeloma.	

1.3 Summary of the clinical effectiveness analysis

1.3.1 Disease burden

Multiple myeloma is an incurable, life-limiting disease requiring a long-term approach to care. The disease is characterised by a pattern of relapse and remission, and ultimately treatment failure.[5]

Many patients relapse after treatment because of the continued presence of resistant cells in the bone marrow, or discontinue therapy due to toxicity.[6-8]

1.3.2 Current treatments

Patients who have relapsed after treatment with both BOR and LEN have few treatment options.

Three treatments are included within the NICE scope for comparison: PANO+BOR+DEX, unlicensed treatment with BEN via the CDF, and unlicensed use of conventional chemotherapy regimens (e.g. cyclophosphamide and melphalan combinations).

Whilst providing an improvement in effectiveness versus BOR+DEX; PANO adds to the toxicity profile of BOR, already a toxic treatment option, and results in a poorer profile particularly in terms of fatigue, high-grade thrombocytopenia and diarrhoea.[9] The PANORAMA 1 trial demonstrated a significantly reduced HRQL for patients receiving PANO when compared to patients receiving BOR+DEX alone.[10] This combination is also not considered suitable for patients with neuropathy or poor response to prior BOR treatment, limiting use to a subgroup of fitter patients.[9]

Comparative effectiveness has not been demonstrated with BEN. Additionaly, patients struggle with the side effects of treatment, including cytopenias, fatigue and infection and, as a result, often stop treatment after only a few cycles.[9] Like BOR, BEN toxicity also tends to be cumulative, limiting its long-term use.[9] THAL, which is frequently used in combination with BEN, is associated with similar problems.

Whilst conventional chemotherapy regimens are still used, clinicians use BEN in preference as the toxicity of the conventional chemotherapy tends to be unacceptably high, and there are no real efficacy data at fourth and fifth line.[11] Conventional chemotherapy agents are therefore generally used as a final option.[11]

Most importantly, due to their toxicity profiles, none of these therapies can be considered as an option for long-term treatment.[9, 12-16]

Current treatments also add to patient burden, requiring IV or SC administration in a hospital setting for up to four hospital visits per month.[12, 13]

In this setting there is therefore a high unmet need for alternative oral treatment combinations, with a different mechanism of action and toxicity profile allowing for continuous treatment to suppress residual disease, this is particularly important for patients refractory to both BOR and LEN who may have limited treatment options.

1.3.3 Pomalidomide

Pomalidomide (POM) addresses this unmet need. POM is an innovative, oral immunomodulatory agent developed with the aim of improving efficacy and reducing toxicity. POM improves efficacy in patients who historically have had a poor prognosis and are hard to treat.[17-19] POM represents a step-change in the management of RRMM, with the following key characteristics, which are not demonstrated by current treatment options:

- **Effectiveness in particularly hard to treat patients:** POM is the first licensed treatment with Phase III data showing activity in disease refractory to both BOR and LEN.[17-19]
- **Favourable toxicity profile allowing continuous treatment to suppress residual disease:** Compared with BEN, PANO, THAL and BOR, POM has a different mechanism of action and toxicity profile (including a low incidence of peripheral neuropathy), which allows for continuous use to suppress residual disease and extended remission. Patients who achieved at least a partial response to POM+ low-dose (Lo)DEX experienced long-term survival with a median of 19.9 months.[20] In responders, the favourable toxicity profile and mechanism of action may leave the patient more able to benefit from subsequent therapies.[4, 9, 12-14, 17, 20-22]
- **Reduction in patient, carer burden and NHS resource use:** POM provides an alternative to intravenous (IV) and injectable therapies such as BEN and BOR, which are given in the hospital setting, thereby reducing treatment burden for patients and carers, allowing patients a greater sense of control over their lives, and relieving the pressure on busy haematology day units[4, 12, 14, 23] This benefit is particularly important for elderly, frail individuals, along with those patients who live far away from hospital.

1.3.4 Clinical trial outcomes for POM+LoDEX in patients with RRMM

A large body of evidence now exists to demonstrate the safety and efficacy of POM+LoDEX. In total, 1,097 patients were enrolled into the MM-002, MM-003 and MM-010 studies.[17-19] These studies are supported by a number of Phase II and observational studies relevant to UK clinical practice.[24-28]

The Phase III MM-003 trial is one of the largest randomised controlled (RCT) studies to date showing activity in disease refractory to both BOR and LEN. The European Medicines Agency (EMA) considered the study to be adequately designed to demonstrate the efficacy of POM+LoDEX against an appropriate comparator (high-dose [Hi]DEX).[2]

In study MM-003, POM+LoDEX demonstrated significant improvement compared to HiDEX (which can be considered similar in its effectiveness to conventional chemotherapy)[29] across a number of outcome measures:

- Significant improvement in PFS:
- Significant improvement in OS despite 56% of patients crossing over from HiDEX to POM:
- Significant higher ORR (≥PR)
- Significantly longer TTP and DOR
- TTP was also significantly longer than that achieved with their last line of therapy (HR, 0.79; *p*=0.008).[20] This outcome is particularly striking given that the usual pattern within multiple myeloma is that, with increasing lines of therapy, there is a decreasing DOR and TTP.[5, 8, 30]

The efficacy seen with POM may partly be attributed to its mechanism of action; in binding directly with cereblon (a component of the E3 ubiquitin-ligase complex), POM inhibits proliferation of LEN-resistant multiple myeloma cell lines. This, coupled with its immunomodulatory activity results in enhanced anti-tumour effects.[21, 31, 32]

POM+LoDEX is a well-tolerated treatment, which is of critical importance for a treatment that is given until disease progression.

Efficacy and safety outcomes were consistent across subgroups; in particular in the hardest to treat refractory patient population and in older age groups, demonstrating the ability of POM+LoDEX to meet the needs of a broad patient population.[17]

In study MM-003, the improvement in effectiveness did not come at the expense of HRQL. Longitudinal analysis using repeated measure mixed-effect models showed significant overall treatment differences between POM+LoDEX and HiDEX over the course of treatment in seven of the eight preselected clinically relevant domains. [33]

1.3.5 Comparison to UK current care

The lack of a relevant comparator in the Phase III MM-003 study makes comparison to the comparators listed in the decision problem difficult, especially given the lack of high quality evidence available for all three comparators in the relevant patient population.

This data gap was listed by the Committee within the original appraisal of POM+LoDEX (TA338) as a source of considerable uncertainty in the comparative effectiveness of POM+LoDEX versus UK current care.[34] Following this original appraisal, the systematic literature review (SLR) has been updated to try to address these evidence gaps, and in addition, extensive efforts were made to source UK patient data on the outcomes of patients receiving relevant treatments post LEN and BOR.

Following a thorough assessment of the evidence base, comparisons were made as follows:

- Comparison to PANO+BOR+DEX: via matched adjusted indirect comparison (MAIC) based upon the PANORAMA 2 trial,[35] which was in patients who had received prior BOR and in the majority (98%) prior LEN
- Comparison to bendamustine + thalidomide + dexamethasone (BTD): via a covariate-adjusted comparison using the patient level data sourced from data gathering exercises
- Comparison to conventional chemotherapy: via the use of HiDEX data as a proxy supported by the limited evidence available

For comparison to PANO+BOR+DEX and BEN both data selection and covariate adjustment techniques were used to attempt to reduce the impact of the differences across datasets on comparative effectiveness assessments. It should be noted that the ability of techniques such as MAIC and covariate-adjustment to account for differences in patient populations is limited by the size of the datasets available for comparators and the quality of reporting within comparator trials. Datasets available for comparators were relatively small (n<100) and reporting of potentially prognostic covariates of relatively poor quality.

Within the base case analysis comparative effectiveness estimates produced indicated:

- A 6.1 month difference in median OS, with a covariate-adjusted HR of 0.58 (95% CI [0.36, 0.94]; *p*=0.026) for POM+LoDEX versus BEN
- A 1 month difference in median PFS, with an adjusted HR of 0.79 (95% CI [0.52, 1.22]; *p*=0.291) for POM+LoDEX versus BEN
- Conflicting non-significant PFS and OS results in comparison to PANO+BOR+DEX;
    - OS HR for PANO+BOR+DEX vs POM+LoDEX of 0.778 (0.555, 1.090)
    - PFS HR for PANO+BOR+DEX vs POM+LoDEX of 1.178 (0.893, 1.555)

1.4 Summary of the cost-effectiveness analysis

POM+LoDex has been demonstrated to be a cost-effective treatment option against all the relevant comparators in UK clinical practice for patients with MM.

[redacted] This shows the commitment of Celgene to make POM available to patients in England and Wales.

The model uses a semi-Markov partitioned survival structure based upon progression status and whether or not the patient was on treatment. Model results were robust to sensitivity analysis with the key areas of uncertainty surrounding:

- The measure used for and 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
- The trial data used for comparison to BTD
- The magnitude of survival benefit compared to PANO+BOR+DEX
- Survival curve fit selection

The results from this submission provide more up to date and robust estimates making use of larger datasets than the previous NICE submission (TA338). This submission differs from the previous NICE submission (TA338) in that:

- It utilises substantially more data than the previous submission.
- Comparability of datasets has been increased by adjusting for covariates,it should be noted, however, that covariate adjustment cannot account for all differences between trials. The direction of bias is however, most likely against POM+LoDEX due to the high level of refractoriness and late line of therapy of patients in the POM+LoDEX trials.
- Resource use and AEs have been collected using a resource use questionnaire.
- The efficacy estimates for POM+LoDEX reported in this submission are notably lower in all comparisons than those reported in the previous NICE submission (TA338) due to the inclusion of additional long-term data to better inform survival curve fits which indicates a lower long-term survival estimate is likely more appropriate. The estimated life years and QALYs associated with PANO+BOR+DEX are similar to the NICE submission (TA380); 2.3 and [redacted] compared with 2.5 and 1.7 from this submission and TA380, respectively. It should be noted that the comparability of life years is a clear sign that the benefit of PANO+BOR+DEX is overestimated in this submission given that TA380 looked at use at third line in comparison to LEN.

POM+LoDEX is considered to meet the NICE end of life criteria in comparison to BEN and conventional chemotherapies:

- Median survival is 3-9 months across patients receiving current care in the UK.[36-40] Modelled mean survival is also < 14 months versus both BEN and conventional chemotherapy.
- The estimated survival benefit compared to BEN and conventional chemotherapy is > 5 months in all comparisons (covariate adjusted and unadjusted, crossover adjusted and unadjusted). Modelled mean survival increase is 7 – 8 months.
- The eligible patient population is expected to be 620 patients

Three sets of base case model results are presented, comparing POM+LoDEX with BTD, PANO+BOR+DEX (where the results are presented against the list-price of panobinostat as Celgene are unaware of the confidential PAS agreed by the manufacturer) and conventional chemotherapies in turn. Full incremental analysis is not presented as the clinical trial dataset used for comparison for POM+LoDEX is different for each comparison. It is therefore not possible to provide comparison versus a consistent estimate for POM+LoDEX. In line with NICE process these are presented including the PAS for POM and using the list price for PANO.

Probabilistic analysis which included the uncertainty around curve fit choice indicated the following probabilities of cost-effectiveness for each comparison: 92.8% versus BTD, 100% versus PANO+BOR+DEX (at list price for PANO), 56.9% versus CTD.

Table 3: Base case results – vs BTD

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
BTD	[redacted]	1.14	[redacted]	-	-	-	-
POM+LoDEX	[redacted]	1.81	[redacted]	[redacted]	0.67	[redacted]	£39,273

Key: BTD, bendamustine, thalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; LoDEX, low-dose dexamethasone; POM, pomalidomide; QALYs, quality-adjusted life years.

Table 4: Base case results – vs PANO+BOR+DEX

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	NMB (£) versus baseline (QALYs)
PANO+BOR+DEX	[redacted]	2.25	[redacted]	-	-	-	-
POM+LoDEX	[redacted]	1.71	[redacted]	[redacted]	-0.53	[redacted]	£42,475

Key: BOR, bortezomib; DEX, dexamethasone; PANO, panobinostat; ICER, incremental cost-effectiveness ratio; LoDEX, low-dose dexamethasone; POM, pomalidomide; QALYs, quality-adjusted life years; NMB, net monetary benefit.

Table 5: Base case results – vs conventional chemotherapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Conventional chemotherapy	[redacted]	0.78	[redacted]	-	-	-	-
POM+ LoDEX	[redacted]	1.45	[redacted]	[redacted]	0.68	[redacted]	£45,164

Key: ICER, incremental cost-effectiveness ratio; LoDEX, low-dose dexamethasone; POM, pomalidomide; QALYs, quality-adjusted life years.

2 The technology

2.1 Description of the technology

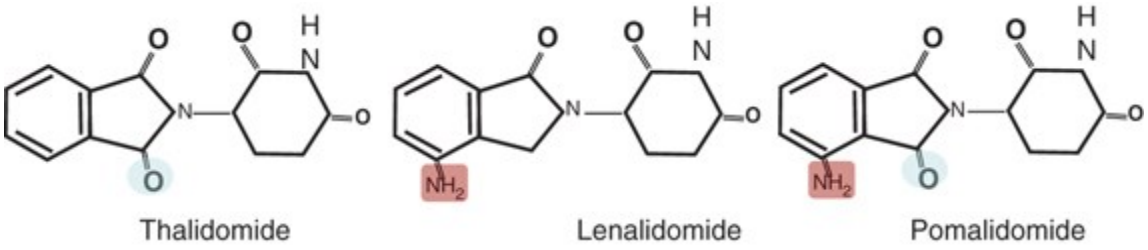
Name: Pomalidomide (IMNOVID®▼).

Pharmacotherapeutic group: Immunomodulating agent.

ATC code: L04 AX06

Pomalidomide (POM) is an immunomodulating agent that has demonstrated a powerful anti-cancer effect in relapsed/refractory multiple myeloma (RRMM), particularly in patients have disease that is resistant, or refractory, to previously used anti-myeloma therapies. POM belongs to a class of agents referred to as immunomodulatory derivatives, to which lenalidomide (LEN) also belongs, and is a structural derivative of thalidomide (THAL). In essence, POM has a combined chemical structure of THAL and LEN (Figure 1).[21]

Figure 1: Chemical structure of pomalidomide, thalidomide and lenalidomide



Source: Quach et al. 2010.[21]

Table 6 summarises the main mechanisms of action of immunomodulatory drugs (IMiDs®) used in the treatment of multiple myeloma, comparing their relative potency.

Table 6: Differences in activity of IMiDs®

Effect	Relative potency		
	THAL	LEN	POM
Immune modulation			
CD4+ and CD8+ T cell co-stimulation	+	++++	+++++
Th1 cytokine production	+	++++	+++++
NK & NK T cell activation	+	++++	+++++
Antibody dependant cellular cytotoxicity	No activity	++++	++++
Interference with tumour micro-environment interactions			
Anti-angiogenesis	++++	+++	+++
Anti-inflammatory properties	+	++++	+++++
Direct anti-tumour effect			
Anti-proliferative activity	+	+++	+++

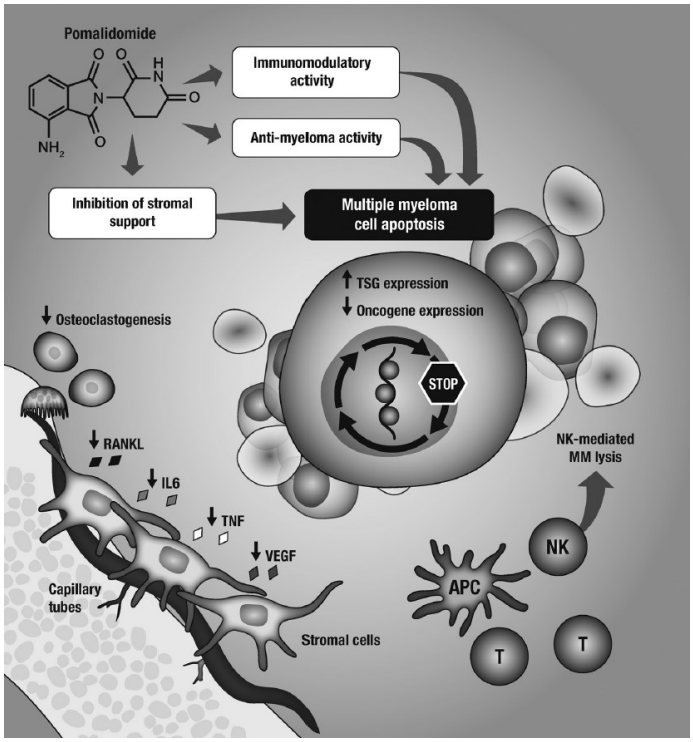
Key: IMiDs, immunomodulatory drugs; LEN, lenalidomide; NK, natural killer; POM, pomalidomide; THAL, thalidomide.
Notes: + indicates a potency factor 10.
Source: Adapted from Quach H et al.[21]

POM's anti-cancer effect is achieved by the following mechanisms (Figure 2):[4, 21, 41]

- Immune modulation
- Effects on tumour micro-environment interactions
- Direct tumour anti-proliferative activity

POM has direct anti-myeloma tumouricidal and immunomodulatory activity. It also inhibits stromal cell support required for multiple myeloma tumour cell growth. Specifically, POM inhibits proliferation and induces apoptosis of haematopoietic tumour cells.

Figure 2: Anti-myeloma, immunomodulatory and stromal-support inhibitory effects of POM



Key: APC, antigen-presenting cell; IL, interleukin; NK, natural killer; RANKL, receptor activator for nuclear factor kB ligand; TNF, tumour necrosis factor; TSG, tumour suppressor gene; VEGF, vascular endothelial growth factor.
Notes: POM has anti-angiogenic and potent anti-proliferative and proapoptotic activity against chemotherapy- and LEN-refractory multiple myeloma cells making it an attractive therapy for patients with RRMM. The proapoptotic effects of POM allow for efficacy even in the setting of heavily pretreated disease where the immune system may be compromised.
Source: Mark et al.[41]

Immune suppression is an important aspect of multiple myeloma pathophysiology. Therapies that enhance the anti-tumour effects mediated by T and natural killer (NK) cells, in addition to restricting tumour growth, may prolong remissions.[41] POM enhances T-cell- and NK cell-mediated immunity and inhibits production of pro-inflammatory cytokines (e.g. tumour necrosis factor-α and interleukin-6) by monocytes and inhibits angiogenesis by blocking the migration and adhesion of endothelial cells.[4]

Importantly, POM retains anti-proliferative activity in multiple myeloma cell lines resistant to the chemotherapeutics melphalan and doxorubicin as well as dexamethasone (DEX) and LEN.[41]

POM binds directly with cereblon, a component of the E3 ubiquitin-ligase complex; the link between this interaction and the immune modulation and anti-cancer action of IMiDs®, including POM, has been the subject of intensive studies.[31, 42, 43] POM has been shown to act in synergy with DEX, inhibiting proliferation and inducing apoptosis in both LEN-sensitive and LEN-refractory cell lines, suggesting a lack of cross-resistance.[31, 32] In LEN-resistant cell lines, POM retains its anti-myeloma activity and ability to modulate gene expression.[41]

Through these mechanisms of action, POM has demonstrated effectiveness in the treatment of RRMM, especially in patients whose disease has progressed during treatment with other IMiDs®. Indeed, in the final appraisal determination for the previous NICE review (TA338), the Committee recognised that patients may benefit from drugs with a new mechanism of action at this stage of the disease.[34]

2.2 Marketing authorisation/CE marking and health technology assessment

2.2.1 UK marketing authorisation for the indication in this submission

POM was granted European Medicines Agency (EMA) marketing authorisation on 05 August 2013 in combination with DEX for the treatment of adult patients with RRMM who have received at least two prior treatment regimens, including both LEN and bortezomib (BOR), and have demonstrated disease progression on the last therapy.[4]

2.2.2 Restrictions and contraindications in the summary of product characteristics (SmPC)

POM is structurally related to THAL, a known human teratogenic that that causes severe, life-threatening birth defects. As a result, POM is contraindicated during pregnancy and in women of childbearing potential unless conditions of a pregnancy prevention programme (PPP) are met. In addition, POM is also contraindicated in male patients unable to follow or comply with the required contraceptive measures and patients with known hypersensitivity to the active substance or to any of the excipients.[4]

Patients receiving POM in combination with DEX have developed venous thromboembolic events (predominantly deep vein thrombosis and pulmonary embolism) and arterial thrombotic events (myocardial infarction and cerebrovascular accident). Patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. The SmPC highlights that action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Prophylactic anti-thrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors.[4]

Neutropenia is a major dose-limiting toxicity of POM. POM treatment must not be started if the absolute neutrophil count is less than 1.0 × 10^9/L and/or platelet counts are less than 50 × 10^9/L. A complete blood cell count, should be performed at baseline, every week for the first 8 weeks of POM treatment and monthly thereafter to monitor for cytopenias. Use of growth factors should be considered in case of neutropenia, and patients should report febrile episodes and signs and symptoms of bleeding including epistaxis. The SmPC describes other warnings and precautions not described here;[4] the full SmPC is provided in Appendix 1.

2.2.3 SmPC and European public assessment report

The SmPC and the European public assessment report (EPAR)[2-4] are provided in Appendix 1.

2.2.4 Main issues discussed in the European public assessment report, and special conditions of the marketing authorisation

The EPAR specified the need for Celgene to submit periodic safety update reports as a requirement to the marketing authorisation. In addition, Celgene is required to perform the pharmacovigilance activities and interventions detailed in the risk management plan, which Celgene administers at its own cost to fulfil regulatory obligations.[2, 3] Additional risk minimisation measures also required included: a controlled distribution system; pregnancy prevention programme; agreed healthcare professional communication and physician information pack; patient card system; and post-authorisation safety study reports.[2]

2.2.5 Date of availability in the UK

POM was launched in the UK in September 2013.

2.2.6 Regulatory approvals of outside the UK

In addition to the 28 EU states and the European Economic Area countries Iceland, Norway and Liechtenstein, as covered by the EMA marketing authorisation, POM is also approved in Canada, the US, Australia, Switzerland and Japan.[3, 44-48]

2.2.7 Other health technology assessments in the UK

No technology appraisals are currently ongoing in the UK. POM has been appraised and recommended as a treatment option within its licensed indication by both the Scottish Medicine Consortium and the All Wales Medicines Strategy Group (AWMSG).[49, 50]

2.3 Administration and costs of the technology

Table 7: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Imnovid 1mg hard capsule: Dark blue opaque cap and yellow opaque body, imprinted "POML" in white ink and "1 mg" in black ink, size 4, hard gelatin capsule Imnovid 2mg hard capsule: Dark blue opaque cap and orange opaque body, imprinted "POML 2 mg" in white ink, size 2, hard gelatin capsule Imnovid 3mg hard capsule: Dark blue opaque cap and green opaque body, imprinted, "POML 3 mg" in white ink, size 2, hard gelatin capsule Imnovid 4mg hard capsule: Dark blue opaque cap and blue opaque body, imprinted "POML 4 mg" in white ink, size 2, hard gelatin capsule	POM SmPC[4]
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]	MIMS[51]
Method of administration	Oral	POM SmPC[4]
Doses	1mg, 2mg, 3mg and 4mg	POM SmPC[4]
Dosing frequency	Daily for 21 days in a 28-day cycle	POM SmPC[4]

	Cost	Source
Average length of a course of treatment	The median number of treatment cycles was 5.0 in the POM+LoDEX arm (range: 1-23 cycles)	MM-003 CSR[17]
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]	POM SmPC[4] MM-003 CSR[17]
Anticipated average interval between courses of treatments	Treatment is continuous until progression	POM SmPC[4]
Dose adjustments	Dose modifications and interruptions are specified within the SmPC for patients experiencing haematological adverse reactions and other Grade 3/4 adverse reactions judged to be related to POM. Please see SmPC Section 4.2 for more details	POM SmPC[4]
Anticipated care setting	POM is an oral therapy and therefore can be self-administered at home, with only outpatient consultations during the course of treatment	POM SmPC[4]
Key: LoDEX, low-dose dexamethasone; PAS, patient access scheme; POM, pomalidomide; SmPC, summary of product characteristics; VAT, value-added tax.		

2.4 Changes in service provision and management

2.4.1 Additional tests, investigations or administration requirements

As per the requirements of the PPP (see section 2.2.2),women of childbearing potential should have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to commencing treatment. A medically supervised pregnancy test should be repeated every 4 weeks, including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.[4]

2.4.2 Main resource use to the National Health Service (NHS) associated with the technology

Complete blood count monitoring is required weekly for the first 8 weeks and monthly thereafter. Monthly blood count monitoring is in line with the requirements for other treatments prescribed for multiple myeloma and is likely to be performed by

a haematologist. Prophylactic anti-thrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors. In patients with renal or hepatic impairment, monitoring is advised for adverse reactions.[4] Pregnancy testing is required for women of childbearing potential as described in Section2.2.2. For further details, please refer to the SmPC in Appendix 1.

2.4.3 Additional infrastructure requirements in the NHS

No additional infrastructure will be required.

2.4.4 Impact of the technology on patient monitoring in clinical practice in England

After the first 8 weeks of treatment with POM+DEX, the subsequent monthly monitoring requirements represent a substantial reduction compared to requirements for more intensive regimens.[4] Compared to POM+DEX, panobinostat (PANO)+BOR+DEX requires more frequent blood count monitoring; complete blood counts should be monitored on Days 1, 4, 8 and 11 of Cycles 1 to 8 and on Days 1 and 8 of Cycles 9 to 16.[13] Furthermore, additional blood counts should be considered during the "rest period" – e.g. on Days 15 and/or 18, especially in patients ≥65 years and patients with a baseline platelet count <150 x 10^9/L. Unlike for POM+DEX, PANO+BOR+DEX requires an electrocardiogram (ECG) recording before the start of therapy and repeated periodically before each treatment cycle. Blood electrolyte monitoring is also required, particularly in patients with diarrhoea, which occurred in 76% of patients who received at least two prior regimens including BOR and an IMiD in the PANORAMA 1 study.[52]

For bendamustine (BEN), in the event of myelosuppression, leukocytes, platelets, haemoglobin and neutrophils must be monitored at least weekly.[12]

For both BEN+THAL±steroids and PANO+BOR+DEX regimens, the presence of THAL and BOR, respectively, requires careful monitoring for symptoms of peripheral neuropathy.[14, 22]

2.4.5 Concomitant therapies specified in the marketing authorisation or used in the key clinical trials

As per the marketing authorisation, POM is indicated in combination with DEX. The recommended starting dose of DEX is 40 mg orally once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle. For patients aged >75 years, the recommended starting dose of DEX is 20 mg once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle. Dosing is continued or modified based on clinical and laboratory findings.[4]

In addition to DEX, most patients in the MM-003 study received concomitant treatments including anti-thrombotic, anti-infective, erythropoietin-stimulating agent and granulocyte-colony stimulating factor therapies, as well as red blood cell and platelet transfusions. Table 8 summarises the use of these concomitant therapies by patients during the MM-003 study.

Table 8: Use of concomitant therapy during treatment in study MM-003

Concomitant medication	POM+LoDEX (n=300)	HiDEX (n=150)
Antithrombotic prophylactic medications[a]	278 (93)	81 (54)
Aspirin	170 (57)	34 (23)
Enoxaparin	47 (16)	14 (9)
Granulocyte colony stimulating factor, n (%)	128 (43)	15 (10)
Anti-infectives (antibiotics, antifungals and antivirals), n (%)	259 (86)	118 (79)
RBC transfusion, n (%)	150 (50)	81 (54)
Platelet transfusion, n (%)	61 (20)	32 (21)

Key: DEX, dexamethasone; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide; RBC, red blood cell.

Notes: [a], This is not an exhaustive list of all anti-thrombotic medications; only the two most common medications are specified here.

Source: MM-003 CSR.[17]

Date cut-off: 01 March 2013.

2.5 *Innovation*

POM represents a step-change in the management of RRMM, it has the following innovative characteristics, which are meaningful to both patients and the NHS, and are unlikely to be fully reflected in the quality-adjusted life year (QALY) calculation:

- Effectiveness in particularly hard to treat patients
- Favourable toxicity profile allowing continuous treatment to suppress residual disease
- Reduction in patient, carer burden and NHS resource use

2.5.1 Effectiveness in hard to treat patients

POM is more potent than THAL and, in most cases, LEN with regard to its anti-proliferative activity, anti-inflammatory properties and ability to stimulate Th1 cytokines and T and NK cells (see Section 2.1).[21] The differences in molecular structure and activity result in efficacy in patients who historically have had a poor prognosis and are hard to treat having previously received treatment with THAL, LEN and BOR.[17, 18]

Significant survival benefits have been observed for POM+LoDEX in study MM-003 (Section 4.7) and these results are supported by similar survival benefits in study MM-002 (Section 4.11.1), MM-010 and UK clinical practice (Section 4.11.2).[17-19, 27, 28]

Benefits of POM+LoDEX in this population may not be fully reflected within the QALY calculation as evidence of effectiveness for comparator treatments does not exist in a heavily pre-treated population predominately refractory to both LEN and BOR.[16, 35, 53]

2.5.2 Impact of more favourable toxicity profile allowing continuous treatment to suppress residual disease

MM is characterised by regression and remission, and ultimately treatment failure, indicating the continued presence of resistant cells in the bone marrow.[5, 7, 54, 55] This pattern suggests that continuous therapy may be required to maintain suppression of

surviving tumour cells.[5] Continuous therapy requires a treatment with a favourable toxicity profile.

POM not only has a different mechanism of action to the comparator agents (BEN, PANO, THAL and BOR), it is also generally well-tolerated and can be given continuously until progression. The main Grade ≥3 AE was neutropenia, and the incidence of Grade ≥3 febrile neutropenia, peripheral neuropathy, deep-vein thrombosis and pulmonary embolism was low. The AE profile is reflected by an improvement in health-related quality of life (HRQL); in terms of physical and emotional functioning, fatigue, pain and improvements in side effects of treatment. These all help treatment to be given until disease progression, to control residual disease.[4, 17, 33, 56]

In study MM-003, the median OS was 19.9 months in patients who responded (≥PR) and continued on treatment (see Section 4.8.4 for further details).[20]

In responders, the lack of cumulative toxicity and immunomodulatory activity of POM resulting in enhanced anti-tumour effects mediated by T and natural killer (NK) cells,[21, 41, 57, 58] may not only prolong remissions but lead to patients being fit enough to receive subsequent therapy. This beneficial immunomodulatory effect is less likely with immunosuppressive regimens that are used in clinical practice[59, 60], which are often limited to short treatment durations due to cumulative toxicities (see Section 4.12.5 for further details).[12-14, 22]

The impact of toxicity on patients cannot be fully reflected within either cost or QALY calculations due to lack of evidence for comparator therapies in a comparable patient population to the POM+LoDEX trials, namely patients predominately refractory to both BOR and LEN.

2.5.3 Reduction in patient burden and NHS resource use

POM is an oral alternative to subcutaneous (SC) and IV therapies. Because POM+LoDEX can be self-administered at home, it is anticipated to be more convenient (less impact on employment status and travel), easier and less distressing for patients and carers than use of injectable or IV combinations (e.g.

PANO+BOR+DEX or BEN-containing regimens), this may be particularly the case for elderly, frail individuals and those who live far away from hospital.

These benefits are unlikely to be fully reflected in the standard QALY measure as, while literature from chemotherapies has been used to include disutility of non-oral therapies for patients in the cost-effectiveness modelling, the disease area these are taken from does not represent such a frail population.[61, 62] No literature is available to assess the benefit to carers.

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

3.1 Overview of the disease

Multiple myeloma is a rare, incurable malignant haematological disease arising from the monoclonal expansion of plasma cells in the bone marrow.[63] It represents approximately 1% of all incident cancers globally and results in more than 43,000 deaths annually worldwide.[64] multiple myeloma is primarily a disease of the elderly, and the median age at diagnosis ranges from 69 to 74 years.[65-67] At diagnosis, almost two-thirds of patients are aged 65 years and over.[66]

Patients suffer from a range of debilitating symptoms, including skeletal destruction – which arises from activation of osteoclasts by multiple myeloma cells and leads to lytic bone lesions (80% of patients), pathological fractures (26%), bone pain (58%), mobility problems, osteoporosis (23%), impaired bone marrow function, hypercalcaemia (symptomatic or asymptomatic; 10-30% of patients), anaemia (75% of patients) and general ill health.[8, 68-70] Secretion of M-proteins by plasma cells results in renal impairment (up to 50%) and kidney failure, and patients are also more susceptible to recurrent infections, due to a compromised B-cell lineage.[8, 70-72]

The course of the disease is not uniform[55, 73], and it varies according to factors related to:

- the patient, such as age, frailty and renal function[8, 74]

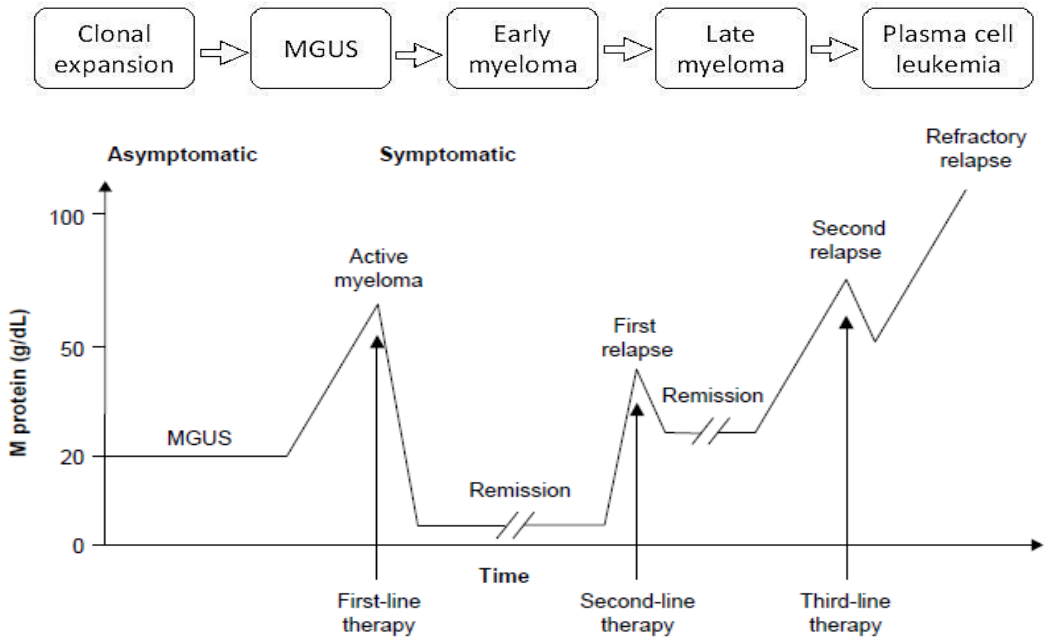
- tumour load, assessed by International Staging System (ISS) as well as Durie and Salmon stages of classification[75, 76]
- cytogenetic anomalies, including translocations (4;14) and (14;16), and deletion 17p[77, 78] (these high-risk cytogenic anomalies were incorporated into a revised ISS staging system in 2015)[79]
- sensitivity of the tumour to treatment[55]

While treatment can result in remission, the course of the disease in response to current treatment regimens, including novel agents, is characterised by cycles of remission and relapse.[5] Many patients relapse because of the continued presence of resistant cells in the bone marrow in the form of minimal residual disease[7], or they will discontinue therapy due to toxicity, for example peripheral neuropathy.[6, 8] With increasing lines of therapy, there is a decreasing DOR and ultimately development of refractory disease.[5, 8, 30] Figure 3 shows the typical pattern of multiple myeloma patient remission and relapse in response to treatment.

This pattern of regression and remission suggest that continuous therapy is required to suppress residual disease, maximise depth of response and prolong remission, helping achieve the main aims of therapy, which are to control disease, maximise HRQL and prolong survival.[5, 7, 8, 80]

The extent of refractoriness to prior treatment plays a large role in determining prognosis in patients with MM. It is therefore important to understand the different definitions used in relapsed/refractory multiple myeloma; presented in Table 9

Figure 3: Characteristic pattern of remission and relapse following conventional chemotherapy in multiple myeloma



Key: MGUS, monoclonal gammopathy of undetermined significance.
Source: Borello 2012[5]

Table 9: Definitions of relapsed and refractory multiple myeloma

Term	Definition
Primary refractory	These are the most challenging group of patients. Disease that is nonresponsive in patients who have never achieved a minimal response or better with any therapy. This group includes: • Patients who never achieve minimal response or better in whom there is no significant change in M protein and no evidence of clinical progression ("non-responding non-progressive"), and • Primary refractory, progressive disease where patients meet criteria for true progressive disease.
Relapsed and refractory	Disease that is nonresponsive while on salvage therapy, or progresses within 60 days of last therapy in patients who have achieved minimal response or better at some point previously before then progressing in their disease course
Relapsed	Previously treated myeloma that progresses and requires the initiation of salvage therapy but does not meet criteria for either "primary refractory myeloma" or "relapsed-and-refractory myeloma" categories.
Key: BOR, bortezomib; DEX, dexamethasone; PANO, panobinostat. **Source:** Rajkumar et al., 2011.[81]	

There are a few different definitions of disease progression, used to assess whether or not patients are refractory to treatment. These include the International Myeloma Working Group (IMWG) criteria and European Society for Blood and Marrow Transplantation (EBMT) criteria.[82, 83] Information from MM-003 indicates that similar outcomes can be expected from IMWG and EBMT criteria in clinical practice (Sections 4.7.2, 4.7.6 and 4.7.7).

Despite the availablility of THAL, BOR and LEN, prognosis remains bleak for patients who relapse or are refractory to these agents, with a median survival of 3-9 months.[36-40]

3.2 Impact of disease on patients, carers and society

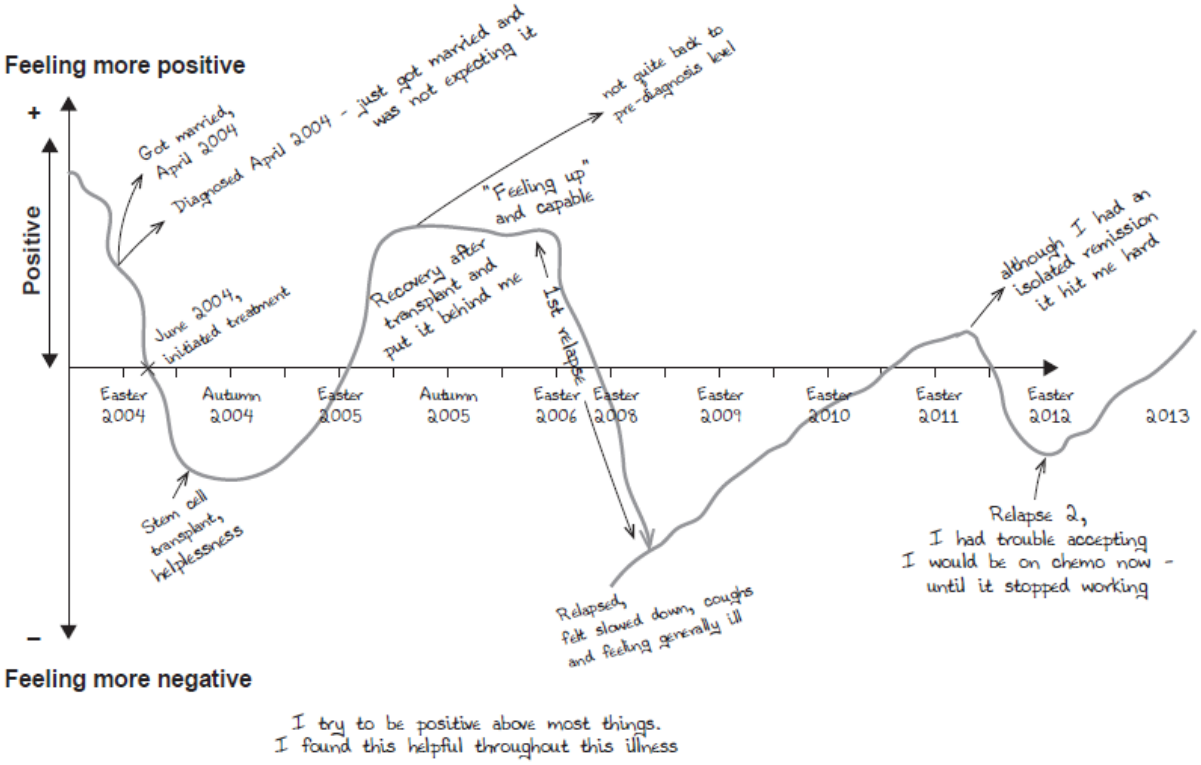
Patients with multiple myeloma experience successive clinical relapses, which are accompanied by debilitating symptoms (Section 3.1). As the disease progresses, patients not only face a worse prognosis but also a greater symptomatic burden, due to the progressive nature of the disease and the cumulative effects of treatment.[55, 84, 85] A major challenge is balancing prolonging survival while optimising quality of life (QoL) with effective supportive care measures.[84]

The different comparator treatment options have differing impacts. For example, in the PANORAMA 1 trial of PANO+BOR+DEX, results from the EORTC QLQ-C30 captured a consistently negative effect of treatment compared to those patients receiving BOR+DEX with mean changes from baseline in global health status/QoL exceeding the threshold defined as a minimal important change.[10] There are limited data on how BEN affects patients QoL, but during a recent advisory board meeting clinical experts highlighted that BEN-based therapies and conventional chemotherapies are associated with toxicities that often cause patients to stop treatment after only a few cycles.[9] In MUK-one, when patients were randomised to receive BEN at either 60 or 100mg/m^2, the 100mg/m^2 arm of the study was closed due to excessive cytopenias, whilst 21% of patients receiving BEN 60mg/m^2 discontinued treatment due to toxicity.[16]

Multiple myeloma has a significant emotional impact on patients, as shown by a recent European study. Qualitative interviews were conducted with 50 patients from

the UK, France, Germany, Italy and Spain; all of whom had had a clinical relapse of multiple myeloma as diagnosed by their physicians.[85] Patients were asked to draw diagrams illustrating changes in their emotional and physical well-being over time (Figure 4). Patients reported a substantial decline in their emotional well-being at diagnosis, which improved following initial treatment, only to decline at first relapse. Patients reported feeling scared, depressed, worried, confused, frustrated and powerless. Some patients reported that multiple relapses were associated with loss of hope and increasing distress as they felt that they were exhausting treatment options and "getting closer to the end".

Figure 4: Patient perspective illustrating changes in their emotional and physical well-being over time



Source: Hulin et al., 2014.[85]

In addition to the symptomatic, HRQL and anxiety burden of the disease itself, current treatments also add to the patient burden. Many current treatment options, including BOR or BEN (which are components of the PANO+BOR+DEX and BEN-containing regimens, respectively), require IV or SC administration in a hospital

setting and are associated with up to four hospital visits per month.[12, 13] Such a requirement for frequent hospital visits is a particular issue for patients with multiple myeloma who are often frail, elderly and have mobility problems related to their condition.[74, 86] It has been demonstrated that with oral administration, patients have fewer hospital visits, a greater sense of control over their disease and less interruption to their daily activities.[23]

The disease and its treatment also impacts employment. As a result of intensive multiple myeloma treatment, many patients are no longer able to return to work, and some decide to take early retirement. One study showed that only half of patients who underwent intensive multiple myeloma treatment were still employed after diagnosis, with a mean age of 61 years.[87]

Caregivers are also affected; treatment for multiple myeloma often involves, weeks or months away from home, requiring a large time commitment from caregivers as well as patients themselves.[87] Caregivers can suffer financial difficulties as a result of a relative being diagnosed with multiple myeloma; they may suffer from loss of wages, difficulty in paying bills, lack of sick leave and premature use of retirement funds.[88]

3.3 Clinical pathway of care and anticipated positioning

Table 10 shows the current clinical pathway of care and the proposed placement of POM+LoDEX within this pathway. As defined by the guidance presented in Section 3.5, for the majority of patients, POM+LoDEX will be placed as a fourth-line treatment, although some patients who have received prior LEN and BOR as part of first- or second-line combinations may be eligible to receive POM+LoDEX at third line. Examples of patients who may be eligible for POM+LoDEX at third line include those who received LEN at first line within a clinical trial setting and those who received LEN at second line whilst this was funded by the Cancer Drugs Fund (CDF).

Table 10: Clinical pathway of care in patients with multiple myeloma

	Transplant eligible patients with MM	Transplant ineligible patients with MM
1st Line (NICE TA311[89]; NICE TA228[90])	BOR+DEX or BOR+THAL+DEX induction followed by ASCT[89]	THAL+ alkalyting agent + steroid (e.g. MPT) BOR+MP (THAL intolerant /contraindicated)[90]
	Note some patients may have received LEN as part of clinical trials	
2nd Line (NICE TA129[91])	• BOR ± DEX having received 1 prior therapy[91] • Conventional chemotherapy (including cyclophosphamide and melphalan) ± steroid[a] • A minority of patients may receive a second ASCT • Some patients may have initiated (and still be receiving) LEN from when this was funded by the CDF	
3rd Line onwards (NICE TA171[92]; TA380[93]; CDF[94])	• Potential placement: POM+LoDEX[b] • LEN+DEX[92] • PANO+BOR+DEX[c] [93] • Conventional chemotherapy (including cyclophosphamide and melphalan) ± steroid ± THAL re-treatment[d] • BEN combinations[94] (via CDF)[e]	

Notes: [a] Primarily received by patients who cannot tolerate THAL, have received BOR at first-line and have recently initiated 2nd line treatment as BOR retreatment is no longer funded by the CDF therefore availability is limited; [b] In patients who have received ≥2 prior lines of treatment including LEN & BOR; [c] PANO+BOR+DEX is reimbursed in patients who have received ≥2 prior lines of treatment including BOR + IMiD (either THAL, LEN or POM); [d]THAL retreatment can only be used in patients who are THAL eligible (i.e., not those who are THAL intolerant or contraindicated); [e] BEN is usually used at 4th line onwards (via the CDF).

Sources: NICE TA311[89], 2014; NICE TA228, 2011[90]; NICE TA129, 2007[91]; NICE TA171, 2009[92]; NICE TA380, 2016[93]; NHS CDF List, 2016[94]

Key: ASCT, autologous stem cell transplant; BEN, bendamustine; BOR, bortezomib; CDF, National Cancer Drugs Fund; DEX, dexamethasone; LEN, lenalidomide; LoDEX, low dose dexamethasone; MP, melphalan, prednisone; MPT, melphalan, prednisone, thalidomide; NICE, National Institute for Health & Care Excellence; PANO, panobinostat; POM, pomalidomide; THAL, thalidomide.

Three treatments are included within the NICE scope for comparison: PANO+BOR+DEX, unlicensed treatment with BEN via the CDF and use of conventional chemotherapy regimens (e.g. cyclophosphamide and melphalan combinations).[1, 95, 96] These combinations may not be suitable for all patients at this stage of the disease, particularly where a patient has received one of the drugs in the combination previously and they have not responded, become contraindicated or intolerant to a drug. The British Committee for Standards in Haematology (BCSH) guidelines highlight that decisions regarding treatment at relapse should be made according to a number of factors including the timing of relapse, efficacy and toxicity of drugs used in prior therapy (e.g., peripheral neuropathy), age, bone marrow and renal function, co-morbidities (e.g., diabetes) and patient preference.[8] In both the PANORAMA 1 & MUK-one studies, a high proportion of patients discontinued treatment due to toxicity.[16, 53]

3.4 Life expectancy

Prognosis is poor for patients who relapse or are refractory to novel agents such as THAL, BOR and LEN. In a multicentre, international, observational study of 286 patients with relapsed multiple myeloma who were refractory to BOR and were relapsed following, refractory to or ineligible to receive an IMiD® (THAL or LEN), the median OS and event-free survival were 9 and 5 months, respectively.[40] Most patients in England will receive POM after relapse on THAL, BOR and LEN. Outcomes in this group of patients are even worse: median OS of approximately 3-7 months across treated patients.[36-39]

3.5 Clinical guidelines

3.5.1 NICE guidance

In February 2016, NICE published a Clinical Guideline on the diagnosis and management of MM.[97] Because PANO+BOR+DEX was recommended just before this guideline was published, it was not included in here. However, it has been included in the Myeloma Pathway, published online.[98] The individual NICE Technology Appraisals, conducted at all lines of multiple myeloma, are summarised in Table 11.

Table 11: NICE recommendations in multiple myeloma

First line	
TA311 (April 2014)[89]	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)[90]	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. This guidance is now on the static list. "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 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 multiple myeloma 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[a]	
TA129 (October 2007)[91]	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 under the following circumstances: "The response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in people who have a complete or partial response (PR; that is, reduction in serum M protein of 50% or more or, where serum M protein is not measurable, an appropriate alternative biochemical measure of response) and; the manufacturer rebates the full cost of bortezomib for people who, after a maximum of four cycles of treatment, have less than a PR (as defined above)." This guidance is now on the static list.
Third line	
TA171 (June 2009)[92]	LEN+DEX recommended as an option for people who have received two or more prior therapies, with the condition that the drug cost of LEN for people who remain on treatment for >26 cycles would be met by the manufacturer. This guidance is now on the static list.
TA380 (January 2016)[93]	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, when the company provides PANO with the discount agreed in the patient access scheme.
Fourth line	
TA338 (February 2015)[34]	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. Submission currently under reconsideration under ID985 in this submission.
Notes: [a], Three NICE technology appraisals are also currently ongoing in the second line setting: Appraisal of LEN after 1 prior treatment with BOR (ID667 [part review of TA171]);[99] appraisal of carfilzomib with LEN+DEX or with DEX after 1 prior treatment (ID934);[100] and the appraisal of ixazomib citrate with LEN+DEX after 1 prior treatment (ID807).[101] **Key:** BOR, bortezomib; DEX, dexamethasone; LEN, lenalidomide; NICE, National Institute of Health and Care Excellence; PANO, panobinostat; POM, pomalidomide; PR, partial response; SCT, stem cell transplantation; THAL, thalidomide.	

3.5.2 Additional relevant guidance and guidelines

A summary of relevant guidance by country/region is provided below.

UK guidelines

The 2014 BCSH guideline highlights that the aims of treatment are similar to those at diagnosis, namely, to achieve disease control, ameliorate symptoms, improve quality of life and prolong survival. However, for significant numbers of patients, the side-effects of treatment limit the choices available. The BCSH state "there is no standard approach for treatment at relapse based on disease heterogeneity and variability in patient-specific factors including co-morbidities and the persistence of toxicities related to previous therapy".[8]

The guideline states that the agents most often used in treating relapsed patients are THAL, BOR and LEN, generally in combination with corticosteroids and sometimes with an alkylating agent. They also recommend that a second autologous SCT may be considered in patients who had a good response to their initial transplant (≥18 months to disease progression). No recommendations are provided in the indication under consideration in this submission, but promising results in early trials are reported for second- and third-generation IMiDs, including POM.

European guidelines

The European Society for Medical Oncology 2013 guidelines highlight that choice of therapy in the relapse setting depends on age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options and the interval since the last therapy.[102] These guidelines make no specific recommendation surrounding treatment in patients who have progressed on LEN and BOR, but they were published before POM was approved in Europe.[2, 3]

A European perspective on multiple myeloma treatment strategies including relapsed/refractory disease was published in 2014.[103] The publication highlights that patients resistant to LEN, BOR and THAL present a particularly challenging group

who require novel strategies with newer agents including third-generation IMiDs like POM.

National Comprehensive Cancer Network guidelines (United States)

The National Comprehensive Cancer Network (NCCN) recommends POM+DEX as a Category 1 option (i.e. based on high-level evidence, with uniform NCCN consensus that the intervention is appropriate) for treatment of patients with multiple myeloma who have received at least two prior therapies, including an immunomodulating agent and BOR, and have demonstrated disease progression on or within 60 days of completion of the last therapy.[104] The NCCN scores POM as 4 out of 5 for efficacy, safety, quality of evidence and consistency of evidence, which is higher than or equivalent to the scores for comparative agents (Table 12).[104]

Table 12: Summaries of NCCN Evidence Blocks for POM vs relevant comparators (5 = best, and 1 = worst)

	POM	BEN	PANO+BOR+DEX
Efficacy	4	3	3
Safety	4	3	2
Quality of evidence	4	3	4
Consistency of evidence	4	3	4

Key: BEN, bendamustine; NCCN, National Comprehensive Cancer Network PANO+BOR+DEX, panobinostat, bortezomib and dexamethasone; POM, pomalidomide.
Source: NCCN, 2016[104]

International guidelines

International guidance from the International Myeloma Working Group has recommended POM-containing regimens (usually with LoDEX but potentially combined with other agents such as BOR) and carfilzomib-containing regimens (preferably in combination with LEN and LoDEX) specifically for treatment of multiple myeloma that is refractory to both LEN and BOR.[105] The International Myeloma Working Group also suggests considering PANO+BOR+DEX for these patients, but it is not presented as the first option of choice.[105]

3.6 Issues relating to current clinical practice

Patients who have relapsed after treatment with both BOR and LEN have a poor prognosis with currently available options (median survival of 3-9 months) across treated patients.[36-40] Recent changes to the CDF (including the removal of POM, BOR retreatment, and LEN) have limited options further.[94] In addition to PANO+BOR+DEX, which was recently recommended by NICE for patients who have received at least two prior regimens including BOR and an immunomodulatory agent (TA380)[93], remaining treatment options for patients who have relapsed after treatment with both BOR and LEN are BEN (available via the CDF) and conventional chemotherapy as a final option. Data for all of these treatments are limited in this patient population. As such, currently there is no established standard of care for patients who have already received both BOR and LEN and treatment is individualised and involves use of unlicensed treatments.

To determine clinical opinion on these relevant comparators, Celgene conducted a myeloma clinical expert advisory board meeting.[9] Outputs of the advisory board, clinical/patient expert opinion from the recent NICE appraisal of PANO+BOR+DEX (TA380) and clinical advisors' comments on the draft scope for POM for the current submission are presented in Table 13.

Table 13: Issues with current comparators to POM+LoDEX

Comparator listed in final NICE scope	Clinical opinion
PANO+BOR+ DEX	• Advisors were more likely to use as a fourth-line combination therapy rather than third-line, with some advisors commenting that they would prefer an oral regimen at third-line[9] • Some advisors felt that PANO adds to the toxicity profile of BOR and results in a poorer profile particularly in terms of fatigue, high-grade thrombocytopenia and diarrhoea[9] • Unlikely to be suitable in patients with a poor response to initial BOR treatment[9] • Not appropriate for patients with neuropathy.[9] During the NICE appraisal of PANO, the Committee noted statements from a patient and carer group, which highlighted patients' concerns that some of the AEs observed with PANO may lead to increased hospitalisation[93]
BEN±THAL retreatment± steroid	• Not appraised by NICE but funded via the Cancer Drugs Fund (CDF); does not currently have a marketing authorisation in the UK for this indication[1] • Has a larger role since POM has been delisted from the CDF[9] • Patients struggle with side effects, including cytopenias, fatigue and infection and, as a result, often stop treatment after only a few cycles[9] • Haematological AEs require careful management[9] • BEN tends to be used to "bridge a gap until other therapies become available", rather than an option for long-term treatment[9] • BEN toxicity tends to be cumulative, limiting its long-term use[9] • Often used with THAL which has been received by the majority of patients earlier in the pathway and can also be associated with cumulative toxicity[106] • Durable response is uncommon[9] • Need for additional clinic visits compared with POM, both for administration of the drug and for blood countsand/or G-CSF administration[9]

Comparator listed in final NICE scope	Clinical opinion
Conventional chemotherapy agents (including cyclophosphamide and melphalan) ± steroid	• Advisors stated that a wide variety of agents and regimens are used in this setting. Whilst conventional chemotherapy regimens are still used, they are not used frequently enough to be a helpful addition to a health economic model in this context[9] • Similar to BEN, these regimens are sometimes used as a bridge to a second transplant or as a bridge whilst waiting for other treatments to become available[9] • Clinical experts consulted at the recent daratumumab scoping meeting (21 March, 2016) advised that they use BEN in preference to conventional chemotherapies as the toxicity of the latter tends to be unacceptably high and there is no real efficacy data at fourth and fifth line[11] • The UK Myeloma Forum and Myeloma UK also stated that conventional chemotherapy such as melphalan and cyclophosphamide would not be a suitable comparator in preference to BEN. Advisors stated that conventional chemotherapy agents are generally used as a final option[11]
Key: AE, adverse event; BEN, bendamustine; BOR, bortezomib; CDF, Cancer Drugs Fund; DEX dexamethasone; G-CSF, granulocyte colony stimulating factor; NICE, National Institute for Health and Care Excellence; PANO, panobinostat; POM, pomalidomide; THAL, thalidomide.	

3.7 Assessment of equality issues

No equality issues relating to the use of POM have been identified or are anticipated.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

An SLR focusing on adult patients previously treated with LEN and BOR was performed and updated for the previous NICE submission (TA338) and this was updated again for this resubmission, with searches performed on 3 March 2016 (Evidence was not considered from the wider multiple myeloma population as patients who have been previously treated with both LEN and BOR represent a particularly hard to treat population of patients; evidence from earlier lines is therefore not appropriate for synthesis from evidence in these patients.) .

Due to changes in the scope between the original and current submission there were some differences in the methods used for the original and updated SLRs:

- Update to patient population
  - This submission included studies where at least 75% of adult RRMM patients had received both BOR and LEN to focus the evidence base to a comparable patient population
- Update to comparators:
  - The updated SLR was restricted to the latest relevant comparators within UK clinical practice, as specified by the NICE scope. Therefore, PANO was added as an additional comparator, and carfilzomib, LEN and vorinostat were removed from the searches.

- Update to search strategies:
  - This resubmission addresses concerns raised by the evidence review group (ERG) in the original NICE review (TA338) regarding the use of study design filters by adding additional terms to the search strategies around study design in order to make the searches more comprehensive. As is standard practice filters have not been entirely removed to keep searches manageable and targeted.[107]

All of the SLRs conducted to form the final evidence base were performed to meet the methodological requirements outlined by NICE.[108]

Details of the searches which informed the original NICE submission (TA338) are available on the NICE website.[34] Full details can be provided on request. Full details of the methods used to inform this resubmission, are presented in Appendix 2, along with the search strategies.

Whilst a substantial body of evidence is available to support the clinical effectiveness of POM+LoDEX in patients who have received and become refractory to both prior BOR & LEN, comparable evidence for comparator treatments used in current English clinical practice is limited. This is not surprising given that, with the exception of PANO+BOR+DEX, the treatment regimens that are currently used are unlicensed. There is limited RCT evidence in this setting: most studies are non-RCT or observational studies. The evidence for conventional chemotherapy is very limited and historical, having been published a long time before the availability of LEN and BOR. The SLR has been updated to try and address these evidence gaps. In addition, extensive efforts were made to source UK patient data on the outcomes of patients receiving relevant treatments post LEN and BOR.

Commissioning via NHS England allowed the use of PANO+BOR+DEX based upon the recommendation in TA380 on the 26th April 2016 meaning that no data are currently available for use in English clinical practice. Data gathering exercises outside of the SLR therefore focused on other current care treatments listed within the scope. The following contacts were made in order to source data for comparative effectiveness:

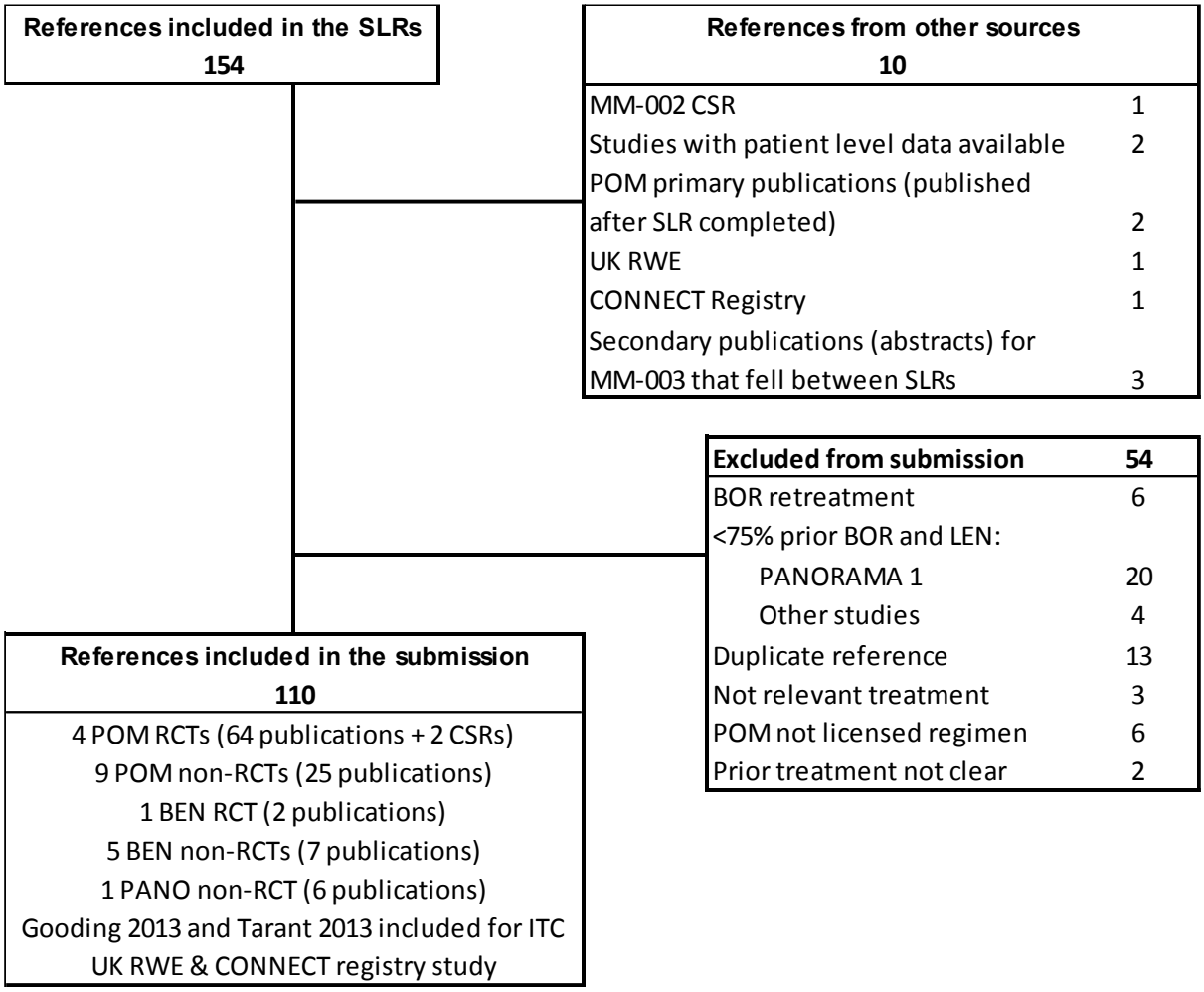
- Initiation of real world evidence (RWE) collection for patients receiving POM+LoDEX, BEN and BOR retreatment across 17 centres in England and Wales and two in Northern Ireland (further details presented in Section 4.11)
- Requests for provision of patient information from clinicians attending advisory boards[9]
- Direct contact with clinicians in key centres treating RRMM including Oxford, Leeds, Guy's and St Thomas Hospital NHS Trust, London
- Sourcing of evidence available from the CONNECT MM registry funded by Celgene in the United States.[109]

Studies included in the submission

Appendix 2 presents the individual Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagrams for each of the SLRs. In total, the SLRs identified 154 references. An additional ten references were included from other sources. Fifty-four of the references identified through the SLRs were not relevant for inclusion in this submission, for the reasons presented in the PRISMA diagram (Figure 5). Therefore a total of 110 references were included in this submission. A list of the studies excluded from the submission, alongside their reason for exclusion, is presented in Appendix 2.

Figure 5 presents the PRISMA diagram for studies identified by the SLRs and included in the submission, including a breakdown of the number of RCTs and non-RCTs for POM and its comparators.

Figure 5: PRISMA flow diagram for evidence included in the submission



Key: BOR, bortezomib; CSR, clinical study report; ITC, indirect treatment comparison; LEN, lenalidomide; POM, pomalidomide; RCT, randomised controlled trial; RWE, real world evidence; SLR, systematic literature review; UK, United Kingdom.

The POM RCTs are presented in detail in Section 4.2 through Section 4.8.

All other supporting qualitative evidence, including POM non-RCTs, comparator RCTs, comparator non-RCTs and the UK RWE, is presented in Section 4.11.

Section 4.10 highlights details of comparator studies including patient level data (MUK-one, Gooding 2015 and Tarant 2013), that has been assessed for inclusion in an indirect comparison comparing BEN and PANO+BOR+DEX with POM+LoDEX.

4.2 List of relevant randomised controlled trials

Table 14 presents a list of all of the relevant RCTs for POM+DEX. The main source of evidence presented for this submission is the MM-003 RCT, supported by data from MM-002 (see Section 4.11.1) and MM-010 (see Section 4.11.2).

All of the secondary publications for these trials are presented in Appendix 2.

Table 14: Relevant POM+DEX primary publications

Study	Intervention	Comparator	Population	Primary study ref.
MM-003[17]	POM+LoDEX	HiDEX	Patients with refractory or RRMM with ≥2 lines of previous therapy including LEN and BOR	CSR
San Miguel et al., 2013[110]				Full paper
MM-002[111]	POM+LoDEX	POM	Patients with RRMM with ≥2 lines of previous therapy including LEN and BOR	CSR
Richardson et al., 2014[19]				Full paper
IFM 2009-02: Leleu et al., 2013[26]	POM (21/28 day)+LoDEX	POM (28/28 day)+LoDEX	Relapsed MM ≥1 previous therapy	Full paper
Baz et al., 2016[25]	POM+DEX	POM+DEX+CYC	Patients with RRMM with ≥2 prior therapies and LEN refractory	Full paper

Key: BOR, bortezomib; CSR, clinical study report; CYC, cyclophosphamide; DEX, dexamethasone; HiDEX, high-dose dexamethasone; LEN, lenalidomide; LoDEX, low-dose dexamethasone; MM, multiple myeloma; POM, pomalidomide; RRMM, relapsed and refractory multiple myeloma.

4.3 Summary of methodology of the relevant randomised controlled trials

The MM-003 study is the primary source of RCT data for this submission and the methodology of and evidence from MM-003 is detailed herein. The other RCTs compare POM with an unlicensed dosing regimen of POM and are presented in Section 4.11 as supportive evidence.

4.3.1 MM-003 trial design

The Phase III study MM-003 was a multicentre, randomised, open-label study, which took place in 93 centres in Europe (including the UK), Russia, Australia, Canada and

the United States. The trial was designed to compare the efficacy and safety of POM+LoDEX versus high-dose dexamethasone (HiDEX) in patients with RRMM who have received at least two prior treatment regimens, including both LEN and BOR.[17] Figure 6 presents an overview of the MM-003 trial design.

Method of randomisation

Patients (n=455) were randomised in a 2:1 ratio by permuted block randomisation using the stratification factors of age (≤75 years of age versus >75 years of age), disease population (refractory subjects versus relapsed and refractory subjects versus refractory/intolerant subjects) and number of previous multiple myeloma treatments (2 versus >2). Randomisation was undertaken using a validated interactive voice/web response system (IVRS/IWRS).

A 2:1 randomisation ratio was used to maximise information regarding POM efficacy and safety, and to allow the maximum number of patients to benefit from POM treatment, as the treatment options for this patient population are extremely limited.

Method of blinding

The study was open label, but the study team remained blinded to the study treatment code up to the final analysis of the primary endpoint. To ensure an unbiased assessment of patient data, an Independent Response Adjudication Committee (IRAC) reviewed all efficacy data in a blinded manner.

Intervention and comparator

Patients were randomised to one of two arms:

- POM (4mg/day) plus LoDEX (40mg on Days 1, 8, 15 and 22 of a 28-day cycle)
- HiDEX (40mg on Days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle)

The DEX dose on both arms was reduced to 20mg in patients >75 years of age.

Dose selection and continuation rules

The dose selection and schedule for POM (4mg/day) in combination with DEX was based on results from Phase I (MM-001)[112, 113] and Phase I/II (MM-002)[19, 114] studies. On the basis that previous registration studies of LEN[115, 116] and BOR[117] in patients with relapsed or refractory multiple myeloma had used HiDEX, the same control was applied in this study. Treatment was continued until progressive disease or unacceptable toxicity. Subjects were evaluated for AEs. Dose interruptions and reductions were permitted throughout the study to manage AEs (a reduction of 1mg on Day 1 of the next treatment cycle). POM was to be discontinued in the event of Grade 4 rash or rash with blistering, or Grade 4 peripheral neuropathy. Appropriate concomitant treatments for AEs were permitted (including anti-infective agents, bisphosphonates and haematopoietic growth factors and platelet and red blood cell [RBC] transfusions).

Duration of follow-up

Following treatment phase discontinuation, patients were assessed at 28 days and then entered a long-term follow-up period with visits four times per year until death or until 5 years after randomisation. During follow-up, patients were evaluated for OS and second malignancies.

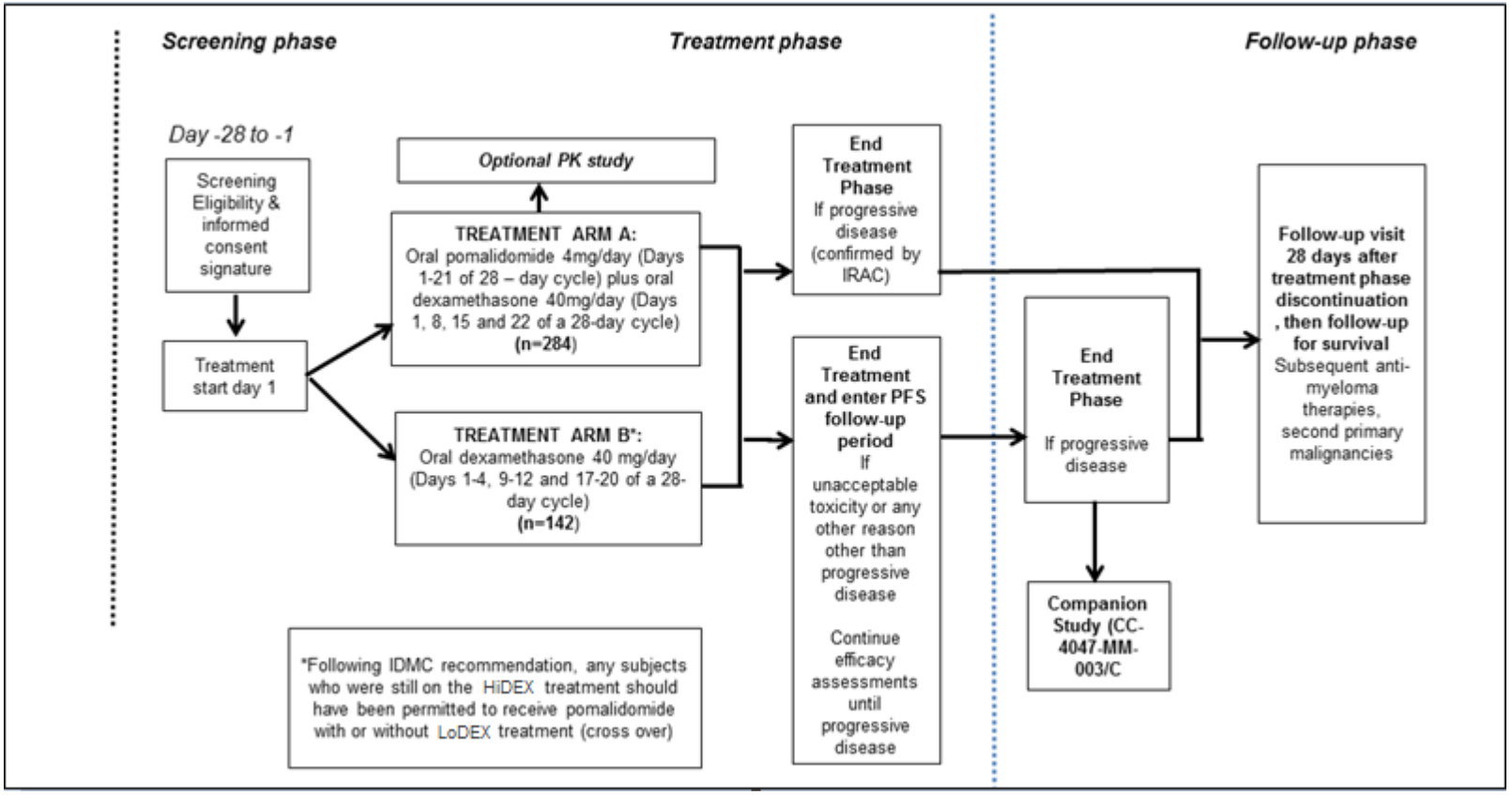
Changes in the conduct of the study

The study protocol was amended four times prior to the data cut-off date of 01 March 2013. The final amendment to the protocol followed a review by the independent data monitoring committee (IDMC) of final progression-free survival (PFS) and interim OS data analysis (7 September 2012). Based on favourable outcomes in the POM+LoDEX treatment arm, the IDMC recommended any subjects who were receiving HiDEX be permitted to cross-over to POM treatment with or without LoDEX at the investigator's discretion, irrespective of whether or not the subject had progressive disease. A full list of changes of conduct can be found in Appendix 9.

Companion study

Patients in the HiDEX treatment arm who experienced disease progression during the randomised treatment phase had the option to receive POM at the same dose as patients in the POM+LoDEX arm (via entry into a companion study; MM-003c).[118]

Figure 6: MM-003 study design



Key: HiDEX, high-dose dexamethasone; IDMC, independent data monitoring committee; IRAC, independent response adjudication committee; LoDEX, low-dose dexamethasone; PFS, progression-free survival; PK, pharmacokinetic.
Note: The sample sizes of N=284 and N=142 represent the planned trial sizes for treatment arms A and B, respectively (i.e. randomisation in a 2:1 ratio)
Source: MM-003 CSR.[17]

4.3.2 MM-003 Eligibility Criteria

The key inclusion and exclusion criteria for patients entering into the MM-003 study are presented in Table 15.

Table 15: Key inclusion/exclusion criteria for MM-003 patients

Inclusion criteria	Exclusion criteria

The key patient eligibility criteria for study MM-003 were as follows:
• Patients must have had either refractory or relapsed and refractory disease defined as documented disease progression during or within 60 days of completing their most recent myeloma therapy
• All patients must have received at least two consecutive cycles of previous treatment that included LEN and BOR, either alone or in combination
• Patients must have received adequate previous alkylator therapy
• All patients must have demonstrated **failure of both LEN and BOR**, using the following criteria for refractoriness that made the patient eligible for the study
  ○ All patients must have had **treatment failure** with the **most recent LEN-containing regimen** in **one** of the following ways:
  ▪ documented PD during or within 60 days of completing treatment with LEN; **or**
  ▪ in case of previous response (≥PR) to LEN, patients must have relapsed within 6 months after stopping treatment with LEN-containing regimens
  ○ All patients must have had **treatment failure** with the most **recent BOR-containing regimen** in using the same criteria described for LEN, **or**:
  ▪ patients who had not had at least a minimal response (MR) and had developed intolerance/toxicity after a minimum of two cycles of a BOR-containing regimen, for example ≥Grade 2 peripheral neuropathy or ≥Grade 2 painful neuropathy. Peripheral neuropathy must have resolved to Grade 1 before study entry
• Women of childbearing potential must have agreed to comply with conditions of a pregnancy prevention programme and male patients were required to follow specified contraceptive measures
	The main exclusion criteria applied to:
	• Patients who were eligible for SCT;
	• Patients who had CrCl <45mL/min;
	• Patients who demonstrated resistance to HiDEX used in the most recent line of therapy; or
	• Patients who had peripheral neuropathy of Grade 2 or higher.

Key: BOR, bortezomib; CrCl, creatinine clearance; HiDEX, high-dose dexamethasone; LEN, lenalidomide; MR, minimal response; PD, progressive disease; PR, partial response; SCT, stem cell transplantation. **Source:** MM-003 CSR.[17]	

4.3.3 MM-003 Outcome measures

Table 16: Outcome measures for MM-003

Endpoint type	Measure	Description
Primary endpoint	PFS	Time from randomisation until documented disease progression, or death, whichever occurred earlier. PFS was assessed by IRAC using IMWG response criteria based on the ITT population [a82] As a secondary analysis, PFS was assessed: by IRAC based on EBMT criteria,[83] and by Investigator based on IMWG criteria[a82]
Secondary outcomes	OS	Time from randomisation to death from any cause based on the ITT population
	Response rate	The primary response analysis was based on the assessments by the IRAC using IMWG response criteria [a82] Response was also assessed by investigator using IMWG criteria. The overall confirmed myeloma response rate (ORR; ≥PR) together with the relative proportions in each response category were examined for IRAC and investigator assessments An analysis of response assessments judged by the EBMT criteria was performed, with response categories of CR, PR, MR, StD, and PD.
	TTP	TTP was calculated as the time from randomisation to the first documented progression confirmed by the IRAC.
	TTR	TTR was calculated as the time from randomisation to the initial documented response (PR or better) based on IMWG or EBMT criteria.
	DOR	The duration of time from when response criteria for CR, VGPR or PR were first met to PD or death, whichever occurred first[a]
	TTF	Time from randomisation to discontinuation of study treatment for any reason including disease progression, toxicity and death[a]
Other	HRQL	QLQ-C30, QLQ-MY20, EQ-5D
Safety	Safety	Evaluation of AEs, physical examination (including vital signs/neurological examination), clinical laboratory evaluations (including haematology), electrocardiogram, concomitant medications/therapies, a pregnancy testing and pregnancy prevention risk management plan and incidence of SPM

Key: AEs, adverse events; CR, complete response; DOR, duration of response; EBMT, European Society for Blood and Marrow Transplantation; EQ-5D, 5-dimension European Quality of Life questionnaire; HRQL, health-related quality of life; IMWG, International Myeloma Working Group; IRAC, Independent Response Adjudication Committee; ITT, intention to treat; MR, minimal response; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QLQ-C30, Quality of Life Questionnaire – Core 30; QLQ-MY20, Quality of Life Questionnaire – Multiple Myeloma 20; SPM, second primary malignancy; StD, stable disease; TTF, time to treatment failure; TTP, time to progression; TTR, time to response; VGPR, very good partial response.

Notes: [a] 01 March 2013 data cut was assessed by IRAC and 01 September 2013 data cut was assessed by the study investigator.

Source: MM-003 CSR.

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

4.4.1 MM-003 Statistical Analyses

Table 17 presents the outcomes that were available for the two main data cuts. There was also an additional data cut at 01 September 2012, which was the final PFS analysis and an interim OS analysis. However, since these data have since been updated, no evidence from this data cut is presented in this submission.

- 01 March 2013: pre-planned data cut-off date for final OS analysis, with a median follow-up of 10 months. At this time sufficient events had occurred to trigger final analysis of OS. PFS analysis according to central assessment (the primary efficacy endpoint) was updated at this time
- 01 September 2013: a post-hoc updated analysis of PFS, TTP, TTF, OS, DOR, time to response (TTR) and overall response rate (ORR) by investigator, with a median follow up of 15.4 months.[20, 119, 120].[17, 20]

Throughout this submission, data are presented primarily for the most up-to-date data cut from 01 September 2013, where these data are available. A full clinical study report has not been produced for the 01 September 2013 data cut therefore evidence from this data cut is reported in the Dimopoulos 2015[119] and San Miguel 2015[20] publications, or from data on file.[120] The 01 March 2013 data cut is presented within the full Clinical Study Report.[17]

Table 17: IRAC or investigator assessed outcome measures available by data cut

Outcome measure[a]	01 March 2013[b]	01 Sept 2013[c]	Used in economic analysis
PFS assessment – IRAC (primary endpoint)	✓	X	X
PFS – investigator assessment	✓	✓	Sept data cut
TTF - IRAC	✓	X	X
TTF - investigator	✓	✓	Sept data cut
TTP - IRAC	✓	X	X
TTP - investigator	✓	✓	X
OS	✓	✓	Sept data cut
Response - IRAC	✓	X	X
Response -investigator	✓	✓	Sept data cut
Time to response – IRAC	✓	X	X
Time to response – investigator	✓	✓	X
Duration of response – IRAC	✓	X	X
Duration of response – investigator	✓	✓	X
QoL	✓	X	Mar data cut
Full safety data[d]	✓	X	Mar data cut
Full CSR	✓	X	X

Key: CSR, clinical study report; IRAC, independent response adjudication committee; OS, overall survival; PFS, progression-free survival; QoL, quality of life; TTF, time to treatment failure; TTP, time to progression.

Notes: [a] All outcomes are presented in Section 4.7.

[b] 01 March 2013 data was from a pre-planned data cut.

[c] 01 September 2013 data was from a post-hoc data analysis.

[d] For the 01 March data cut, full safety data are presented in the MM-003 CSR; for the 01 September data cut, updated safety data are presented in the Dimopoulos 2015 publication, but this is not a full safety dataset[119]

Sources: 01 March data cut: MM-003 CSR[17]; 01 September data cut: Dimopoulos 2015[119];San Miguel 2015[20] and data on file[120]

Table 18: Summary of statistical analyses in MM-003

Hypothesis objective	To compare the efficacy and safety of POM+LoDEX to HiDEX in subjects with refractory or RRMM
Statistical analysis	PFS and OS were estimated with the KM product-limit method, and a log-rank test (stratified by the three randomisation stratification variables) was used as the primary analytic method to compare survivorship functions between treatment groups Two-sided 95% CIs for the median time-to-event in each treatment group, the event-free rate at specific time-points, and the hazard rate (risk) ratio (based on Cox proportional hazards model comparing treatment groups using the stratification factors as prognostic variables) were computed. An unstratified log-rank test was performed in addition to the stratified analysis The Cox proportional hazards model was used in exploratory analyses to determine which demographic and prognostic variables most affected treatment outcome and to adjust the treatment comparisons for these variables As secondary analyses, PFS based on IRAC assessed response using the EBMT criteria and PFS based on the investigator-assessed response (IMWG criteria only) were analysed similarly. The primary analysis followed the censoring rules based on the EMA guideline on the evaluation of anti-cancer medicinal products and Appendix 1.[121] Alternative censoring rules based on the FDA guideline were used as a sensitivity analysis.[122] A comparison of time to treatment failure between the two groups was also carried out as a sensitivity analysis Exact test procedures were used to compare response rates. Analyses were performed both to compare the distribution of responses over all response categories (CR, VGPR, PR, stable disease and PD), and to compare the proportions showing at least a confirmed PR. The percentage and 95% CIs were provided for myeloma response data. The Cochran–Mantel–Haenszel test was used to compare response rates (≥PR) between the two treatment arms, using the stratification factors as prognostic variables Analysis for TTP and DOR (responders only) used the same methods as PFS analysis. Time to response (responders only) was compared between treatment arms using the Wilcoxon rank sum test, with subjects with the longest TTR having the highest rank. In addition, time to first response (PR or better) and time to VGPR or better, based on IRAC assessment using IMWG criteria only, were compared between treatment groups using the Wilcoxon rank sum test Censoring for TTP (with progressive disease as an event) and DOR (with both progressive disease and death on study as events) followed the same rules for PFS The QoL compliance was computed at each visit and compared between treatment groups for EORTC QLQ-C30, QLQ-MY20, and EQ-5D. The subscale scores at each assessment and the changes from baseline for post-baseline assessments were summarised by treatment group. Change from baseline was tested for statistical significance using a paired t-test for within-treatment comparisons and using an unpaired t-test for between-treatment comparisons. Time to QoL worsening was calculated as the time from baseline to the first worsened minimally important difference, calculated as the smallest change in an HRQL score considered important to patients that would lead the patient or clinician to consider a change in therapy
Sample size, power calculation assessment timing and patient withdrawals	A total of 426 patients (284 in the POM+LoDEX group, 142 in the HiDEX group) were planned for enrolment in the study. The primary analysis for PFS was planned to be performed after 242 patients progressed or died during the study (PFS events), with 85% power to detect a hazard ratio of 1.5 (HiDEX vs POM+LoDEX) or 0.67 (POM+LoDEX vs HiDEX) for PFS between the two treatment groups (from 5 to 7.5 months) at the two-sided significance level of 0.05 (equivalent to a one-sided alpha of 0.025). Interim analysis for PFS using a group sequential procedure (for futility only) was performed at 50% information when approximately 121 subjects across both

	treatment arms had progressed or died during the study. Statistical analysis for OS was the same as for PFS and was based on the ITT population. The final OS analysis was to be done after 212 patients from both treatment arms died during the study. An interim analysis of OS was planned at the same time as the final PFS analysis (or at 50% OS information, whichever was later) and used the stringent O'Brien–Fleming boundary for superiority. For the analysis of PFS, missing assessments or discontinuations due to reasons other than progressive disease were handled by censoring rules based on the EMA guideline on the evaluation of anti-cancer medicinal products and it's Appendix 1.[121]
Key: CI, confidence intervals; CR, complete response; DOR, duration of response; EBMT, European Society for Blood and Marrow Transplantation; EMA, European Medicines Agency; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, EuroQol five dimensions questionnaire; FDA, Food and Drug Administration; HiDEX, high-dose dexamethasone; HRQL, heath-related quality of life; KM, Kaplan-Meier; IMWG, International Myeloma Working Group; IRAC, independent response adjudication committee; ITT, intention to treat, LoDEX, low-dose dexamethasone; OS, overall survival; PD, progressive disease; PFS, progression-free survival; POM, pomalidomide; PR, partial response; QLQ-C30, Core Quality of Life questionnaire; QLQ-MY20, Quality of life Questionnaire – Multiple Myeloma Module; QoL, quality of life; RRMM, relapsed and refractory multiple myeloma; TTP, time to progression; TTR, time to response; VGPR, very good partial response. **Source:** MM-003 CSR[17]	

4.4.2 MM-003 Subgroup analyses

Subjects were divided into subgroups based on stratification factors of age (≤75 versus >75 years), disease population (refractory versus relapsed and refractory versus refractory/intolerant), and prior anti-myeloma therapies (2 versus >2 prior anti-myeloma therapies). Pre-planned subgroup analyses were performed for efficacy endpoints, including PFS, OS, myeloma response rate and response duration based on IRAC assessment using IMWG criteria.[17]

Additional pre-planned subgroup analyses were conducted for gender, race, baseline Eastern Cooperative Oncology Group (ECOG) Performance Status, baseline cytogenetic categories (high risk versus non-high risk), parameters of prognostic significance (e.g., baseline renal impairment), refractoriness to selected prior anti-myeloma therapies, and for subjects randomised at least 6 months prior to the data cut-off.[17]

Each subgroup was evaluated separately using analysis methods described for primary and secondary efficacy outcomes. If too few subjects fell into any subgroup, analysis within that subgroup may not have been performed or alternative cut-off

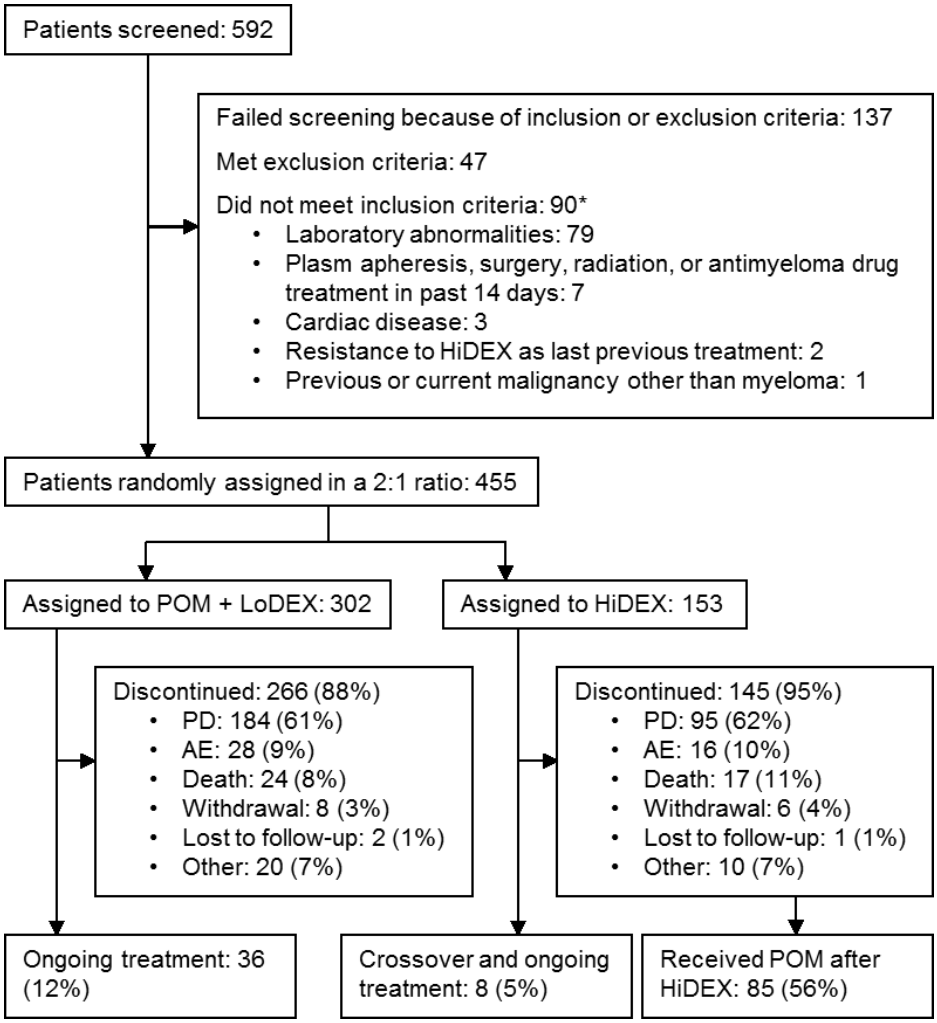
points (e.g., in age or number of prior anti-myeloma therapies) may have been considered.

4.5 Participant flow in the relevant randomised controlled trials

4.5.1 MM-003 participant flow

A total of 455 subjects were randomised: 302 in the POM+LoDEX arm and 153 in the HiDEX arm (Figure 7).

Figure 7: CONSORT flow diagram for MM-003



Note: *Two patients excluded for more than one reason.
Key: AE, adverse event; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; PD, progressive disease; POM, pomalidomide.
Source: MM-003 CSR[17]; San Miguel 2015[20]; San Miguel, 2013[110]

As previously stated, there were two pre-planned data cut-off points in the study: 07 September 2012 for final PFS and interim OS analysis (median follow-up 4.2 months) and 01 March 2013 for updated PFS and final OS (median follow-up 10.0 months)[17], as well as an extended follow-up data cut at 01 September 2013 (median follow-up 15.4 months).[20, 119, 120] At the final analysis for PFS and the interim analysis for OS, the IDMC recommended that people in the HiDEX group who had not progressed should have the option to receive POM (with or without LoDEX), as the results achieved with POM+LoDEX were favourable compared to HiDEX.[17]

A total of 85 patients (56%) crossed over to the POM group, either from entering the companion study[118] due to progressive disease on HiDEX (MM-003c) (n=74)[123] or as a result of the IDMC recommendation (n=11). Thus the updated PFS data and final OS data are confounded. The original switching of patients on HiDEX to POM±LoDEX, and the later crossover of patients on HiDEX to POM±LoDEX is expected to have reduced the difference in OS between treatment groups at final analysis. PFS data are confounded to a lesser extent than OS data as the majority of patients crossed over to POM based on disease progression, and not as a result of the later IDMC decision.[17]

4.5.2 MM-003 baseline characteristics

Baseline characteristics of the study populations in both treatment groups were well balanced (Table 19). The median age, age distribution, sex and ISS stage were similar in both treatment groups. The median time since diagnosis was 5.3 years and 6.1 years, respectively, in the POM+LoDEX and HiDEX groups. The median number of prior anti-myeloma regimens was five in both treatment groups. Similar percentages of patients in both treatment groups were refractory to prior treatments. The majority of patients were refractory to LEN (95% in the POM+LoDEX group and 92% in the HiDEX group). The same high percentage of patients was refractory to BOR in the POM+LoDEX and HiDEX groups (79%). Most patients were also refractory to both LEN and BOR (75% in the POM+LoDEX group and 74% in the HiDEX group).

Baseline characteristics for stratification factors were also well balanced. Approximately 92% of subjects in both treatment arms were ≤75 years of age. In each treatment arm, over 80% of subjects (based on stratification factor for Disease Population Group 1) were refractory and had progressed on or within 60 days of both

LEN and BOR-based treatments and over 94% of subjects had more than two prior anti-myeloma therapies. The full detailed baseline characteristics are presented in Appendix 2.

Table 19: Baseline characteristics & prior treatments: ITT population MM-003

	POM+LoDEX (n=302)	HiDEX (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, 31.8)	4.4 (1.6, 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)		
<30mL/min	2 (0.7),	3 (2.0),
30 - <45mL/min	28 (9.3)	15 (9.8)
45 - <60mL/min	65 (21.5)	41 (26.8)
60 - <80mL/min	97 (32.1)	41 (26.8)
≥80mL/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)

Key: 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.
Notes: [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.[17, 110]
Data cut-off: 01 March 2013.

4.6 *Quality assessment of the relevant randomised controlled trials*

Table 20: Quality assessment results for MM-003

Was randomisation carried out appropriately?	Yes. Patients were randomised in a 2:1 ratio by permuted block randomisation. Randomisation was undertaken using a validated interactive voice/web response system (IVRS/IWRS).
Was the concealment of treatment allocation adequate?	MM-003 is an open-label study.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Baseline characteristics of the study populations in both treatment groups were well balanced in terms of age, age distribution, sex, disease stage, performance status, cytogenic risk, median time since diagnoses, median number of prior anti-myeloma regimens, and previous treatments. Patients were also well balanced for baseline beta-2-microglobulin, baseline distribution of beta-2-microglobulin, baseline albumin, baseline distribution of albumin, baseline renal function and baseline ECG.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Although the study was open-label, the sponsor's study team was blinded to the study treatment code until the final analysis of the primary endpoint. An independent Response Adjudication Committee (IRAC) reviewed all efficacy data in a blinded manner, independent of investigator response to ensure an unbiased assessment of the data.
Were there any unexpected imbalances in drop-outs between groups?	No. The majority of patients in both treatment groups discontinued treatment due to progressive disease (61% of discontinuations for the POM+LoDEX group versus 62% for the HiDEX group). Similar percentages of patients in both treatment groups discontinued due to AEs or death. Similar percentages withdrew from the study, were lost to follow-up or withdrew due to other causes (see Section 4.5).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All treatment outcomes were reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The analysis included an ITT population, which was the most appropriate population as it included all randomised patients. A safety population, defined as all patients who took at least one dose of study medication, and an efficacy evaluable population, defined as all ITT patients who took at least one dose of study treatment and who had baseline disease measurement and at least one post-baseline efficacy assessment or PFS were also included. Appropriate censoring methods were used to account for missing data. Missing assessments or discontinuations due to reasons other than progressive disease were handled by censoring rules based on the EMA guidelines on the evaluation of anti-cancer medicinal products and Appendix 1.[121]
Key: AEs, adverse events; ECG, electrocardiogram; EMA, European Medicines Agency; HiDEX, high-dose dexamethasone; ITT, intention to treat; IVRS, interactive voice response system; IWRS, interactive web response system; LoDEX, low-dose dexamethasone; PFS, progression-free survival; POM, pomalidomide.	

4.7 *Clinical effectiveness results of the relevant randomised controlled trials*

4.7.1 MM-003 Efficacy results summary

- POM+LoDEX treatment produced statistically significantly better outcomes than HiDEX in terms of PFS, TTP, TTF, DOR and objective response rate (ORR). In addition, POM+LoDEX treatment led to a statistically significantly longer OS; despite 56% of patients crossing over on the HiDEX arm.[17, 20, 119]
- Relative to HiDEX, POM+LoDEX significantly improved HRQL in terms of side effects of treatment, disease symptoms, physical and emotional functioning, fatigue, pain and utility change from baseline. Over the course of treatment there was a significant improvement in utility on the EQ-5D.[33, 56]
- Response rates and PFS associated with POM+LoDEX were similar regardless of number and type of prior therapies.[20]
- In patients who achieved at least a PR (≥50% M Protein reduction) to treatment with POM+LoDEX, the associated median PFS and OS was 8.4 and 19.9 months, respectively.[20] Even in patients who achieved at least a MR (≥25% M Protein reduction), associated median PFS and OS were 7.4 and 17.2 months, respectively.

Table 21: MM-003 efficacy results summary: ITT population

Outcomes[a]	01 March 2013 data cut[b]		01 September 2013 data cut[c]	
	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 [*p*-value]	0.49 [<0.001]		0.50 [<0.001]	
OS, median, months	12.5	8.1	13.1	8.1
HR [*p*-value]	0.70 [0.009]		0.72 [0.009]	
ORR, %	23.5	3.9	32	11
OR [*p*-value]	7.53 [<0.001]		3.79 [<0.001]	

Outcomes[a]	01 March 2013 data cut[b]		01 September 2013 data cut[c]	
	POM+LoDEX	HiDEX	POM+LoDEX	HiDEX
TTP, median, months	4.6	2.1	4.7	2.1
HR [*p*-value]	0.46 [<0.001]		0.49 [<0.001]	
TTF, median, months	2.9	1.8	2.9	1.8
HR [*p*-value]	0.48 [<0.001]		0.50 [<0.001]	
DOR, median, months	8.1	6.5	7.5	5.1
HR [*p*-value]	0.53 [0.224]		0.52 [0.031]	

Key: DOR, duration of response; HiDEX, high-dose dexamethasone; HR, hazard ratio; IRAC, Independent Response Adjudication Committee; ITT, intention to treat; LoDEX, low-dose dexamethasone; NR, not reported; PFS, progression-free survival; OR, odds ratio; ORR; overall response rate; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; TTF; time to treatment failure; TTP, time to progression.
Notes: [a]Values in months have been converted from weeks (as they were reported in the MM-003 CSR and in the September 2013 data cut tables data on file) using the conversion factor of 0.22998 (calculated by 7/365.25*12)
[b] 01 March 2013 data cut was from a pre-planned assessment by IRAC using IMWG criteria.
[c] 01 September 2013 data cut was from a post-hoc analysis using investigator assessed outcomes by IMWG criteria.
Sources: for 01 March data cut: MM-003 CSR[17]; for 01 September data cut: Dimopoulos, 2015[119]; San Miguel 2015[20] and data on file[120]

In the following sections, all data from the 01 March 2013 data cut are taken from the MM-003 CSR unless otherwise stated.[17] All data from the 01 September data cut are taken from the San Miguel publication[20] where reported, and supplemented by the data on file data tables.[120]

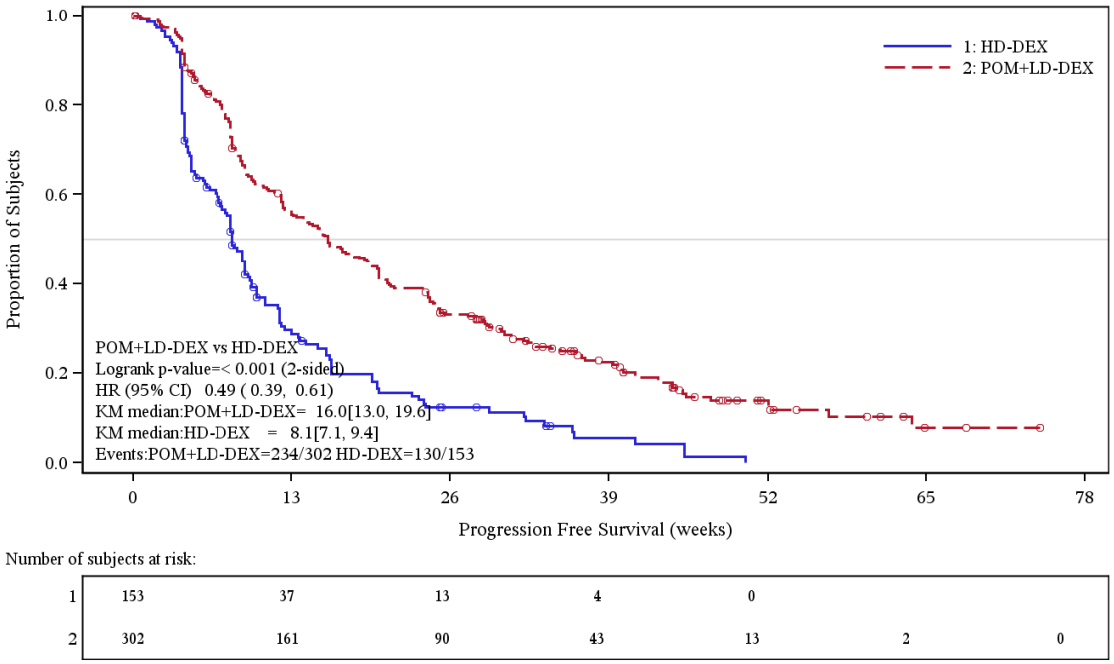
4.7.2 MM-003 progression-free survival

PFS results: IRAC assessment, 01 March 2013 data cut-off

PFS data for study MM-003 demonstrate that POM+LoDEX until disease progression was a more effective regimen than HiDEX. At the planned 01 March 2013 analysis, POM+LoDEX significantly improved PFS as compared with HiDEX (HR=0.49, 95% CI 0.39–0.61, p<0.001). The difference in median PFS between POM+LoDEX (3.7 months) and HiDEX (1.9 months) was 1.8 months. Note that the final PFS data analysis had already been conducted on 01 September 2012, as the required number of events had been surpassed.[17]

Figure 8 shows KM estimates of PFS based on the IRAC review for the primary comparison between POM+LoDEX and HiDEX at the 01 March 2013 data cut-off.

Figure 8: KM curves of PFS (based on IRAC review by IMWG criteria) for MM-003 (01 March 2013 data cut-off)



Key: HD-DEX, high-dose dexamethasone; HR, hazard ratio; IMWG, International Myeloma Working Group; IRAC, Independent Review Adjudication Committee; ITT, intention to treat; KM, Kaplan-Meier; PFS, progression-free survival; POM+LD-DEX, pomalidomide in combination with low-dose dexamethasone.
Notes: PFS based on IRAC Review of Response by IMWG Criteria using the later data cut-off (stratified log rank test) (ITT population).
Source: MM-003 CSR.[17]

Consistent PFS results were found by IRAC review based on EBMT criteria, investigator assessment based on IMWG criteria and in the efficacy evaluable population.

Investigator assessment, 01 September 2013 data cut-off

The PFS advantage for POM+LoDEX compared with HiDEX was also seen by investigator assessment using IMWG criteria at the 01 September 2013 data cut-off. POM+LoDEX significantly improved PFS as compared with HiDEX (HR=0.50; p<0.001). The difference in median PFS between POM+LoDEX (4 months) and HiDEX (1.9 months) was 2.1 months.[20, 120]

The results for PFS by IRAC assessment for the 01 March 2013 data cut, and by investigator assessment for the 01 September 2013 are presented in Table 22.

Table 22: PFS using protocol-defined censoring rules: ITT population

	01 March 2013 data cut-off[a17] (IRAC)		01 September 2013 data cut-off[b20, 120] (Investigator)	
	POM+LoDEX (N = 302)	HiDEX (N = 153)	POM+LoDEX (N = 302)	HiDEX (N = 153)
Median follow-up, mths[c]	10.0		15.4	
PFS events, n (%)				
Censored	68 (22.5)	23 (15.0)	49 (16.2)	15 (9.8)
Progressed/Died	234 (77.5)	130 (85.0)	253 (83.8)	138 (90.2)
PFS time, months				
Median (95% CI)[c]	3.7 (3.0-4.5)	1.9 (1.6-2.2)	4.0 (3.6-4.7)	1.9 (1.9-2.2)
HR (95% CI)	0.49 (0.39–0.61)		0.50 (0.41-0.62)	
Log-rank test *p*-value	*p*<0.001		*p*<0.001	

Key: CI, confidence interval; HiDEX, high-dose dexamethasone; HR, hazard ratio; ITT, intention to treat; LoDEX, low-dose dexamethasone; PFS, progression-free survival; POM, pomalidomide.

Notes: [a]01 March 2013 data cut was from a pre-planned assessment by IRAC using IMWG criteria.

[b]01 September 2013 data cut was from a post-hoc analysis using investigator assessed outcomes based on IMWG criteria.

[c]Values in months have been converted from weeks (as they were reported in the MM-003 CSR and in the September 2013 data cut tables data on file) using the conversion factor of x 0.22998 (calculated by 7 / 365.25 x 12).

Sources: 01 March 2013 data cut: MM-003 CSR[17]; 01 September 2013 data cut: San Miguel 2015[20] and data on file[120]

4.7.3 MM-003: overall survival

Overall survival results: 01 March 2013 data cut-off

OS was statistically significantly longer in POM+LoDEX treated patients compared with those taking HiDEX. Median OS was 12.5 months in the POM+LoDEX group, compared with 8.1 months in the HiDEX group (HR=0.70 [95% CI: 0.54-0.92]; *p*=0.009). The 1-year event-free survival rate was 70.4±2.68% for the POM+LoDEX arm and 59.5±4.07% for the HiDEX arm. A total of 155 (51.3%) patients assigned to the POM+LoDEX arm and 67 (43.8%) patients initially assigned to the HiDEX arm were alive as of 01 March 2013. The relatively high percentage of patients surviving on the HiDEX arm is reflective of the cross-over effect with patients receiving treatment with POM+/-LoDEX.

Overall survival results: 01 September 2013 data cut-off

At the 01 September 2013 cut-off OS was statistically significantly longer in POM+LoDEX treated patients compared with those taking HiDEX. Median OS was

13.1 months in the POM+LoDEX group, compared with 8.1 months in the HiDEX group (HR=0.72 [95% CI: 0.56-0.92]; *p*=0.009; Figure 9).[20] This OS advantage was observed despite 85 patients (56%) on the HiDEX arm receiving subsequent POM-based treatment. A total of 126 (41.7%) patients assigned to the POM+LoDEX arm and 52 (34.0%) patients initially assigned to the HiDEX arm were alive as of 01 September 2013.[120]

OS results for the efficacy evaluable population were consistent with those observed in the ITT population.

Table 23: OS: ITT population

	01 March 2013 data cut-off[a17]		01 September 2013 data cut-off[b20, 120]	
	POM+LoDEX (n=302)	**HiDEX (n=153)**	**POM+LoDEX**	**HiDEX**
Median follow-up, mths[c]	**10.0**		**15.4**	
OS events, n (%)				
Censored	155 (51.3)	67 (43.8)	126 (41.7)	52 (34.0)
Died	147 (48.7)	86 (56.2)	176 (58.3)	101 (66.0)
OS, months				
Median (95% CI)[c]	12.5 (10.5-15.3)	8.1 (6.9-9.0)	13.1 (11.0-15.4)	8.1 (6.9-9.2)
HR (95% CI)	0.70 (0.54-0.92)		0.72 (0.56-0.92)	
Log-rank test *p*-value	0.009		0.009	

Key: CI, confidence interval; HiDEX, high-dose dexamethasone; HR, hazard ratio; ITT, intention to treat; LoDEX, low-dose dexamethasone; OS, overall survival; POM, pomalidomide.

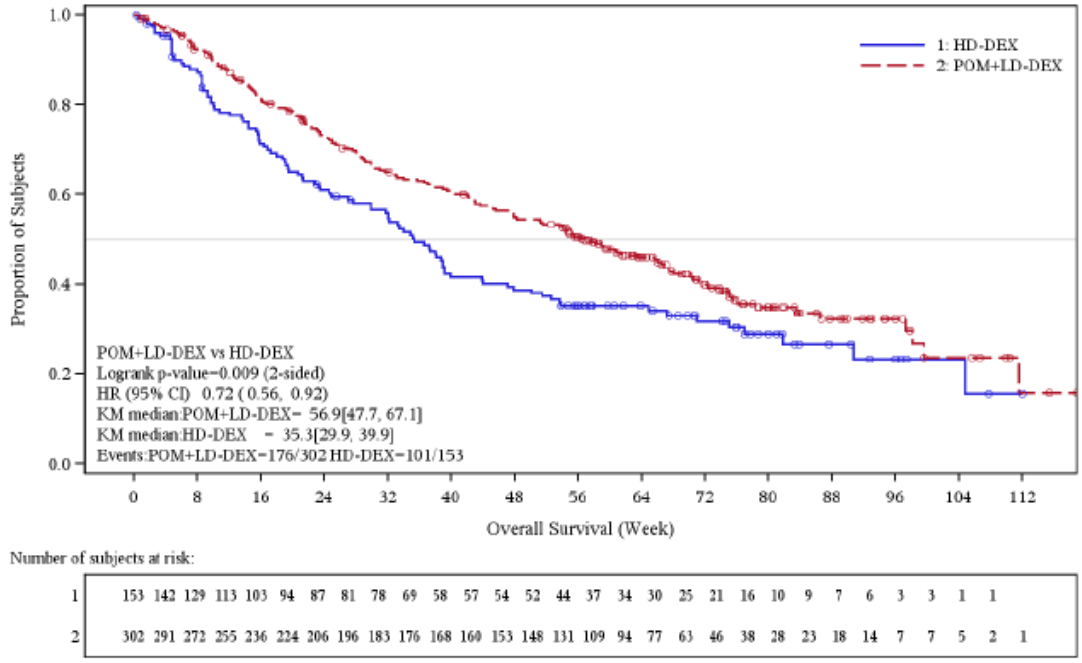
Notes: [a]01 March 2013 data cut was from a pre-planned assessment by IRAC using IMWG criteria.

[b]01 September 2013 data cut was from a post-hoc analysis using investigator assessed outcomes based on IMWG criteria.

[c]Values in months have been converted from weeks (as they were reported in the MM-003 CSR and in the September 2013 data cut tables data on file) using the conversion factor of x 0.22998 (calculated by 7 / 365.25 x 12).

Sources: 01 March 2013 data cut: MM-003 CSR[17]; 01 September 2013 data cut: Data on file[120]

Figure 9: KM curve of OS (ITT population), 01 September 2013 data cut



Key: CI, confidence interval; HD-DEX, high-dose dexamethasone; HR, hazard ratio; ITT, intention to treat; KM, Kaplan-Meier; OS, overall survival; POM+LD-DEX, pomalidomide in combination with low-dose dexamethasone.
Source: Data on file.[120]
Data cut-off: 01 September 2013.

OS analysis adjusting for crossover

Due to extensive treatment switching and trial crossover away from the HiDEX arm, conventional survival analysis methods are likely to produce biased estimates of HiDEX survival.[124] Two methods were used to account for treatment switching using the 01 March 2013 data cut; the two-stage method[125] and the rank preserving structure failure time model (RPSFTM) approach (Table 24).

The two-stage method compares survival estimates from the non-switching population and the switching population, and estimates the difference using an acceleration factor (AF). The adjusted OS estimates are then calculated using the pre-progression OS estimates and post-progression OS estimates which are 'shrunk' by the AF. The resulting OS estimates for HiDEX remove the biasing effect of treatment switching and trial crossover.[126]

The two-stage method is preferred over other commonly used methods for the following reasons:

- The two-stage Weibull approach does not differentiate between the patients who switched to POM monotherapy via the companion study or those who experienced traditional, 'within-trial' crossover to POM+LoDEX. While the two-stage method does require the assumption of there being no unmeasured cofounders, this is only true at the point of disease progression
- The RPSFTM method requires the assumption of a common treatment effect which was deemed too restrictive given that the majority of patients switch to monotherapy and the vast majority of patients who switch do so having experienced an additional disease progression which may impact outcomes (potential non-commonality)
- The inverse probability of censoring weight method requires the assumption of no unmeasured confounders throughout the period being evaluated. It is not possible to meet this assumption as the majority of patients who switch treatments do so via the companion study MM-003c.[118] While OS is captured post-switching for these patients via the original study protocol, no other information is captured.

Table 24: Summary of crossover adjustment results

Median OS in months	POM+LoDEX (n = 302)	HiDEX (n = 153)	Difference
Intent-to-treat, median OS	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)
After crossover adjustment, median OS, 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)
After crossover adjustment, median OS, 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)

Key: CI, confidence interval; HiDEX, high-dose dexamethasone; HR, hazard ratio; LoDEX, low-dose dexamethasone; OS, overall survival; POM, pomalidomide; RPSFTM, rank preserving structure failure time model

Source: Morgan, 2015[126]

4.7.4 MM-003 time to progression

Time to Progression: 01 March 2013 data cut-off

TTP was conducted as a sensitivity analysis to PFS. Median TTP by IRAC review based on IMWG criteria in the ITT population was significantly longer for POM+LoDEX compared with HiDEX (4.6 versus 2.1 months; HR=0.46 [95% CI: 0.36-0.59]; p<0.001). The results from this sensitivity analysis corroborate the results from the primary analysis.[17]

Time to Progression: 01 September 2013 data cut-off

Data from the 01 September 2013 data cut support the earlier analysis. Median TTP by investigator review based on IMWG criteria in the ITT population was significantly longer for POM+LoDEX compared with HiDEX (4.7 versus 2.1 months; HR=0.49 [95% CI: 0.38-0.61]; p<0.001).[120] TTP for patients treated with POM+LoDEX was significantly longer than that with their last line of therapy (median 4.7 versus 4.4 months; HR=0.79; p=0.008). In contrast, patients treated with HiDEX progressed significantly more quickly than with their last prior line of therapy (median: 2.1 versus 4.3 months; HR 1.76; p<0.001).[20]

4.7.5 MM-003 time to treatment failure

Table 25 presents the TTF results for the ITT population for both data cuts.

Time to treatment failure: 01 March 2013 data cut-off

TTF was conducted as an additional sensitivity analysis to PFS. Median TTF by IRAC review based on IMWG criteria in the ITT population was significantly longer for POM+LoDEX compared with HiDEX (2.9 versus 1.8 months; HR=0.48 [95% CI: 0.39-0.60]; p<0.001).[17]

Time to treatment failure: 01 September 2013 data cut-off

Data from the 01 September 2013 data cut support the earlier analysis. Median TTF by investigator review based on IMWG criteria in the ITT population was significantly longer for POM+LoDEX compared with HiDEX (2.9 versus 1.8 months; HR=0.50 [95% CI: 0.40-0.61]; p<0.001).[120]

Table 25: Time to treatment failure: ITT population

	01 March 2013 data cut-off[a] [17] (IRAC)		01 September 2013 data cut-off[b] [120] (Investigator)	
	POM+LoDEX (n=302)	HiDEX (n=153)	POM+LoDEX (n=302)	HiDEX (n=153)
Censored, n (%)	43 (14.2)	3 (2.0)	25 (8.3)	1 (0.7)
Treatment failed, n (%)	259 (85.8)	150 (98.0)	277 (91.7)	152 (99.3)
Time to treatment failure (months)				
Median[c] [two sided 95% CI][d,e]	2.9 [2.7, 3.7]	1.8 [1.1, 1.9]	2.9 [2.7, 3.7]	1.8 [1.1, 1.9]
HR (POM+LoDEX:HiDEX) [two sided 95% CI][f]	0.484 [0.393, 0.596]		0.496 [0.404, 0.609]	
Stratified log-rank test (two sided *p*-value)[g]	< 0.001		< 0.001	

Key: CI, confidence interval; HiDEX, dexamethasone; HR, hazard ratio; IMWG, International Myeloma Working Group; IRAC, independent review adjudication committee; ITT, intention to treat; LoDEX, low-dose dexamethasone; POM, pomalidomide.

Notes: [a]01 March 2013 data cut was from an additional sensitivity analysis of PFS, based on assessment by IRAC using IMWG criteria; [b]01 September 2013 data cut was from an additional sensitivity analysis to PFS using investigator assessed outcomes based on IMWG criteria; [c]The median is based on Kaplan–Meier estimate; [d]95% CI about the median progression-free survival time; [e]Values in months have been converted from weeks (as they were reported in the MM-003 CSR and in the September 2013 data cut tables data on file) using the conversion factor of x 0.22998 (calculated by 7 / 365.25 x 12); [f]Based on Cox proportional hazards model comparing the hazard functions associated with treatment groups, stratified by age (≤75 vs >75), diseases population (refractory to both lenalidomide and bortezomib vs not refractory to both drugs), and prior number of anti-myeloma therapies (=2 vs > 2); [g]The p-value is based on a stratified log-rank test with the same stratification factors as the above Cox model.

Sources: 01 March 2013 data cut: CSR[17]; 01 September 2013 data cut: data on file[120]

4.7.6 MM-003: Myeloma response rates

A summary of myeloma response rates for each data cut is presented in Table 26.

Myeloma response rates: 01 March 2013 data cut-off

At the 01 March 2013 data cut-off, myeloma response rates for the ITT population were assessed by IRAC based on IMWG criteria. Complete response (CR) was observed in one patient in the POM+LoDEX arm. Objective responses (≥ partial response [PR]) were observed in 23.5% of patients in POM+LoDEX group and 3.9% of patients in the HiDEX group. Consistent results in response rates were observed

by IRAC review based on EBMT criteria, in the efficacy evaluable population and by investigator assessment.[17]

Myeloma response rates: 01 September 2013 data cut-off

At the 01 September 2013 data cut-off, myeloma response rates for the ITT population were only assessed by the investigator. At this data cut-off, a statistically significantly higher overall response rate (PR or better) was achieved in patients treated with POM+LoDEX compared to HiDEX (32% versus 11%; p<0.001). 40% of patients receiving POM+LoDEX compared to 15% of patients receiving HiDEX achieved a minimal response or better associated with a survival benefit.[20]

Table 26: Myeloma response rates using IMWG criteria: ITT population

	01 March 2013 data cut-off[a] [17] (IRAC)		01 September 2013 data cut-off[b] [120] (Investigator)	
Statistics	**POM+LoDEX (n=302)**	**HiDEX (n=153)**	**POM+LoDEX (n=302)**	**HiDEX (n=153)**
Response[c], n (%)	302 (100.0)	153 (100.0)	302 (100.0)	153 (100.0)
SCR	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
CR	1 (0.3)	0 (0.0)	3 (1.0)	0 (0.0)
VGPR	8 (2.6)	1 (0.7)	17 (5.6)	1 (0.7)
PR	62 (20.5)	5 (3.3)	76 (25.2)	16 (10.5)
StD	173 (57.3)	87 (56.9)	150 (49.7)	77 (50.3)
PD	36 (11.9)	42 (27.5)	29 (9.6)	41 (26.8)
Response not evaluable (NE)[d]	22 (7.3)	18 (11.8)	26 (8.6)	18 (11.8)
With at least one post-baseline assessment	10 (3.3)	9 (5.9)	0 (0.0)	0 (0.0)
No post-baseline assessment	12 (4.0)	9 (5.9)	26 (8.6)	18 (11.8)
p-value[e,f]	<0.001		<0.001	
Dichotomised response, n (%)	302 (100.0)	153 (100.0)	302 (100.0)	153 (100.0)
SCR or CR or VGPR or PR	71 (23.5)	6 (3.9)	97 (32.1)	17 (11.1)
StD or PD or NE[d]	231 (76.5)	147 (96.1)	205 (67.9)	136 (88.9)
p-value[g]	<0.001		<0.001	
OR (95% CI)[h]	7.53 (3.19,17.77)		3.79 (2.16, 6.62)	
p-value[i]	<0.001		<0.001	

Key: CI, confidence interval; CR, complete response; HiDEX, high-dose dexamethasone; IMWG, International Myeloma Working Group; IRAC, independent review adjudication committee; ITT, intention to treat; LoDEX, low-dose dexamethasone; NE, not evaluable; OR, odds ratio; PD, progressive disease; POM, pomalidomide; PR, partial response; SCR, stringent complete response; StD, stable disease; VGPR, very good partial response.
Notes: [a]01 March 2013 data cut was from a pre-planned assessment by IRAC using IMWG criteria. [b]01 September 2013 data cut was from a post-hoc analysis using investigator assessed outcomes based on IMWG criteria; [c]Response is the best overall response; [d]Including patients who did not have any response assessment data, or whose only assessment was response not evaluable; [e]Probability from Wilcoxon rank sum test; [f]p-value calculation excludes the category 'response not evaluable (NE)'; [g]Probability from Fisher exact test; [h]Odds ratio is for POM+LoDEX:HiDEX; [i]p-value is based on a Cochran–Mantel–Haenszel test stratified by age (≤75 years vs >75 years), diseases population (refractory to both lenalidomide and bortezomib vs not refractory to both drugs), and previous number of anti-myeloma therapies (2 vs >2).
Sources: 01 March 2013 data cut: CSR[17]; 01 September 2013 data cut: data on file[120]

4.7.7 MM-003: Duration of response and time to response

Duration of response and time to response: 01 March 2013 data cut-off

Among responders to treatment, response was faster and more durable in the POM+LoDEX group than the HiDEX group. Using the 01 March 2013 data cut-off, the median time to first response (assessed by IRAC based on IMWG criteria) for the ITT population was 1.9 months (min, max: 0.9, 11.0) in the POM+LoDEX group and 2.4 months (min, max: 0.9, 9.7) in the HiDEX group.[17] Furthermore, DOR (assessed by IRAC based on IMWG criteria) was 8.1 months (95% CI: 6.5, 12.2) for patients treated with POM+LoDEX, compared to 6.5 months (95% CI: 4.6, 8.5) for patients treated with HiDEX (HR=0.53 [95% CI: 0.19, 1.51]; *p*=0.224).[17]

Duration of response and time to response: 01 September 2013 data cut-off

At the 01 September 2013 data cut-off, the median time to first response (assessed by Investigator based on IMWG criteria) for the ITT population was faster with POM+LoDEX compared with HiDEX 1.9 [min, max: 0.9, 12.1] versus 3.0 months (min, max: 0.9, 19.9), which was almost statistically significant (*p*=0.073). The median DOR (by Investigator assessment based on IMWG criteria) was statistically significantly longer with POM+LoDEX than with HiDEX (7.5 [95% CI: 6.0, 9.5] versus 5.1 months [95% CI: 1.7, 8.5]; HR=0.52 [95% CI: 0.29, 0.95]; *p*=0.031).[120]

Consistent results for TTR and DOR were observed by EBMT criteria and investigator assessment.[17]

4.7.8 MM-003: Health-related quality of life

HRQL data were only reported from the 01 March 2013 data cut. Evidence is presented from the Song 2015 publication for a cross-sectional analysis and a longitudinal analysis and from the Wiesel 2015 publication for a logistic regression analysis and an assessment of minimally important difference (MID).[33, 56]

HRQL questionnaires were completed on Day 1 of each treatment cycle and at treatment discontinuation for three complementary questionnaires: the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, the myeloma-specific EORTC QLQ-MY20 and the EQ-5D. The patient-reported outcome

(PRO) questionnaire population included any ITT study participants with at least one active treatment and at least one PRO measurement item completed.

Because of the progressive nature of RRMM, participant numbers dropped over time. However, up to cycle 10, overall reporting compliance was generally high and comparable across treatment groups: 96.8% or higher at the Cycle 1 visit[127] and ≥77.8% for each HRQL questionnaire across all assessment time points considered.[33, 56]

Health-related quality of life results over time

Data from the PRO population (n=433) were analysed to evaluate the changes from baseline in the following HRQL measures: QLQ-MY20 side effects, QLQ-MY20 disease symptoms, QLQ-C30 global health status, QLQ-C30 physical functioning, QLQ-C30 emotional functioning, QLQ-C30 fatigue, QLQ-C30 pain and EQ-5D health utility.[33, 56]

In the cross-sectional analysis, there was a trend for HRQL scores to be better for POM+LoDEX compared to HiDEX for all domains at every cycle. In the POM+LoDEX arm, the mean score improved significantly from baseline (p<0.05) for the health utility domain and deteriorated significantly for side effects of treatment. In the HiDEX arm, no domains showed improvement and five showed deterioration from baseline: physical functioning, health utility, fatigue, disease symptoms and side effects of treatment. Between treatment groups there were no domains with statistical significance favouring the HiDEX arm. Moreover, there were statistically significant differences favouring POM+LoDEX in change from baseline for the following five out of eight HRQL domains[33]

- QLQ-MY20 side effects at Cycle 7 (p<0.05)
- QLQ-C30 physical functioning at Cycle 3 and Cycle 4 (p<0.05)
- QLQ-C30 emotional functioning at Cycle 3, Cycle 4 and Cycle 5 (p<0.05)
- QLQ-C30 fatigue at Cycle 9 (p<0.05)
- EQ-5D health utility at Cycle 6 and Cycle 8 (p<0.05)

In a longitudinal analysis, using repeated measure mixed-effect models, there were significant (p<0.05) overall treatment differences between POM+LoDEX and HiDEX over the course of treatment in seven of the eight pre-selected clinically relevant domains: global health status (p=0.0451), physical functioning (p<0.0001), emotional functioning (p=0.0003), health utility (p=0.005), fatigue (p=0.0008), pain (p=0.0049), and side effects of treatment (p=0.0253). Only disease symptoms did not demonstrate a significant difference. Comparisons of adjusted means of score differences from baseline between treatment arms at each cycle confirmed the superiority of POM+LoDEX treatment arm in these seven domains.[33]

In repeated-measures logistic regression analyses five out of eight domains demonstrated a trend or statistically significant improvement in OR favouring POM+LoDEX versus HiDEX (Figure 10): a statistically significant (p<0.05) OR was shown for EORTC QLQ-C30 domains of physical functioning, emotional functioning and fatigue, whereas a trend (p<0.01) was shown for EORTC QLQ-MY20 side effects of treatment and EQ-5D health utility.[56]

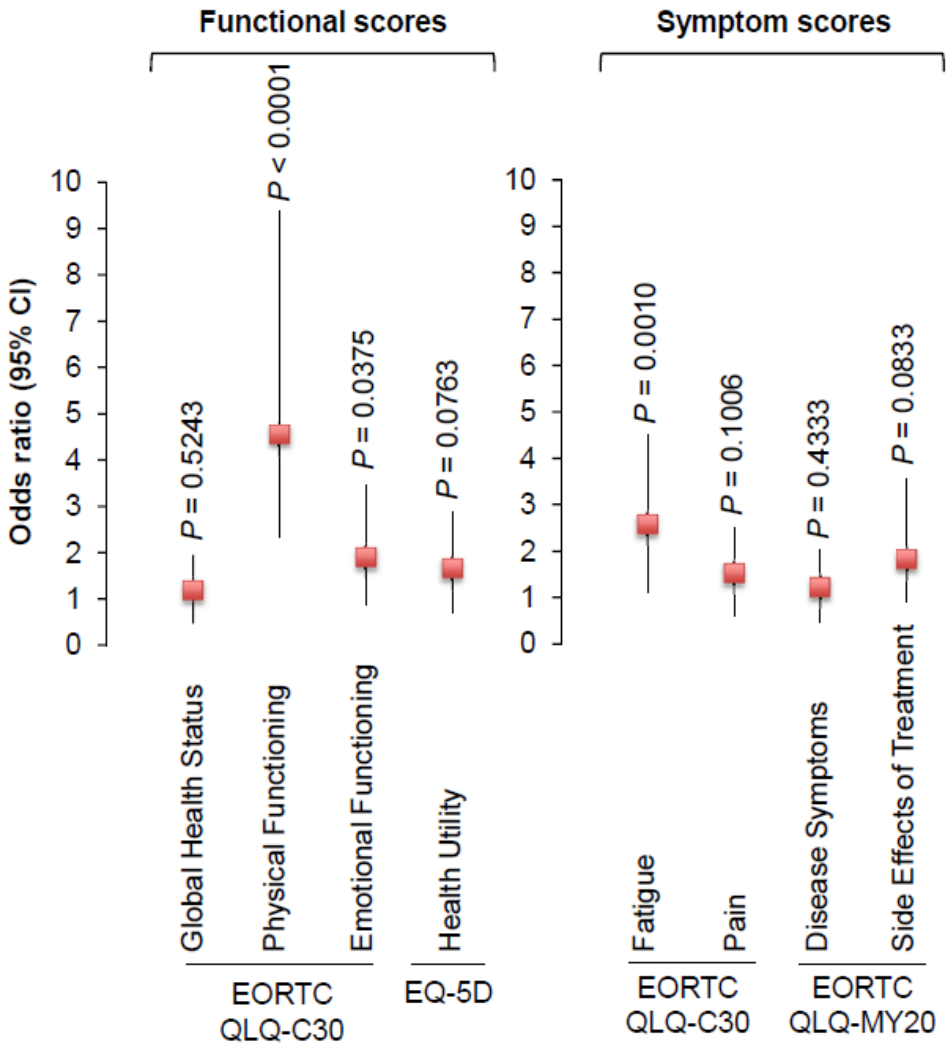
Moreover, mixed-model analysis of the EQ-5D utility index score showed that there was a significant effect for treatment (p=0.005) on utility (Table 27).[127]

Table 27: Type 3 tests of fixed effects for mixed model results on EQ-5D health index changes from baseline

Domain	Effect	Num df	Den df	F-value	p-value[a]
EQ-5D utility index	Treatment	1	574	7.9419	0.0050*
	Time	5	1141	0.4599	0.8062
	Treatment x time	5	1141	1.9736	0.0799

Key: Den, denominator; df, degrees of freedom; EQ-5D, EuroQoL five dimensions; Num, numerator.
Notes: [a], p-value was calculated using an F-test; *, p<0.05
Model was adjusted for age group, RRMM type, and prior previous anti-myeloma therapies.
Source: Adelphi report, 2013.[127]
Data cut-off: 1 March 2013.

Figure 10: Odds of improvement in HRQL for POM+LoDEX versus HiDEX



Key: CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-Life questionnaire - cancer; EORTC QLQ-MY20, European Organisation for Research and Treatment of Cancer Quality-of-Life questionnaire - myeloma; EQ-5D, EuroQoL five dimensions; HiDEX, high-dose dexamethasone; HRQL, health related quality of life; POM+LoDEX, pomalidomide in combination with low-dose dexamethasone.
Source: Wiesel et al., 2015[56]

Over time, clinically meaningful improvements in HRQL, as determined by the minimally important difference (MID), were more frequently observed in patients receiving POM+LoDEX than in those receiving HiDEX, as supported by the proportion of patients achieving "improved" MID in each treatment arm. Changes in HRQL scores from baseline generally favoured POM+LoDEX over HiDEX. Overall, in seven of the eight domains of clinical interest (physical functioning, emotional functioning, health utility, fatigue, pain, disease symptoms, and side effects of

treatment), higher percentages of patients randomised to POM+LoDEX had improved HRQL compared with HiDEX. Similarly, patients randomised to HiDEX more frequently had worsened HRQL. Significant differences (p<0.05) in MID-based responses in favour of patients randomised to POM+LoDEX were observed at specific time points in physical functioning, emotional functioning, health utility, and fatigue scores. In addition, trends (p<0.10) favouring POM+LoDEX were also observed at specific time points in global health status, emotional functioning, fatigue, and pain scores. No differences in favour of the HiDEX treatment arm were observed.

4.7.9 MM-003: Subsequent anti-myeloma therapies

By the time of the 01 September 2013 data cut, 56% (85/153) of patients on the HiDEX arm received subsequent therapy with POM. 11 patients (7.2%) entered MM-003 companion study and received POM as they progressed on HiDEX. The remaining 74 patients (48.4%) received POM (with or without LoDEX) at the final analysis for PFS and the interim analysis for OS based on the IDMC recommendation that people in the HiDEX group who had not progressed should have the option to receive POM. The most commonly used subsequent therapies were DEX, cyclophosphamide, BOR and BEN, which may have been used alone or in combination. A summary of subsequent therapy by treatment arm is presented in Table 28.

Table 28: Subsequent post-study anti-myeloma therapy (ITT population) (01 September 2013 data cut)

Subsequent therapy, n (%)[a]	POM+LoDEX (N = 302)	HiDEX (N = 153)
≥1 subsequent anti-myeloma drug	134 (44.4)	92 (60.1)
Pomalidomide	1 (0.3)	74 (48.4)[b]
Dexamethasone	88 (29.1)	36 (23.5)
Cyclophosphamide	64 (21.2)	17 (11.1)
Bortezomib	54 (17.9)	24 (15.7)
Bendamustine	34 (11.3)	13 (8.5)

Key: HiDEX, high-dose dexamethasone; ITT, intention to treat; LoDEX, low-dose dexamethasone; POM, pomalidomide.

Note:;[a] Patients may have received more than one of the subsequent treatments listed therefore numbers listed for individual drugs do not necessarily correlate with the total number of patients receiving ≥1 subsequent anti-myeloma drug. [b] An additional 11 patients crossed over to the POM+DEX arm during the study after IDMC review

Source: Data on file, 2016[128]

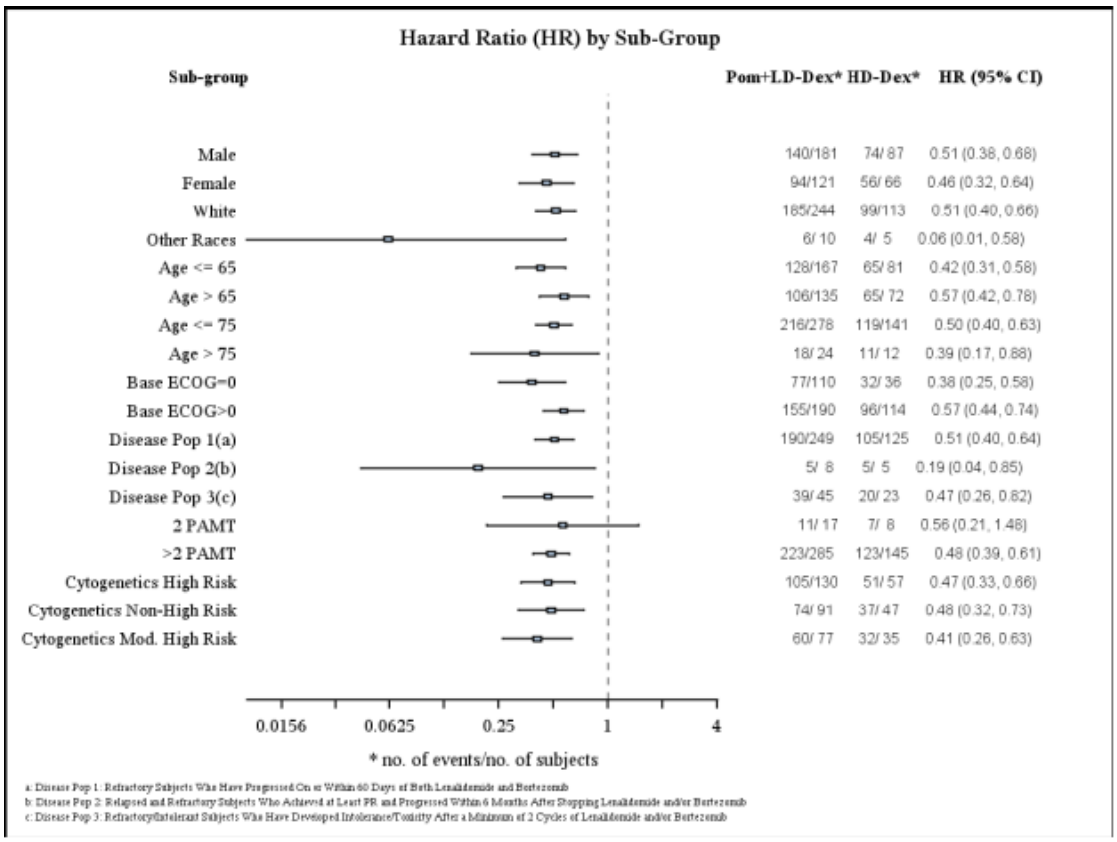
4.8 MM-003 Subgroup analysis

Methodology of the subgroup analyses is presented in Section 4.4.2. Unless stated otherwise, all subgroup analyses are based on the 01 March 2013 data cut and are taken from the MM-003 CSR.[17]

4.8.1 MM-003: Results of PFS analysis by subgroup

PFS subgroup results were consistent with the primary analysis (Figure 11), showing a statistically significant benefit for POM+LoDEX versus HiDEX in the majority of subgroups, except in those with too few patients. Median PFS for the ITT population based on the three stratification factors of age, disease population and number of prior anti-myeloma therapies was generally consistent with the ITT population (Appendix 3).[17] Irrespective of previous exposure to anti-myeloma therapies, POM+LoDEX significantly improved PFS based on IMWG criteria. Importantly, POM+LoDEX significantly improved PFS irrespective of refractoriness to previous therapies.[17] Further details on subgroup analyses, including forest plots for the additional subgroups of prognostic factors, are presented in Appendix 3.

Figure 11: Hazard ratios (95% CI) of effect of POM+LoDEX on PFS by IRAC review based on IMWG criteria in subgroups (ITT population)



Key: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HD-DEX, high-dose dexamethasone; HR, hazard ratio; IMWG, International Myeloma Working Group; IRAC, independent response adjudication committee; ITT, intention to treat; LD-DEX, low-dose dexamethasone; LoDEX, low-dose dexamethasone; PAMT, prior anti-myeloma therapy; PFS, progression-free survival; POM, pomalidomide.

Source: CSR.[17] Data cut-off: 01 March 2013.

4.8.2 MM-003: Results of PFS analysis by response

A secondary analysis was conducted to look at PFS outcomes by depth of response.[20] PFS was assessed in patients according to reduction in M-protein levels. Median PFS in POM+LoDEX-treated patients with M-protein reductions of greater than a minimal response (≥25% M-protein reduction) and greater than a partial response (≥50% M-protein reduction) were 7.4, and 8.4 months, respectively.

4.8.3 MM-003: Results of OS analysis by subgroup

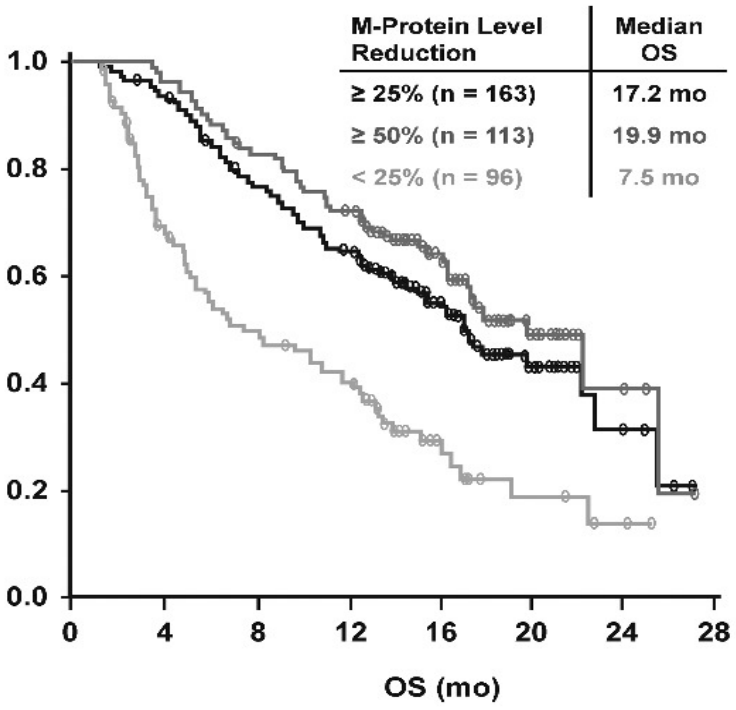
OS subgroup analysis was also generally consistent with the overall ITT population. Appendix 3 contains forest plots for the subgroups of prognostic factors and

refractoriness to previous therapies and tables containing median OS by stratification factor and prior SCT.

4.8.4 MM-003: Results of OS analysis by response

A secondary analysis was conducted to look at OS outcomes by depth of response.[20] OS was assessed in patients according to reduction in M-protein levels. Median OS in POM+LoDEX-treated patients with M-protein reductions of greater than a minimal response (≥25% M-protein reduction), and greater than a partial response (≥50% M-protein reduction) were 17.2, and 19.9 months, respectively (Figure 12). Like the PFS analysis, this trend was also seen in very elderly patients (>75 years), and in patients both with and without high-risk cytogenetic factors and highlights that for patients who respond to POM+LoDEX (≥ minimal response [MR]) a significant survival benefit exists.

Figure 12: OS by depth of response measured by degree of M-protein level reduction for patients assigned to POM+LoDEX



Key: LoDEX, low-dose dexamethasone; mo, months; OS, overall survival; POM, pomalidomide.
Source: San Miguel, 2015[20]

4.8.5 Results of response analysis by subgroup

The response rate was consistent among all subgroups, including those with LEN and BOR as their most recent treatment. Across a range of subgroups, POM+LoDEX produced higher response rates compared with HiDEX. Data for subgroup analyses are provided in Appendix 3.

4.9 Meta-analysis

A meta-analysis was not conducted as there were no additional RCTs identified in a comparable population to MM-003.

4.10 Indirect and mixed treatment comparisons

4.10.1 Overview and process for data selection

As stated previously, while a substantial body of evidence is available to support the clinical effectiveness of POM+LoDEX in patients who have received treatment with both BOR and LEN, this is not the case for other treatments used in current clinical practice in England.

The ability to produce a valid estimation of comparative effectiveness is further compounded by the strict inclusion/exclusion criteria applied within the Phase III and Phase IIIb studies for POM+LoDEX that mean that only the most refractory and hardest to treat patients have been included within these trials. In both MM-003 and MM-010, 75-80% patients were refractory to both LEN and BOR. These patients historically have had a poor prognosis with limited options for subsequent treatment.

Appendix 4 presents all of the studies identified within the new SLR, the SLR from the original submission and patient level data gathering exercises, and whether or not they were able to be included in quantitative analysis of comparative effectiveness, with reasons for their inclusion or exclusion. Appendices 5 and 6 present additional information including inclusion / exclusion comparison of MM-002, MM-003 and MM-010 and quality assessments for studies used for comparison.

Selection of studies for statistical analyses – POM+LoDEX

The decision whether to include or exclude studies for POM+LoDEX from quantitative analysis of comparative effectiveness was taken on the basis of study size (only studies with >50 patients were considered given the large body of evidence available), study population (studies analysing comorbidity subgroups were not considered), generalisability and comparability to comparator studies and availability of patient level data for analysis. Based on these criteria, three studies were considered for inclusion in analyses: the MM-003 Phase III trial, the MM-002 Phase II trial and the MM-010 Phase IIIb trial. Tabulated summaries of the methods, baseline characteristics and results of these studies are presented in Appendix 4.

The dataset selected for comparison was determined based upon comparability with the available comparator datasets. The MM-002 Phase II trial represented the trial that was the most comparable to available comparator studies for BEN, whereas the full trial dataset (MM-002, MM-003 and MM-010) was most comparable to the data for PANO+BOR+DEX. The comparison to the pooled dataset of all three studies (MM-002, MM-003 and MM-010) is also presented as sensitivity analysis for comparison to BEN.

Selection of studies for statistical analyses – Comparators

The systematic review did not identify any comparator RCTs allowing the formation of a traditional network meta-analysis: no RCTs have been run in this setting by any of the therapies listed within the NICE decision problem except for the MUK-one trial, which compared two doses of BEN.

Non-RCT evidence identified within the SLR in this patient population was also limited, primarily consisting of small single arm trials and observational studies. None of these sources, with the exception of PANORAMA 2, provided information suitable for inclusion in quantitative analysis. The reasons for this are provided within Appendix 4, but primarily stem from issues surrounding both sample size and patient population.

The UK RWE gathering exercise initiated by Celgene unfortunately did not provide additional evidence to allow assessment of comparative effectiveness due to issues

with data collection, which led to the outcomes collected not being sufficiently comparable to those available from the POM+LoDEX trials including:

- Definition of progression being different across participating centres and poor input of information on serum-M protein preventing recalculation of PFS according to the IMWG criteria used in the POM+LoDEX trials – this lack of comparability of outcomes is immediately apparent when the PFS estimated for POM+LoDEX (8 months in the study) is compared to the outcomes from all other studies using IMWG criteria (approximately 4 months)
- Presence of crossover to POM: 17/58 patients on the BEN arm received subsequent POM, which is likely to confound OS outcomes
- Per protocol lack of collection of data from patients who did not complete treatment within the dataset: this eliminates responders with a durable response from data collection, which is most likely to bias against POM+LoDEX
- High levels of missing covariate data precluding the use of statistical techniques to adjust for the substantial differences in patients treated with POM+LoDEX and other therapies at the time
- Having spoken to the clinicians involved in data collection, it has been confirmed that the short PPS seen with POM+LoDEX and the limited amount of subsequent treatment given after POM+LoDEX in this dataset is not reflective of clinical practice, and indicates that the treatment has been used with palliative intent in many of the centres participating in data collection compared to treatment with BEN, which was used earlier in the treatment pathway with active intent. Clinicians stated that at the time POM+LoDEX became available on the CDF "patients had been in a holding pattern waiting for POM to be made available."

An agreement was made allowing use of patient level trial data from the Myeloma UK One study (MUK-one) which studied BTD in patients with relapsed or refractory MM.[16] These data have increased the extent of UK patient level data on BEN within this submission to 78 patients (a considerable improvement on the 56 patients

available for analysis in the previous submission, which contained a mix of therapies, some of which are no longer available for use in current clinical practice).

Little evidence was identified for patients receiving conventional chemotherapy in the correct patient population in the original or updated SLRs.[37, 38] Patient level data gathering identified only 14 patients in the Gooding and Tarant datasets. Another 15 patients were identified within the CONNECT MM registry run by Celgene in the US.[109] Five patients receiving BEN were also identified in this dataset; no patients received PANO+BOR+DEX. This dataset was not included for quantitative analysis as patient characteristics were not collected, and therefore comparability of patient information to the POM+LoDEX trials could not be assessed.

Final evidence selected for comparison to BEN

Based upon the evidence identified, the patient level data available from the MUK-one trial and the Gooding and Tarant datasets are considered the most reliable and comparable data available for the outcomes expected with the use of BEN in UK clinical practice. These study datasets are unlikely to have been influenced by patients receiving subsequent POM+LoDEX as the work was conducted before POM was commercially available.

Final evidence selected for comparison to PANO+BOR+DEX

The PANORAMA 2 trial of PANO+BOR+DEX was identified as the most relevant and comparable study to trials of POM+LoDEX based on similar but not identical patient characteristics. Patients in this trial are most comparable to those within the trials for POM+LoDEX, all patients have received prior BOR and the vast majority (94%) of patients have also received prior LEN, additionally all patients are refractory to prior BOR. There are, however, still differences in the patient populations included; in particular the number of prior lines of treatment received (median 4 lines vs 5 lines in the POM+LoDEX trials) and lack of reporting of refractoriness to LEN, which limit the ability to make a valid comparison.

The PANORAMA 1 trial[53], which forms the main basis of the PANO+BOR+DEX submission to NICE (TA380), was not identified within the SLR as this represents a much less advanced patient population (as evidenced by the inclusion of LEN as a NICE comparator): only 19% of patients had received prior LEN in the study, and in

the licensed subgroup (≥2 prior regimens including BOR and an IMiD) reporting for patients receiving prior IMiD still fails to meet the inclusion criteria for the SLR (86% of patients had received prior THAL versus 38% receiving prior LEN). There is a high likelihood of confounding of OS results from use of subsequent LEN in this trial within a patient population who have not received, let alone become refractory to, this treatment, which rules out use of this study when comparing to the POM+LoDEX trials.

Final evidence selected for comparison to conventional chemotherapy

As no evidence was identified enabling a robust comparison to be made, HiDEX outcomes are used as a proxy for outcomes with conventional chemotherapy. An analysis of the potential for bias in this approach is provided later within this section.

Summary

Based upon the data available, quantitative comparison is presented to the relevant comparators using the evidence sources available as follows:

- Comparison to BEN is conducted using available English patient level data sources
- Comparison to PANO+BOR+DEX is conducted using a matched adjusted indirect comparison (MAIC) based upon the PANORAMA 2 trial
- Comparison to conventional chemotherapy is conducted through the assumption of equivalence in outcomes to HiDEX

The following sections detail the methodology and rationale for each of these comparisons and are presented by relevant comparators, as per the NICE final scope.

4.10.2 BEN

Analysis methods

As stated above, in the absence of direct head-to-head trial data comparing POM+LoDEX versus BEN, an indirect treatment comparison was required in order to estimate relative efficacy. Individual patient data (IPD) from three sources evaluating long-term follow-up of BEN were available, comprising data from Tarant, Gooding

and MUK-One.[16, 37, 38] POM+LoDEX data were available from one Phase II trial (MM-002)[19], a Phase III trial (MM-003)[17] and a single-arm Phase IIIb study (MM-010).[18] Across all data sources, only patients who had received prior bortezomib and lenalidomide therapy were considered relevant for inclusion within the statistical analysis.

Data for various prognostic factors identified to be influential on time-to-event outcomes were also available. Study populations varied in terms of baseline characteristics; an expected consequence of pooling data arising from multiple sources. In order to attempt to account for some of these differences between studies a two-step process was undertaken:

- POM+LoDEX data was selected from the study most comparable to the data available for BEN
- A series of patient level parametric survival regression models were fitted to the data, adjusting for potential prognostic factors.

This approach attempts to account for the imbalances between studies in terms of patient demographics, which may be influential on survival.

Selection of prognostic factors

Three sources of information were considered when selecting which prognostic factors were to be used for study and covariate selection captured (subject to data availability):

- A SLR of prognostic factors in RRMM
- Consultation with clinical experts at a recent advisory board to gain their insight into which factors they expected to influence prognosis for patients at this line of therapy
- Covariates included in the analysis submitted in TA338 (determined via a review of prognostic factors within the MM-003 trial and clinical input derived as part of the original submission)

Multicollinearity was assessed between prospective covariates where data was available to ensure that covariates which were highly correlated were not included

conjointly within the analysis. Correlation between all prospective prognostic factors was assessed by estimation of pairwise Pearson product-moment correlation coefficients (Appendix 12). Table 29 presents a summary of the information collected regarding the potential relevance of each prognostic factor considered.

Table 29: Prognostic factor selection

Covariate	Identified as influential on median survival time in prognostic factor SLR?		Included in TA338?	Identified as relevant by clinicians?	Issues with multicollinearity?	Data availability
	OS (reports/ significance)	PFS (reports/ significance)				
Treatment arm	N/A	N/A	Current care inc. as 1	Y	N	All
Age at start of treatment	11 / 5	11 / 2	Y	Y	Correlated with prior SCT	All
Disease duration (time since diagnosis)	4 / 2	2 / 2	Y	N	Correlated with no of prior lines	All
Prior lines of therapy	7 / 3	8 / 5	N	Y	Correlated with disease duration	All
ISS stage	10 / 3	9 / 0	Y	Y	N	MM-003, MM-010, Tarant, MUK-one
Prior THAL	7 / 2	4 / 1	Y	Y	N	All
Prior SCT	9 / 2	10 / 0	Y	N	Correlated with age	All
Refractory to LEN	9 / 6 [a]	3 / 2 [a]	Y	Y	N	All
Refractory to BOR			Y	Y	N	MM-003, MM-010, MM-002, Tarant, Gooding
ECOG status at start of treatment	4 / 3	2 / 0	N	Y	-	MM-003, MM-010, MM-002
Creatinine clearance at start of treatment	NR, 5 /2 for renal function	8 / 1	N	Y	-	MM-003, MM-010, MM-002
Cytogenetics (note difference categorisations used across papers)	19 / 9	18 / 13	N	N[b]	-	MM-003, MM-010, MM-002
Disease history (extramedullary manifestations and osteolytic lesions)	2 / 0	NR	N	N		NR
Sex	7 / 2	8 / 1	N	N		All
Durie-Salmon Stage	3 / 1	2 / 1	N	N		MM-003, MM-010, MM-002

Covariate	Identified as influential on median survival time in prognostic factor SLR?		Included in TA338?	Identified as relevant by clinicians?	Issues with multicollinearity?	Data availability
	OS (reports/ significance)	PFS (reports/ significance)				
Haemoglobin	6 / 4	3 / 1	N	N		MM-003, MM-010, MM-002
LDH	8 / 6	3 / 1	N	N		MM-003, MM-010, MM-002
Paraprotein class	8 / 0	7 / 0	N	N		MM-003, MM-010, MM-002
Platelets	4 / 3	1 / 0	N	N		MM-003, MM-010, MM-002
Beta 2 microglobulin	6 / 5	2 / 2	N	N		MM-003, MM-010, MM-002
Albumin	NR	2 / 1	N	N		MM-003, MM-010, MM-002
Light chain type	3 / 1	2 / 1	N	N		MM-003, MM-010, MM-002

Key: BOR, bortezomib; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; LDH, lactate dehydrogenase; LEN, lenalidomide; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival; SCT, stem cell transplantation; SLR, systematic literature review; TA, technical appraisal; THAL, thalidomide.

Notes: [a] refractoriness / type relapse or progression, [b] Clinicians stated non informative and not used at this stage of disease.

Colour coding used for prognostic SLR: Green: 5 or more reports and >50% were significant, Yellow: Either 5 or more reports or >50% of reports were significant, Red: Neither of the above.

Based on the SLR of prognostic factors in RRMM, the variables with the most evidence to support their prognostic importance in OS and/or PFS are cytogenetics, refractoriness and number of prior lines of therapy. Full information on the SLR can be found in the separate reference supplied)[129] There is also a reasonable amount of evidence to support the prognostic importance of biomarkers such as LDH, beta 2 microglobulin and haemoglobin on OS, unfortunately these variables were not collected in comparator datasets although beta 2 microglobulin is a component of ISS stage. The prognostic SLR identified a lot of papers looking at the impact of ISS stage, however, the prognostic significance was undetermined with few papers reporting a significant impact.

As evidence of multicollinearity was found between age and SCT and disease duration and number of lines of prior therapy, clinical advice and the targeted review of prognostic factors was used to determine which covariate to include. Evidence from the SLR indicated greater significance from number of prior lines of therapy and was inconclusive on the relative merits of including age compared to SCT. Clinicians indicated that prior SCT was not prognostically relevant to patients at this line of treatment and that number of prior lines of therapy was more prognostically relevant than duration of disease. Consequently, SCT and duration of disease were not included as prognostic factors.

The following covariates were therefore considered within the analysis, which represent the factors identified as prognostically important where data were available for at least 50% of the patients available for analysis for both BEN and POM+LoDEX:

- Treatment arm [POM+LoDEX/BEN]
- Age at the start of treatment [continuous]
- Number of prior lines of therapy [continuous]
- Receipt of prior THAL [Yes/No]
- Refractory to LEN [Yes/No]
- ISS stage [1/2/3]

Refractoriness to BOR could not be included within the analysis despite knowledge that this is prognostically significant as this variable was not recorded within the MUK-One trial. Lack of inclusion is likely to bias against POM+LoDEX as less patients were refractory to BOR in the Gooding and Tarant datasets versus the POM+LoDEX trials.

All other variables identified as potentially relevant (for example ECOG status and cytogenetics) were entirely missing from the evidence available for BEN. The direction of impact of non-inclusion is therefore unknown.

It should be noted that treatment arm is highly correlated with prior lines of therapy, receipt of prior THAL and refractoriness to LEN. It is unsurprising that treatment arm should be correlated with prognostic factors due to imbalances between study populations and synthesis of both observational data and RCT evidence.

Summary of datasets included

Baseline characteristics for each of the studies considered for analysis are presented in Table 31. There are a number of imbalances between the POM+LoDEX trials and BEN studies, most notably, refractory to LEN; there is a much higher proportion of patients who are refractory receiving LEN in the POM+LoDEX studies (78-96%) versus BEN (18-25%). The mean number of prior lines of therapy is also lower for BEN (3.5-3.9) than for POM+LoDEX (4.9-5.6).

The MM-002 trial alone was selected for use for POM+LoDEX within the base case analysis due to the lower levels of refractoriness exhibited within this trial (78%) compared to the remainder of the POM+LoDEX data (95%). This lower level of refractoriness was considered more comparable to the BEN data (18-25%) across sources. As this covariate was identified as most prognostically important by clinicians and is difficult to adjust for with the current datasets (given that the overlap between datasets is low) it was considered more important to select the more comparable dataset for analysis than to retain the maximum number of patients for analysis in the POM+LoDEX arm. Additionally both MM-003 and MM-010 required patients to have failed prior LEN and BOR according to defined criteria for study inclusion. MM-002 was less strict and did not require this. This is more in line with the inclusion / exclusion for MUK-1.

Sensitivity analysis is presented looking at the impact of using all POM+LoDEX data but should be viewed within the context of the lower comparability of the trials included (sensitivity analysis 1).

In addition, while it is believed that ISS stage is an influential predictor of survival outcomes, this variable was not measured in either the Gooding or MM-002 datasets. Consequently, two scenario analyses were performed to evaluate the effect of including ISS stage (where reported) or excluding ISS stage using the four datasets where this variable was reported (sensitivity analyses 2 and 3).

A summary of each of the statistical analyses is summarised in Table 30.

Table 30: Summary of statistical analyses

Analysis	Data sources		Covariates				
	BEN	POM+LoDEX	Age	Prior lines of therapy	Receipt of prior THAL	Refractory to LEN	ISS stage
Base case (N=191[a]/ 187[b])	Tarant Gooding MUK-One	MM-002	✓	✓	✓	✓	X
Sensitivity analysis 1 (N=1175[a] /1171[b])	Tarant Gooding MUK-One	MM-002 MM-003 MM-010	✓	✓	✓	✓	X
Sensitivity analysis 2 (N=999[a]/ 996[b])	Tarant MUK-One	MM-003 MM-010	✓	✓	✓	✓	✓
Sensitivity analysis 3 (N=999[a]/ 996[b])	Tarant MUK-One	MM-003 MM-010	✓	✓	✓	✓	X

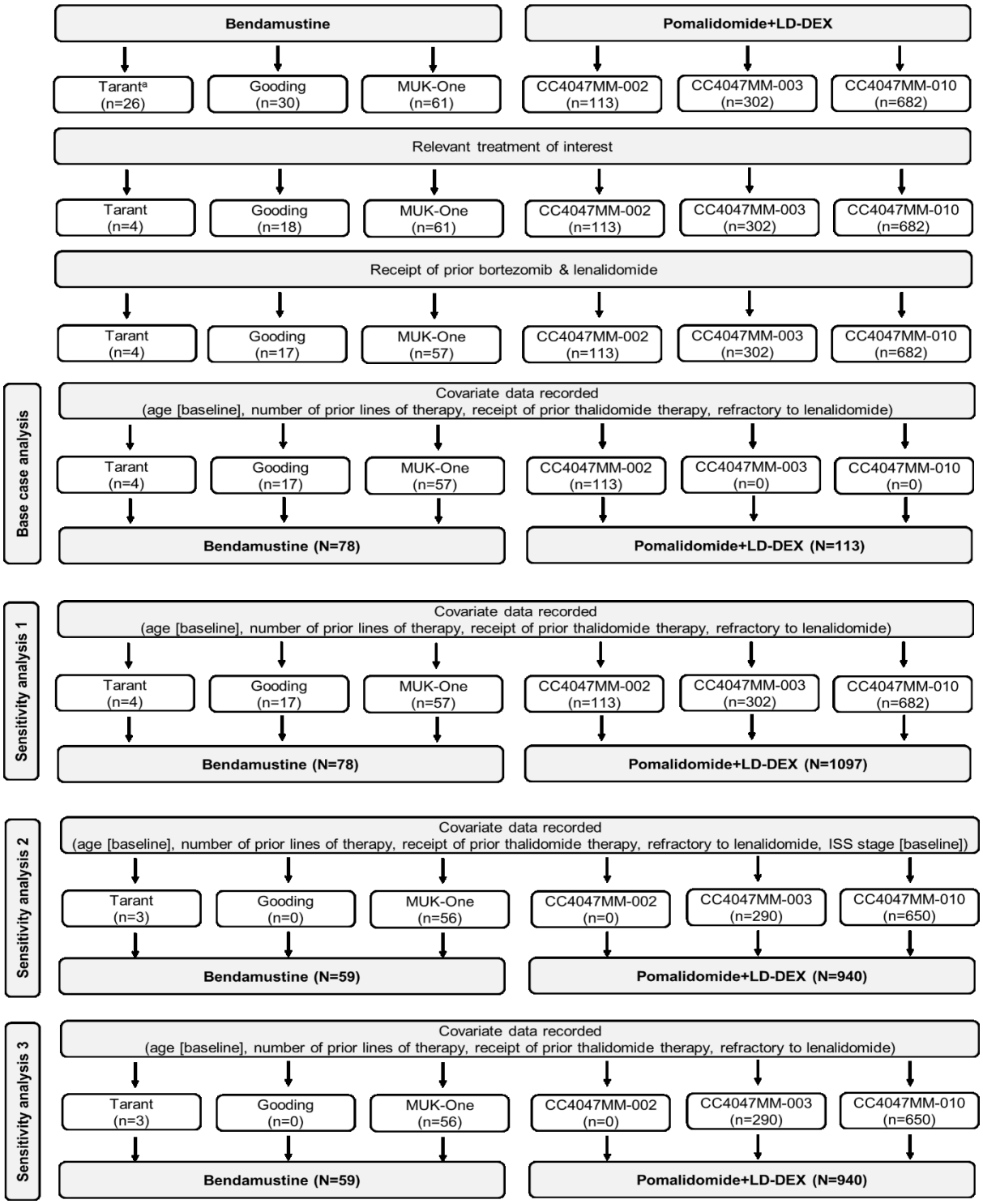
Key: BEN, bendamustine; ISS, International Staging System; LEN, lenalidomide; MM, multiple myeloma; N, number of patients; POM+LoDEX, pomalidomide plus low-dose dexamethasone; THAL, thalidomide.

Notes: a, sample size for OS; b, sample size for PFS; Tarant does not report PFS data.

A flow chart showing the data available for both POM+LoDEX and BEN for each of the analyses is presented in Figure 13 by trial. This shows the number of patients with data available for OS. PFS was not recorded in the Tarant dataset, and therefore analyses for PFS do not include the four patients receiving BEN in this dataset.

A total of 191 patients were included in the base case analysis (113 POM+LoDEX, 78 BEN), arising from four separate data sources.

Figure 13: Flow chart of data selection



Key: ISS, International Staging System; MM, multiple myeloma; LD-DEX, low-dose dexamethasone.

Table 31: Patient demographics for all populations

Study	Treatment	N	Age, mean (SD)	Number of prior lines of therapy, mean (SD)	Receipt of prior THAL (% yes)	Refractory to LEN (% yes)	Previous SCT (% yes)	Disease duration (years), mean (SD)	ISS stage (%) (1, 2, 3, NR)
Tarant	BEN	4	57.5 (12.6)	3.5 (0.6)	50.0	25.0	75.0	8.3 (3.6)	50.0, 25.0, 0.0, 25.0
MUK-One	BEN	57	63.4 (8.7)	3.8 (0.8)	100.0	24.6	71.4 [N=56]	6.4 (3.3) [N=56]	26.3, 29.8, 42.1, 1.8
Gooding	BEN	17	63.6 (8.3)	3.9 (0.8)	88.2	17.6	58.8	4.3 (2.1) [N=15]	0, 0, 0, 100
MM-010	POM+LoDEX	682	65.4 (9.1)	4.9 (2.1)	54.5	95.9	66.1	6.2 (3.6)	21.4, 39.3, 34.6, 4.7
MM-002	POM+LoDEX	113	64.4 (9.2)	5.6 (2.4)	68.1	77.9	74.3	6.2 (3.6)	0, 0, 0, 100
MM-003	POM+LoDEX	302	63.6 (9.3)	5.1 (2.0)	57.3	94.7	70.9	6.2 (4.0)	26.8, 38.4, 30.8, 4.0
Overall		**1175**	**64.7 (9.2)**	**4.9 (2.1)**	**59.2**	**89.0**	**68.3 [N=1174]**	**6.2 (3.7) [N=1172]**	**20.8, 34.2, 30.0, 15.0**

Key: BEN, bendamustine; ISS, International Staging System; LEN, lenalidomide; LoDEX, low-dose dexamethasone; MM, multiple myeloma; NR, not reported; POM, pomalidomide; SCT, stem cell transplantation; SD, standard deviation; THAL, thalidomide.

Methods used for covariate adjustment

Based upon prognostic covariates identified above, comparison between POM+LoDEX and BEN was made for both OS and PFS outcomes using covariate-adjusted IPD regression analyses using statistical software package R.

Covariate-adjustment is a limited approach to facilitate an indirect treatment comparison in the absence of head-to-head trial data between comparators of interest. It may account for some study population differences, however, such adjustments can only be reliably made if prognostic factors are consistently measured and the regression analyses performed rely on this assumption. Furthermore, it is assumed that the time-to-event endpoints are measured consistently between studies, as covariate-adjustment cannot address any discrepancies in outcome definitions.

It was not possible to include study as a fixed-effect in the statistical models due to linear dependence (i.e. each study included only one treatment), and therefore it was impossible to determine the study effect when simultaneously estimating the treatment effect.

TTF was only evaluated for POM+LoDEX (as no data were available for BEN). Section 5.3 includes details of the modelling of TTF.

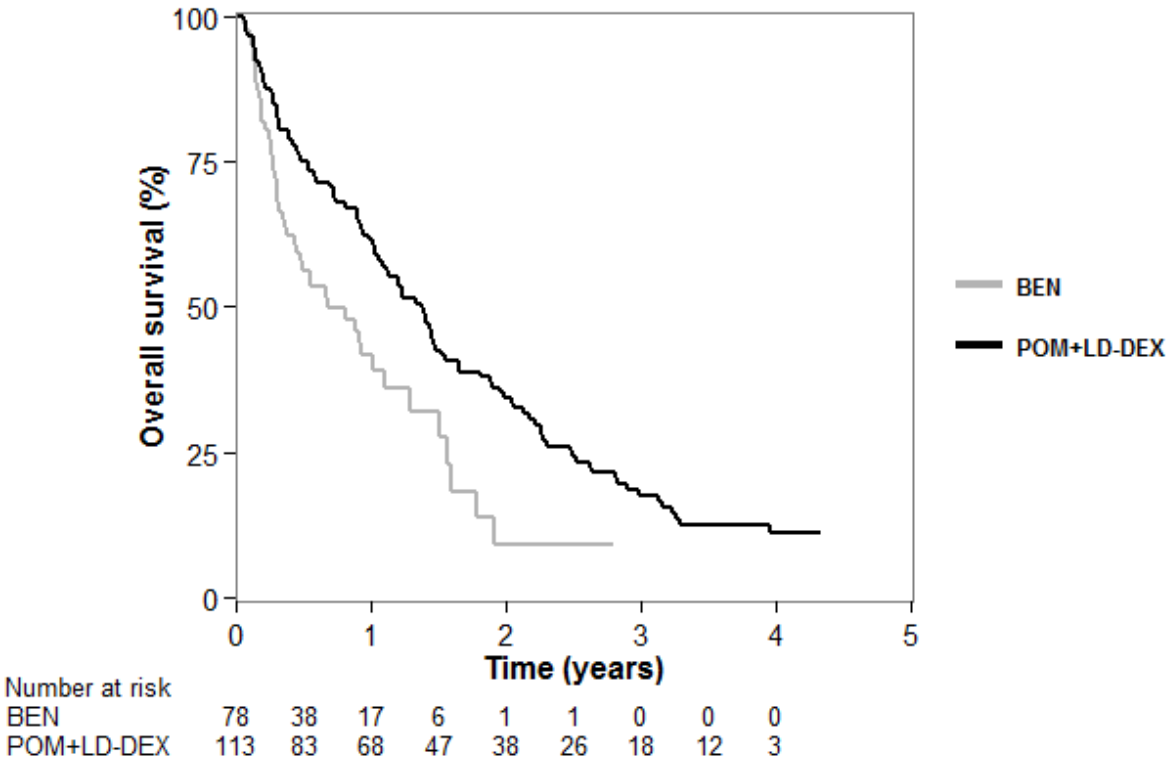
Results – Base case – Overall survival

Results for the base case analysis and sensitivity analysis 1 are presented, with sensitivity analysis 2 and 3 results included in Appendix 12. KM curves (unadjusted for covariates) for the individual studies are presented in Appendix 12 for BEN. The unadjusted KM curve for POM+LoDEX utilises data exclusively from MM-002, and this is presented in Figure 14. The unadjusted BEN curves appear quite different; there are only four patients included from the Tarant study, meaning it is difficult to compare these data with the remaining BEN data; patients within MUK-One experienced better outcomes than those in the Gooding dataset. The reason for these differences is unknown given the apparent similarities in reported patient characteristics but may be due to the strict inclusion criteria for the MUK-One trial or simply due to limited patient numbers in the two datasets. In terms of exclusion criteria platelet count and neutrophil count were both restricted, for example, only

allowing the fittest patients to be included; similar restrictions were not applied in MM-002 It should be noted that PFS data are similar in the two trials indicating that the potential difference is most likely to lie in patient fitness and ability to benefit from subsequent therapies.

Figure 14 shows the unadjusted (i.e. not accounting for differences between studies) KM curves for POM+LoDEX and BEN, pooling data from all sources. The median OS times are 16.5 months (95% CI [12.6, 19.8]) and 8.1 months (95% CI [5.3, 15.5]) for POM+LoDEX and BEN, respectively, indicating a 8.4 month difference, with an unadjusted HR of 0.55 (95% CI [0.38, 0.81]; p-value=0.002) for POM+LoDEX versus BEN.

Figure 14: Unadjusted KM OS curves based on pooled study data for BTD and MM-002 for POM+LoDex

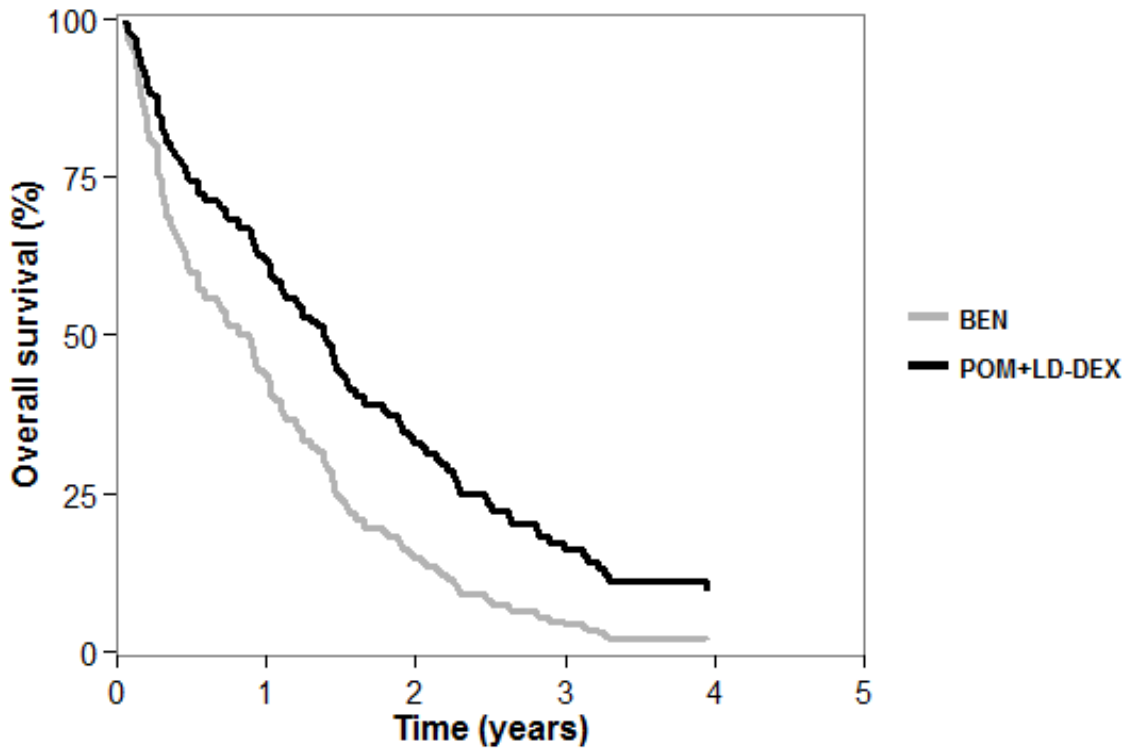


Key: BEN, bendamustine; KM, Kaplan-Meier; LD-DEX, low-dose dexamethasone; POM, pomalidomide.

Covariate-adjusted curves are presented (Figure 15) using the mean value for continuous covariates (age, number of prior lines of therapy) and the proportion in categorical covariates (refractory to lenalidomide, receipt of prior thalidomide, ISS

stage [sensitivity analysis 2]) based on a Cox proportional hazards regression model. Following adjustment for covariates, the median OS times are 16.6 months (95% CI [12.6, 21.3]) and 10.5 months (95% CI [5.8, 14.8]) for POM+LoDEX and BEN respectively, indicating a 6.1 month difference, with a covariate-adjusted HR of 0.58 (95% CI [0.36, 0.94]; p-value=0.026) for POM+LoDEX versus BEN. Along with the treatment arm, both age at baseline and receipt of prior THAL are statistically significant covariates; with the hazard of death increasing with age (HR 1.02, 95% CI [1.00, 1.04]) or receipt of prior THAL (HR 1.61, 95% CI [1.02, 2.54]). Full Cox regression model output is presented in Appendix 12.

Figure 15: Adjusted KM OS curves based on pooled study data for BTD and MM-002 for POM+LoDex



Key: BEN, bendamustine; KM, Kaplan-Meier; LD-DEX, low-dose dexamethasone; POM, pomalidomide.

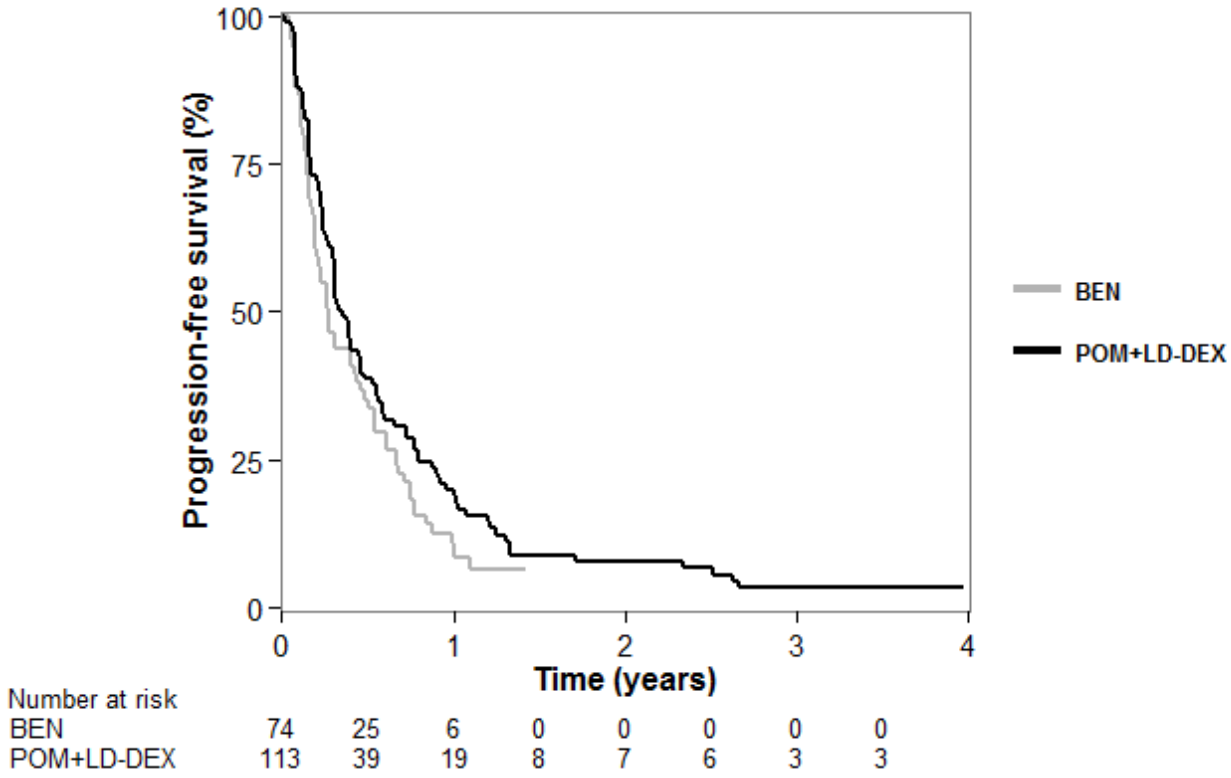
Results – Base case – Progression-free survival

No PFS data are recorded for Tarant, and therefore the PFS analysis includes four less patients (n=187) compared with OS (n=191).

Curves for each individual study evaluating BEN are presented in Appendix 12. As for OS, data for POM+LoDEX is exclusively from MM-002. The unadjusted curves for BEN from Gooding and MUK-One are similar until approximately 6 months post-baseline, despite the low number of patients in the Gooding dataset. Follow-up for PFS for BEN is much shorter (just over one year) compared to POM+LoDEX (almost four years).

Figure 16 shows the unadjusted KM curves (i.e. not accounting for differences between studies) for POM+LoDEX and BEN, pooling data from all sources. The median PFS times are 4.2 months (95% CI [3.7, 5.8]) and 3.3 months (95% CI [2.5, 5.5]) for POM+LoDEX and BEN, respectively, indicating a 0.9 month difference, with an unadjusted HR of 0.76 (95% CI [0.56, 1.05]; p-value=0.098) for POM+LoDEX versus BEN.

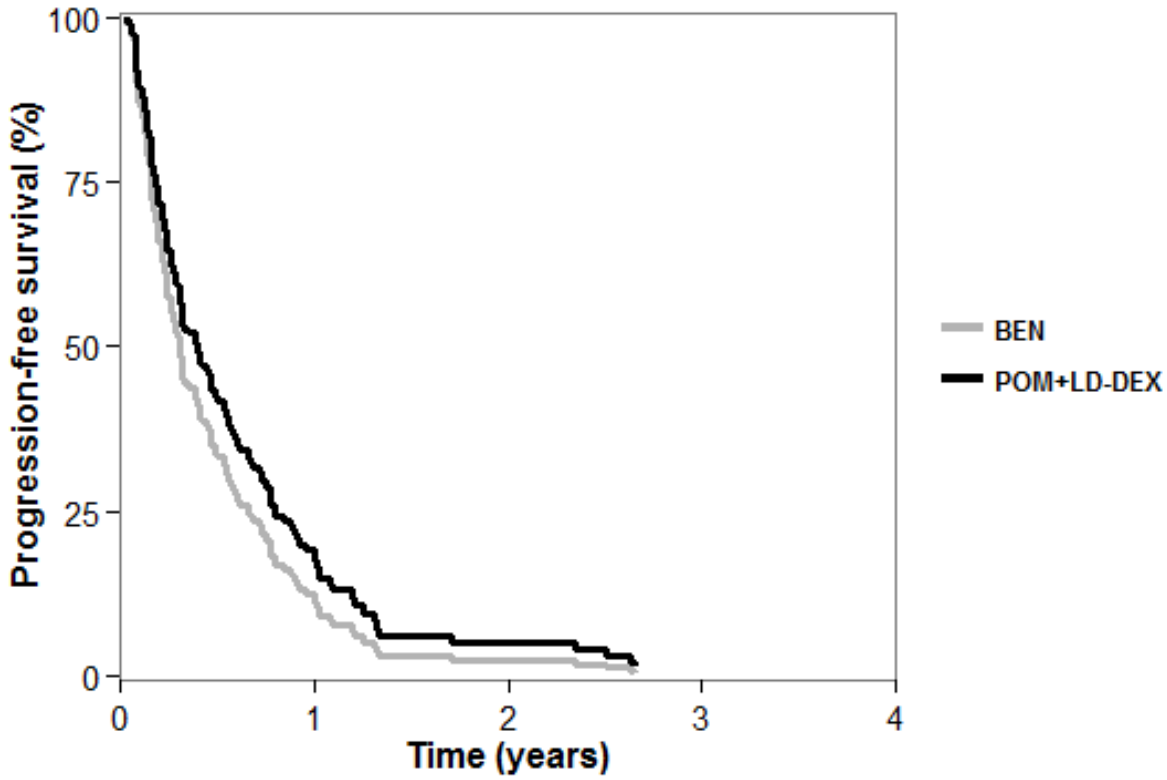
Figure 16: Unadjusted KM PFS curves based on pooled study data for BTD and MM-002 for POM+LoDex



Key: BEN, bendamustine; KM, Kaplan-Meier; LD-DEX, low-dose dexamethasone; POM, pomalidomide.

The KM curves, once adjusted for the specified prognostic factors, are presented in Figure 17 based on a Cox proportional hazards model. Once adjusted for covariates, the median PFS times are 4.7 months (95% CI [3.7, 6.6]) and 3.7 months (95% CI [2.8, 5.6]) for POM+LoDEX and BEN, respectively, indicating a 1 month difference, with an adjusted HR of 0.79 (95% CI [0.52, 1.22]; p-value=0.291) for POM+LoDEX versus BEN. Two prognostic factors were statistically significant in the Cox regression model; receipt of prior THAL (HR 2.15, 95% CI [1.33, 3.46]) and refractory to LEN (HR 1.58, 95% CI [1.09, 2.29]). Full Cox regression model output is presented Appendix 12.

Figure 17: Adjusted KM PFS curves based on pooled study data for BTD and MM-002 for POM+LoDex



Key: BEN, bendamustine; KM, Kaplan-Meier; LD-DEX, low-dose dexamethasone; POM, pomalidomide.

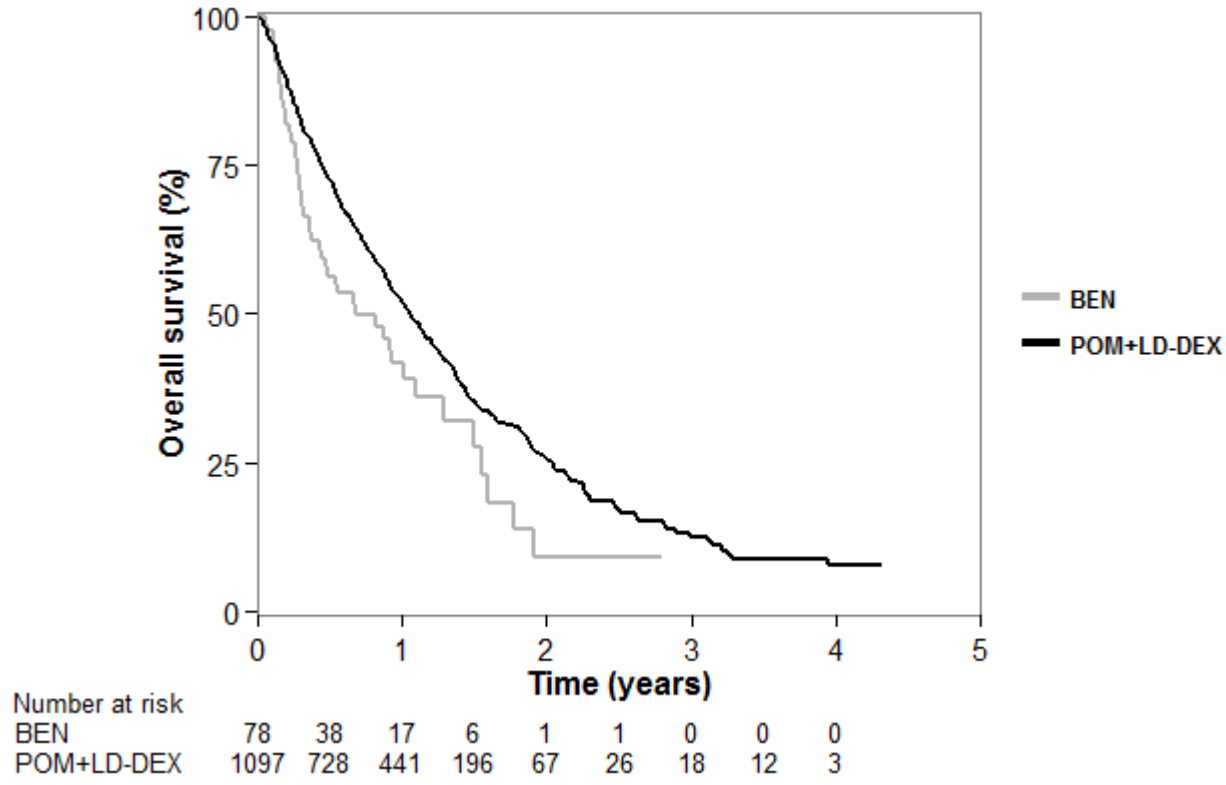
Results – Sensitivity analysis 1 – Overall survival

KM curves (unadjusted for covariates) for the individual studies for both POM+LoDEX and BEN are presented in Appendix 12. In this sensitivity analysis,

POM+LoDEX data arises from MM-002, MM-003 and MM-010, however BEN data is unchanged from that included in the base case analysis. The POM+LoDEX curves for MM-003 and MM-010 show a great deal of overlap, however MM-002 shows higher survival probabilities from approximately 6 months post-baseline.

Figure 18 shows the unadjusted (i.e. not accounting for differences between studies) KM curves for POM+LoDEX and BEN, pooling data from all sources. The median OS times are 12.6 months (95% CI [11.6, 13.8]) and 8.1 months (95% CI [5.3, 15.5]) for POM+LoDEX and BEN, respectively, indicating a 4.5 month difference, with an unadjusted HR of 0.68 (95% CI [0.51, 0.92]; p-value=0.011) for POM+LoDEX versus BEN.

Figure 18: Unadjusted KM OS curves based on pooled study data for BTD and POM+LoDex

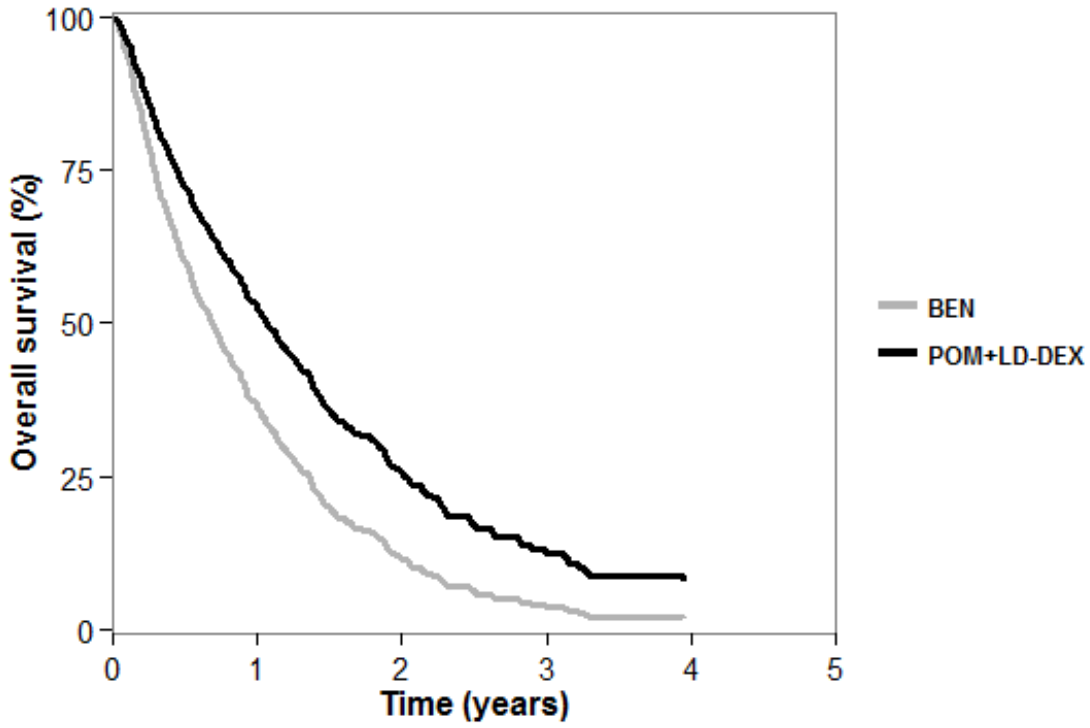


Key: BEN, bendamustine; KM, Kaplan-Meier; LD-DEX, low-dose dexamethasone; POM, pomalidomide.

Following adjustment for covariates, the median OS times are 12.7 months (95% CI [11.9, 13.9]) and 8.1 months (95% CI [6.1, 12.4]) for POM+LoDEX and BEN

respectively, indicating a 4.6 month difference, with a covariate-adjusted HR of 0.64 (95% CI [0.45, 0.91]; p-value=0.013) for POM+LoDEX versus BEN. Along with treatment arm, receipt of prior THAL is a statistically significant prognostic factor (HR 1.17, 95% CI [1.00, 1.38]). Full Cox regression model output is presented in Appendix 12.

Figure 19: Adjusted KM OS curves based on pooled study data for BTD and POM+LoDex



Key: BEN, bendamustine; KM, Kaplan-Meier; LD-DEX, low-dose dexamethasone; POM, pomalidomide.

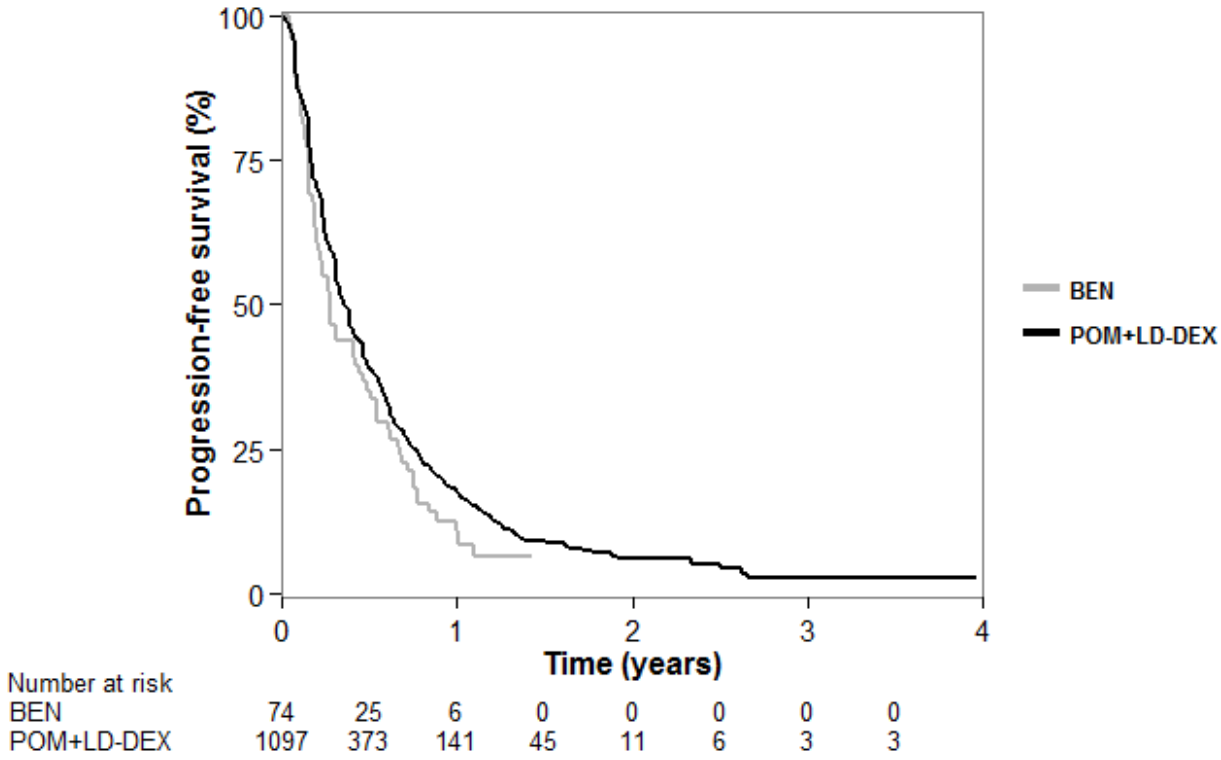
Results – Sensitivity analysis 1 – Progression-free survival

No PFS data are recorded for Tarant, and therefore the PFS analysis includes four less patients (n=1171) compared with OS (n=1175).

Curves for each individual study are presented for POM+LoDEX and BEN in Appendix 12. PFS data for POM+LoDEX arises from MM-002, MM-003 and MM-010. The POM+LoDEX curves are extremely similar, overlapping consistently until approximately 2 years post-randomisation.

Figure 20 shows the unadjusted KM curves (i.e. not accounting for differences between studies) for POM+LoDEX and BEN, pooling data from all sources. The median PFS times are 4.3 months (95% CI [3.9, 4.7]) and 3.3 months (95% CI [2.5, 5.5]) for POM+LoDEX and BEN, respectively, indicating a 1 month difference, with an unadjusted HR of 0.80 (95% CI [0.62, 1.03]; *p*=0.082) for POM+LoDEX versus BEN.

Figure 20: Unadjusted KM PFS curves based on pooled study data for BTD and POM+LoDex

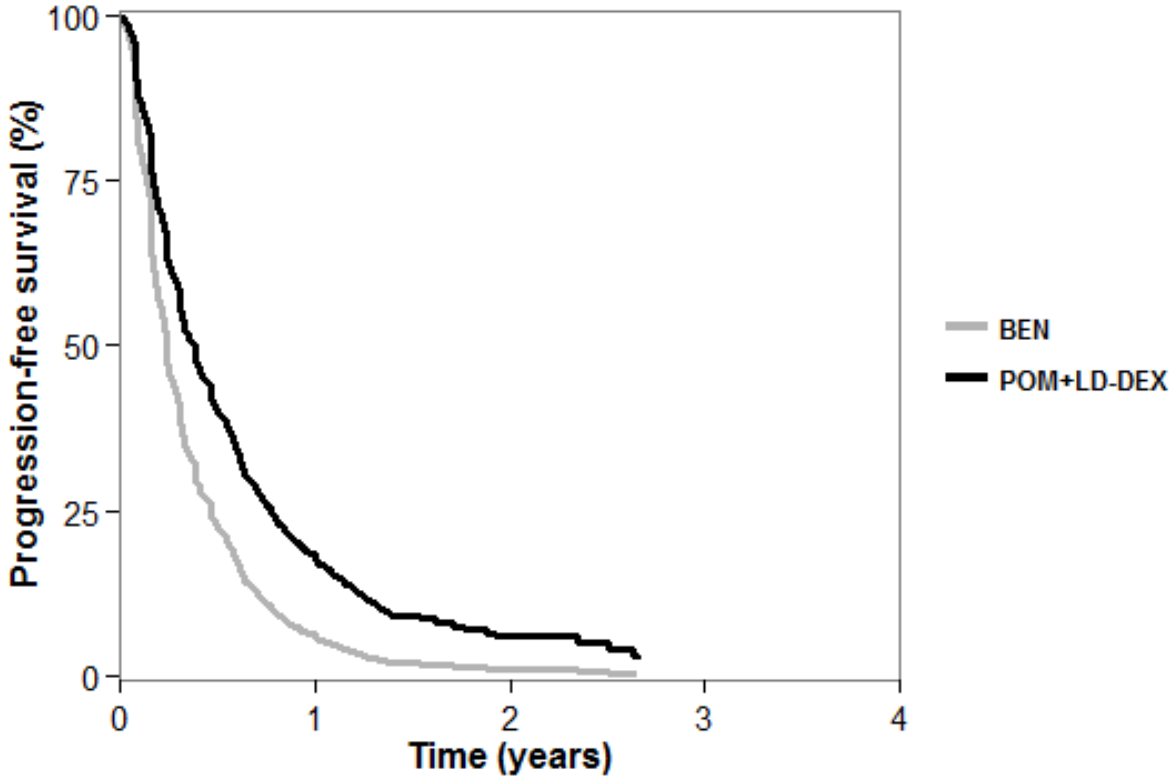


Key: BEN, bendamustine; KM, Kaplan-Meier; LD-DEX, low-dose dexamethasone; POM, pomalidomide.

The KM curves, once adjusted for the specified prognostic factors, are presented in Figure 21 based on a Cox proportional hazards model. Once adjusted for covariates, the median PFS times are 4.6 months (95% CI [3.9, 4.8]) and 2.8 months (95% CI [2.2, 3.8]) for POM+LoDEX and BEN, respectively, indicating a 1.8 month difference, with an adjusted HR of 0.61 (95% CI [0.45, 0.84]; p-value=0.002) for POM+LoDEX versus BEN. The covariate-adjustment increased the median PFS time for POM+LoDEX and reduced the median PFS time for BEN, creating a larger treatment

effect than that obtained when naively pooling the data and stratifying solely by treatment. Along with treatment arm, refractory to LEN is also a statistically significant prognostic factor (HR 1.44, 95% CI [1.12, 1.85]). Full Cox regression model output is presented in Appendix 12.

Figure 21: Adjusted KM PFS curves based on pooled study data for BTD and POM+LoDex



Key: BEN, bendamustine; KM, Kaplan-Meier; LD-DEX, low-dose dexamethasone; POM, pomalidomide.

Summary of sensitivity analyses 2 and 3

Sensitivity analysis 2 includes an additional prognostic factor (ISS stage) which is believed to be influential on survival prospects, however this results in exclusion of MM-002 and Gooding data sources due to missing ISS stage data. Data included in sensitivity analysis 3 is identical to that used in sensitivity analysis 2, however, ISS stage is no longer included as a covariate. This is to evaluate the differences in treatment effect once ISS stage is no longer adjusted for.

Both covariate-unadjusted and adjusted KM curves based on pooled study data for each of POM+LoDEX and BEN are presented for OS and PFS in Appendix 12. Results from the Cox proportional hazards model for OS and PFS for sensitivity analyses 2 and 3 are presented in Appendix 12.

Post covariate-adjustment including ISS stage, the HR for OS is 0.72 (95% CI [0.47, 1.11]) (p=0.133). Only ISS stage is a statistically significant predictor. ISS stages two and three show an increased hazard of death versus stage one, and the effect increases as stage increases (HR 1.71, 95% CI [1.35, 2.18], HR 3.10, 95% CI [2.45, 3.92] for stage two versus one and stage three versus one, respectively).

For PFS including ISS stage post covariate adjustment produces a HR of 0.62 (95% CI [0.43, 0.90]) (p=0.011). Treatment arm, age, ISS stage and refractory status to LEN are statistically significant predictors of PFS. ISS stages two and three show an increased hazard of progression versus stage one, and the effect increases as stage increases (HR 1.25, 95% CI [1.04, 1.50], HR 1.80, 95% CI [1.49, 2.16] for stage two versus one and stage three versus one, respectively).

As in sensitivity analysis 2, there are no statistically significant prognostic factors once ISS is removed. The covariate-adjusted HR for the treatment effect for OS is 0.82 (95% CI [0.54, 1.27]) for POM+LoDEX versus BEN. This means that when synthesising these data sources, when ISS is not accounted for, the treatment effect reduces slightly.

For PFS, in sensitivity analysis 3, only the treatment effect remains statistically significant, with a HR of 0.62 (95% CI [0.43, 0.89]) for POM+LoDEX vs BEN. The HR is identical to that obtained in sensitivity analysis 2, indicating that the treatment effect has remained consistent, even when ISS stage is not account for in the regression model.

Comparison of sensitivity analyses with base case

The results of sensitivity analysis 1 shows reasonably different results to those obtained in the base case analyses. The differences in median OS between POM+LoDEX and BEN post-covariate adjustment are 6.1 months (base case) versus 4.6 months (sensitivity analysis 1). The differences in median PFS between POM+LoDEX and BEN post-covariate adjustment are 1.0 months (base case) are

1.8 months (sensitivity analysis 1). The treatment-effect HRs for POM+LoDEX vs BEN for OS are 0.58 (95% CI [0.36, 0.94]) (base case), 0.64 (95% CI [0.45, 0.91]) (sensitivity analysis 1), 0.72 (95% CI [0.47, 1.11]) (sensitivity analysis 2) and 0.82 (95% CI [0.54, 1.27]) (sensitivity analysis 3). The treatment-effect HRs for POM+LoDEX vs BEN for PFS are 0.79 (95% CI [0.52, 1.22]) (base case), 0.61 (95% CI [0.45, 0.84]) (sensitivity analysis 1), 0.62 (95% CI [0.43, 0.90]) (sensitivity analysis 2) and 0.62 (95% CI [0.43, 0.89]) (sensitivity analysis 3). This shows the results are sensitive to the data sources included in the regression model, particularly for OS.

The covariate-adjusted treatment effect is statistically significant in both the OS base case analysis (p=0.026) and sensitivity analysis 1 (p=0.013), with POM+LoDEX showing reduced hazard of death versus BEN.

ISS stage (included only in sensitivity analysis 2) is shown to be an important prognostic factor of survival outcomes (both OS and PFS), however this variable has not been measured in the base case analysis POM+LoDEX dataset (MM-002). When not accounted for in a model using identical data sources as sensitivity analysis 2, the treatment effect for OS reduces when ISS is not included in the analysis; for PFS the treatment effect remained constant, which suggests it is conservative to exclude this variable.

Limitations of analysis

There are a number of limitations of the statistical analyses presented, namely due to the assumptions required in order to undertake the statistical modelling:

- This approach of modelling data arising from several data sources breaks randomisation and the pooling of data, and, even after adjustment for prognostic factors, cannot replace direct head-to-head trial data between POM+LoDEX versus BEN.
- There is a notable amount of heterogeneity observed between studies in terms of patient demographics and study design (combination of observational, Phase II and III trial data). Once pooling all data sources in a single analysis, adjustment for this heterogeneity is limited. These covariate-

adjusted analyses are may not be adequately powered to identify and account for all study differences.

- MM-003 – documented OS time for two patients was shorter than their recorded PFS time, due to withdrawal of consent. In this case, these patients' OS time was substituted with their PFS time.
- Patients with missing data for any of the clinically-relevant prognostic factors were not included in the analyses.
- It is possible that not all influential prognostic factors were captured, for example, ISS stage is not recorded in MM-002 or Gooding, meaning that additional sensitivity analyses are required to attempt to tease out the covariate effect versus removal of data sources. In addition, there may be other prognostic factors that are unmeasured in some or all data sources which may influence survival outcomes (for example the strict inclusion criteria used within MUK One); in the absence of direct head-to-head trial data, covariate-adjusted models can only go so far in accounting for study differences and it may not be possible to adjust for all influential factors.
- This lack of reporting of all potentially relevant prognostic characteristics is further complicated by the individualisation of treatment at this line of therapy – only fitter patients are capable of receiving toxic regimens such as BEN and it is highly likely that many measures of comparative fitness have not been captured within the current analysis
- Subsequent therapy information was not captured within either the MUK-One or Tarant datasets meaning that any differences in subsequent therapy use could not be assessed.

Comparison of statistical analyses with previous submission

The updated statistical analyses address previous concerns about the paucity of comparator data when estimating relative effectiveness between POM+LoDEX and BEN. Additional comparator data for BEN has been included using IPD from MUK-One trial; this increases the number of patients from 56 to 78, all of whom are in receipt of BEN. Previous analyses included additional comparator treatments (such

as BOR, Cyclophosphamide + thalidomide + dexamethasone (CTD) or melphalan + prednisone + thalidomide (MPT) complex chemotherapy) and was classed as UK standard of care, however patients receiving a comparator treatment other than BEN are no longer included in the IPD analyses.

Previous analyses included POM+LoDEX data arising from MM-002 and MM-003. In the updated analyses, additional POM+LoDEX data has been sourced from a Phase IIIb trial (MM-010). The updated base case analyses presented, however, only include POM+LoDEX data from MM-002 to increase comparability of the dataset used for POM+LoDEX to that used for BEN.

The selection of prognostic factors has also changed; disease duration, ISS stage and SCT were previously adjusted for in IPD analyses. In the series of updated regression models, disease duration was superseded with number of prior lines of therapy, SCT was no longer included due to the presence of correlation with age, and ISS stage is only included within sensitivity analysis due to lack of recording within all datasets. Note within the previous submission it was thought that ISS stage was recorded within all datasets but on further investigation of the data MM-002 and the Gooding dataset in fact recorded Durie-Salmon stage.

Conclusion

The updated statistical analyses address previous concerns about the paucity of comparator data when estimating relative effectiveness between POM+LoDEX and BEN. All analyses show a trend of improved OS and PFS prognosis for POM+LoDEX versus BEN, however results are sensitive to the data sources included in the analyses. There may be factors which are influential on survival prognosis which have not been measured consistently between data sources. This means that any estimation of comparative efficacy may be limited based on available covariate data. Whilst the IPD regression analyses presented here attempt to account for some of the observed differences between data sources, the results are limited by the trials available for comparison. Estimates of OS for BEN are generally in line with those found in other non RCTs identified within the SLR (see Section 4.11).

The direction of bias from comparison is, however, clearly in favour of BEN given the poorer prognosis of patients included within the POM+LoDEX trials compared to the BEN datasets. Despite this bias significant and substantial (>4 months) improvements in OS were seen both within the base case analysis and sensitivity analysis 1.

4.10.3 Panobinostat

To indirectly compare POM+LoDEX (from trials MM-002, MM-003, and MM-010) with PANO+BOR+DEX (PANORAMA 2), in the absence of patient level data for PANORAMA 2, or a common comparator in each trial, a propensity matched adjusted indirect comparison (MAIC) approach was adopted using statistical software package SAS.[130] The MAIC reweights patient level data for POM+LoDEX to reflect a population of similar baseline characteristics to the PANO+BOR+DEX population. As the full population of PANORAMA 2 were refractory to BOR but not primary refractory, to aid comparability of the populations, the subgroup of patients (approximately 81%) in the POM+LoDEX trials that were refractory to BOR but not primary refractory were used for the MAIC.

Table 32 shows the comparison of baseline characteristics between the combined POM+LoDEX data and PANORAMA 2.

The patient characteristics between the selected POM+LoDEX and PANO+BOR+DEX data are relatively similar across trials with only small differences noted between age, ECOG, prior lines of therapy, and prior THAL.

Table 32: Comparison of baseline characteristics between the pooled trial dataset for POM+LoDEX (pomalidomide arm) and PANORAMA 2 (panobinostat arm)

	Panobinostat PANORAMA-2[35, 131]	Pomalidomide Combined MM-002, MM-003 and MM-010 datasets (subgroup refractory to bortezomib but not primary refractory)
N	55	886
Age **Median (range)** **Mean**	 61 (41-88) Not reported	 66 (34-88) 64.7
ECOG (%) **0** **1** **2** **3**	 47.3 (26/55) 45.5 (25/55) 7.3 (4/55) 0 (0)	 40.1 47.0 12.9 0.1
ISS stage (%) **1** **2** **3** **Missing**	 33.3 (18/54) 42.6 (23/54) 24.1 (13/54) 1/55	MM-003 and MM-010*: 23.5 (373/1588) 41.0 (651/1588) 35.5 (564/1588) 78/1666
Prior lines of therapy **Median (range)** **Mean**	 4 (2-11) Not reported	 5 (2-18) 5.0
Prior thalidomide therapy (%)	69.1	56.9
Refractory to bortezomib (%)	100	100

Key: ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; POM, pomalidomide, LoDex, low-dose dexamethasone, MM, multiple myeloma.
*Not reported in MM-002

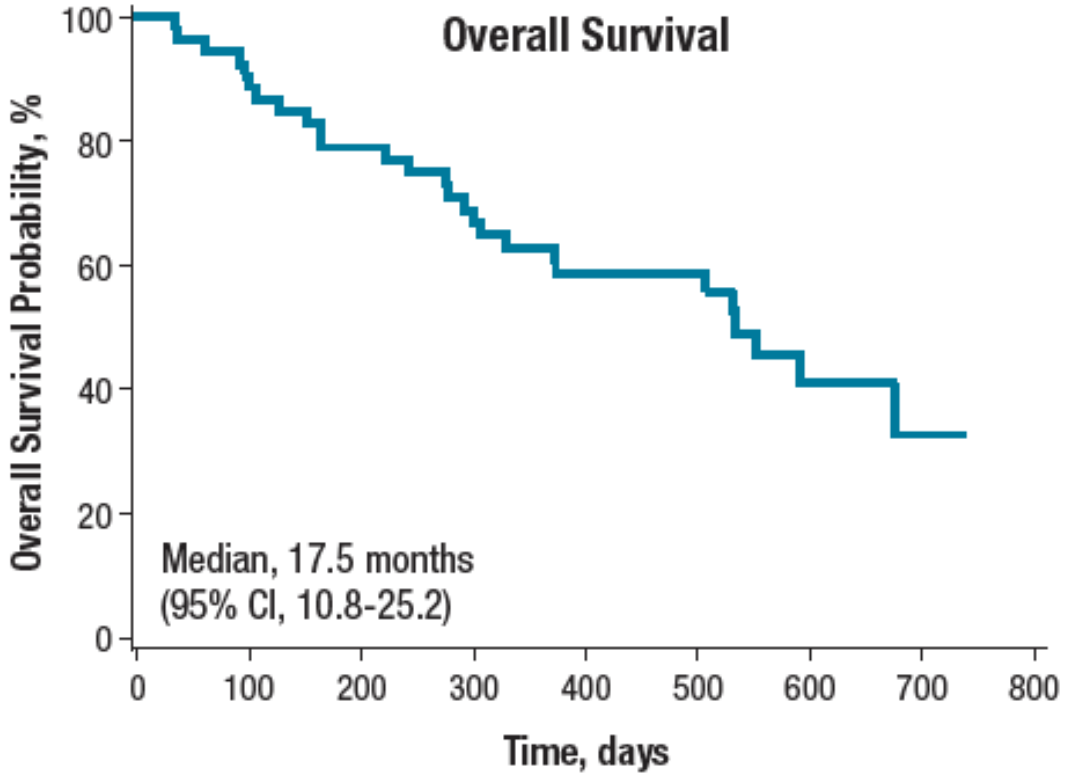
With the exception of ECOG, the baseline characteristics presented in

Table 32 are the same as those prognostic factors identified as clinically important for comparison to BEN (see Table 31) and are used to estimate propensity weights. ECOG is an important prognostic factor, but was not previously included in the parametric survival analyses as ECOG was not captured in the comparator data for BEN. Refractoriness to LEN was not included as this variable was not reported in the paper for PANORAMA 2. All except 1 patient had received prior LEN.[35]

As previously, ISS stage was not collected in MM-002 and therefore could not be included as a covariate for the MAIC. This likely biases against POM+LoDEX given more patients in MM-003 and MM-010 are at ISS stage 3 than in PANORAMA 2 (35.5% vs 24.1%). As the MAIC uses mean values for continuous covariates, and PANORAMA 2 only reported median values for age and number of prior lines of therapy, the median values were used as a proxy to the mean in PANORAMA 2. This assumption appears reasonable given the closeness of means and medians for these covariates in the POM+LoDEX datasets.

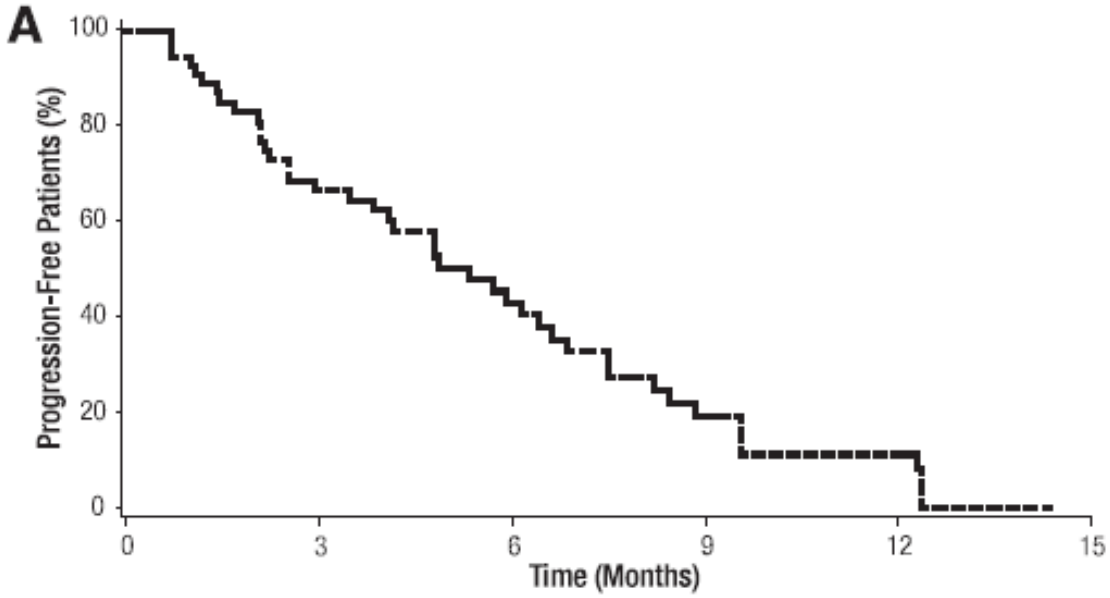
The source data for PANORAMA 2 were taken from Figure 3 in Richardson 2013a[131] for OS and from Figure 2a in Richardson 2013b[35] for PFS, and are reproduced below for reference in Figure 22 and Figure 23.

Figure 22: OS for panobinostat in PANORAMA 2



Key: OS, overall survival.

Figure 23: PFS for panobinostat in PANORAMA 2



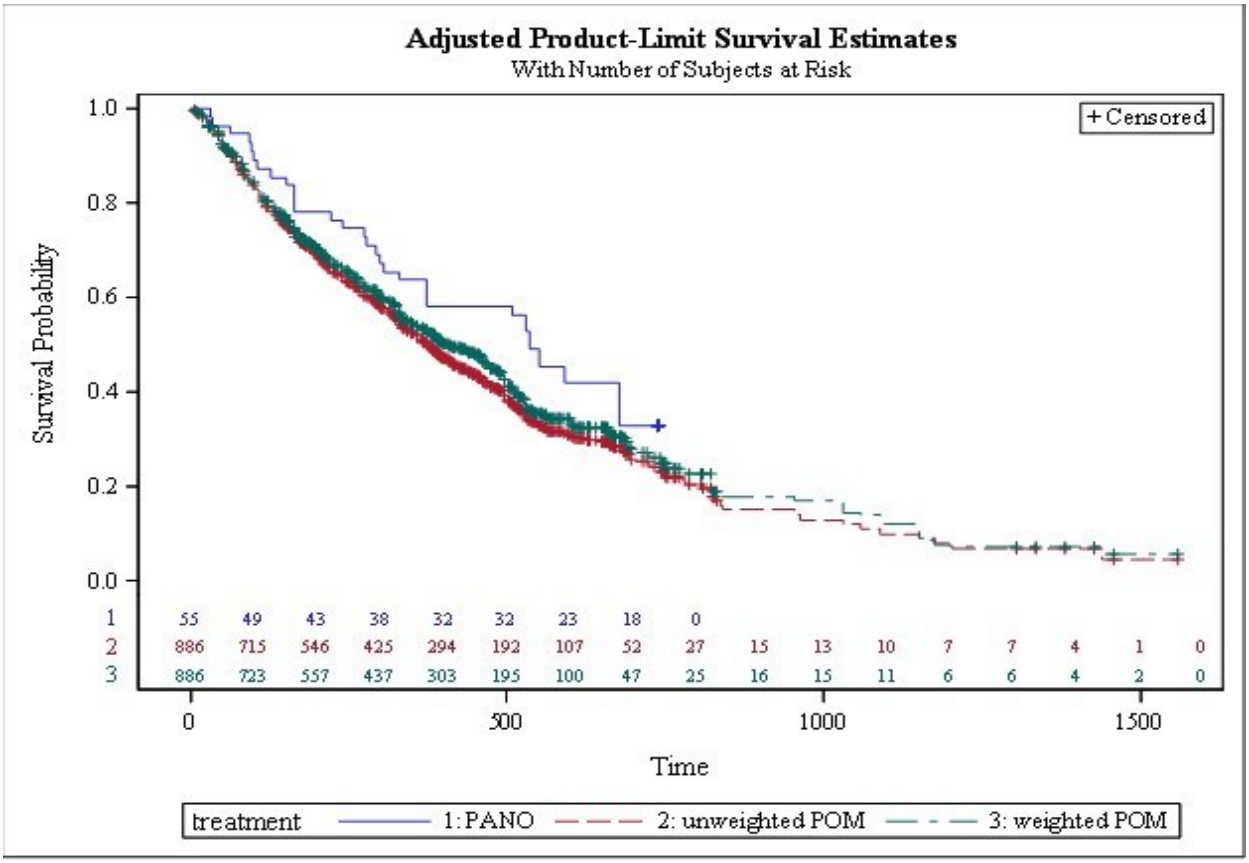
Key: PFS, progression-free survival.

OS and PFS KM data for PANO+BOR+DEX were estimated from the published KM curves using digitisation software. Using the estimated KM data, pseudo patient level data were created for PANO+BOR+DEX using the Guyot 2012 method.[132]

The propensity weighted POM+LoDEX data, the unweighted/unadjusted POM+LoDEX data, and the PANO+BOR+DEX data are presented in Figure 24 (for OS) and Figure 25 (for PFS). Median survival times are presented in Table 33.

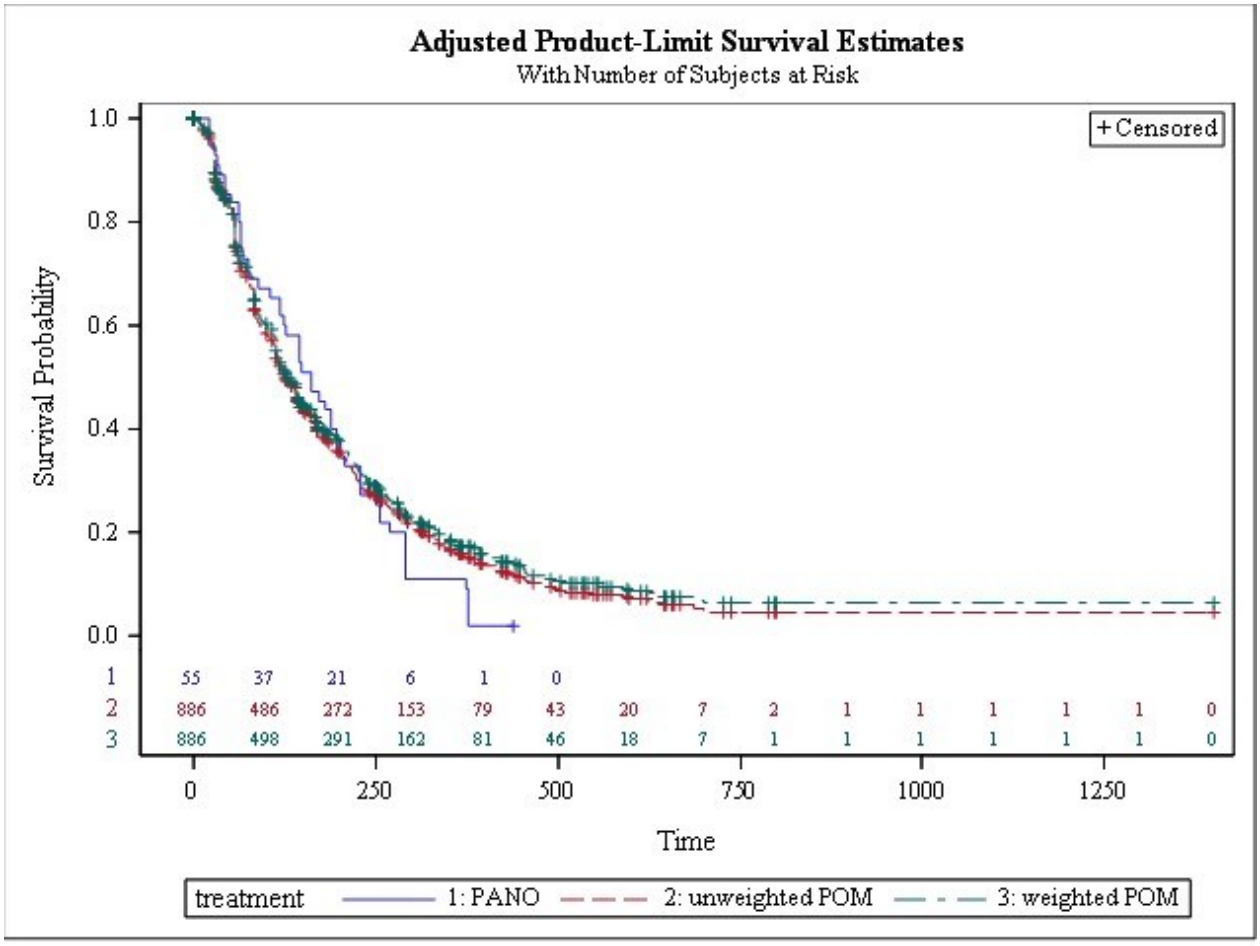
Generally the KM survival curves shift slightly to the right for POM+LoDEX, after adjustments for propensity weighting. This implies there was a slightly better baseline prognosis in the PANO+BOR+DEX patients than in the POM+LoDEX patients, at least when considering the four covariates included in the calculation of the propensity weights.

Figure 24: KM curves of OS for PANO+BOR+DEX and POM+LoDEX (weighted and unweighted)



Key: BOR, bortezomib; DEX, dexamethasone; KM, Kaplan-Meier; LoDEX, low-dose dexamethasone; OS, overall survival; PANO, panobinostat; POM, pomalidomide.

Figure 25: KM curves of PFS for PANO+BOR+DEX and POM+LoDEX (weighted and unweighted)



Key: BOR, bortezomib; DEX, dexamethasone; KM, Kaplan-Meier; LoDEX, low-dose dexamethasone; PANO, panobinostat; PFS, progression-free survival; POM, pomalidomide.

Table 33: Median OS and PFS times for PANO+BOR+DEX and POM+LoDEX

Treatment/data	Median OS, months (95% CI)	Median PFS, months (95% CI)
Pomalidomide (unweighted)	12.4 (11.1, 13.4)	4.1 (3.7, 4.6)
Pomalidomide (weighted)	13.4 (11.4, 15.6)	4.2 (3.7, 4.8)
Panobinostat	17.5 (10.8, 22.2)	5.3 (3.9,6.6)
Key: BOR, bortezomib; DEX, dexamethasone; LoDEX, low-dose dexamethasone; OS, overall survival; PFS, progression-free survival; PANO, panobinostat; POM, pomalidomide.		

The weighted patient level data for POM+LoDEX and pseudo patient level data for PANO+BOR+DEX were included in a Cox proportional hazards model to calculate a MAIC HR between PANO+BOR+DEX and POM+LoDEX. For comparison, a separate Cox proportional hazards model was performed using unadjusted (unweighted) POM+LoDEX data. These results are presented in Table 34.

Table 34: MAIC results - Cox proportional hazards model results

Comparison	OS HR (95% CI)	PFS HR (95% CI)
MAIC: panobinostat vs pomalidomide (weighted)	0.778 (0.555, 1.090)	1.178 (0.893, 1.555)
Naïve: panobinostat vs pomalidomide (unweighted)	0.731 (0.522, 1.023)	1.121 (0.849, 1.479)
Key: CI, confidence interval; HR, hazard ratio; MAIC, Matched adjusted indirect comparison; OS, overall survival; PFS, progression-free survival.		

Consistent with the observations on the KM curves, the effect of weighting the POM+LoDEX data to 'match' the patient characteristics of the PANO+BOR+DEX patients, moves the HRs more in favour of PANO+BOR+DEX when compared to unadjusted estimates (naïve comparisons) for both OS and PFS.

Similar to the comparison presented to BEN there are asome limitations to the statistical analyses presented, namely due to the assumptions required in order to undertake the statistical modelling primarily:

- This approach of modelling data arising from several data sources breaks randomisation and the pooling of data, and, even after adjustment for prognostic factors, cannot replace direct head-to-head trial data between POM+LoDEX versus PANO+BOR+DEX.
- Refractory to LEN status was not measured in PANORAMA 2 and therefore could not be included as a covariate.
- It is possible that not all influential prognostic factors were captured; this is complicated by the fact that only fitter patients are capable of receiving toxic regimens such as the PANO+BOR+DEX combination and it is highly likely

that many measures of comparative fitness have not been captured within the current analysis.

- In particular the impact of subsequent therapy on outcomes could not be considered as data was not available for PANORAMA 2.

Conclusion

These analyses indicate a modest benefit for POM+LoDEX compared to PANO+BOR+DEX for PFS and a modest benefit for PANO+BOR+DEX compared to POM+LoDEX for OS.

These comparative effectiveness analyses produce clinically non-plausible results for OS, given that both UK clinicians and the NCCN assess POM+LoDEX to be the more efficacious treatment based upon available data. This surprising result is not the case for PFS indicating that it is highly likely that an unknown confounder (such as differential use of subsequent therapy) is having an impact on outcomes.

4.10.4 Conventional chemotherapy

Although three studies were identified from the original SLR of clinical evidence presenting data on conventional chemotherapy in patients with RRMM, none of these studies have been included in the submission nor can be used to inform a statistical comparison. As stated above, the reason for this is that they are conducted in patient populations not comparable to the population in MM-003.

However, HiDEX data can be used as a proxy for other conventional chemotherapy regimens. In using HiDEX as a proxy, we can assume that the efficacy and safety results observed in the MM-003 study for POM+LoDEX versus HiDEX are equivalent for all conventional chemotherapy regimens. This is considered reasonable as patients on the HiDEX arm of the MM-003 trial receive HiDEX for only a short time period (TTF = 1.8 months) with the majority (60.1%) of patients going on to receive subsequent alternative active treatment.[128]

Conventional chemotherapy combinations such as melphalan + prednisone (MP) and cyclophosphamide + dexamethasone have been in use since the 1960s and, as demonstrated within the previous review conducted for TA338,[34] there is little high

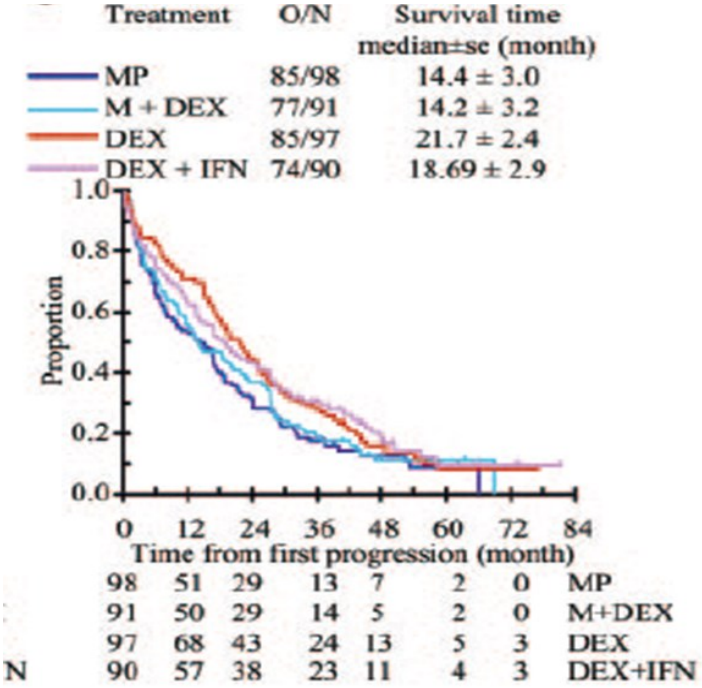
quality evidence demonstrating the effectiveness of these treatments. The same is true for repeated use of THAL.

Within the MM-003 trial, HiDEX was adopted as the control arm as it represented a standard anti-myeloma therapy for the treatment of subjects with relapsed or refractory disease at the time the trials were initiated.[133, 134]

In terms of published evidence, in 2006 the IFM group published data on HiDEX compared with MP in transplant-ineligible patients, which demonstrated no significant difference in OS between the 4 regimens studied: MP, HiDEX, melphalan + DEX, and DEX + interferon alpha.[29] Whilst this study is in first-line patients, this represents the only study available comparing outcomes in patients receiving conventional chemotherapy compared with HiDEX (Figure 26).

A comparison of HiDEX outcomes from the MM-003 trial and outcomes for patients receiving conventional chemotherapy in the Gooding and Tarant combined patient level data and CONNECT MM registry (Figure 27) does not provide any evidence to indicate that the assumption of similar effectiveness is inappropriate.

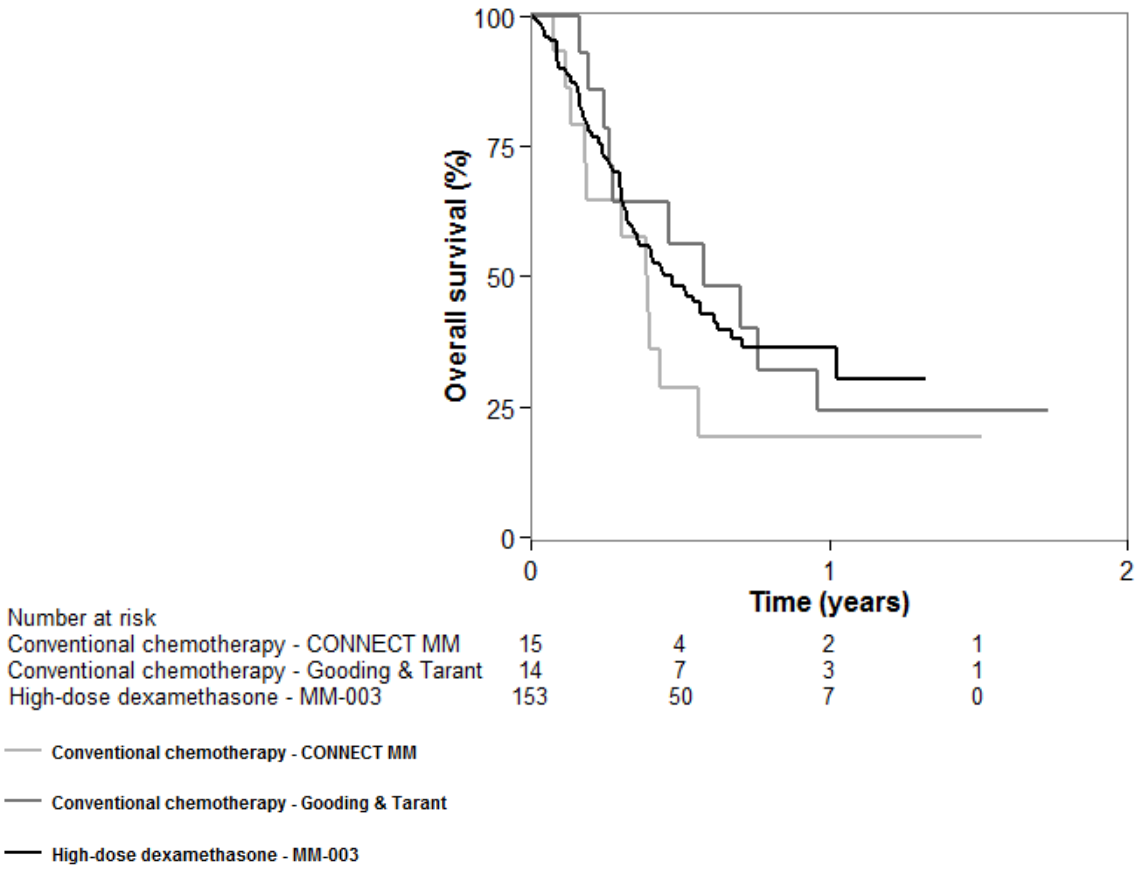
Figure 26: OS for MP versus DEX



Key: DEX, dexamethasone; IFN, interferon alpha; OS, overall survival; MP, melphalan + prednisone.

Source: Facon et al., 2006.[29]

Figure 27: Comparison of outcomes for patients receiving HiDEX versus conventional chemotherapy: CONNECT MM and Gooding and Tarant datasets



Key: HiDEX, high-dose dexamethasone; MM, multiple myeloma.

It should also be noted that within the original TA171 review of LEN+DEX, outcomes from the Medical Research Council database for patients treated with conventional chemotherapy were accepted as a suitable proxy for outcomes for patients receiving HiDEX in TA171.[92]

In summary, the evidence obtained from the comparison of HiDEX and conventional chemotherapy from the patient level data, coupled with the similar comparison in the first-line population does not indicate any difference in outcomes between patients receiving HiDEX and those receiving conventional chemotherapy.

4.11 Supporting evidence

4.11.1 Efficacy evidence from other supporting RCTs for POM

A brief summary of MM-002 is provided below, and tabulated details of all supporting POM RCTs relevant to this submission (including a summary of study design, baseline characteristics and results), are presented in Appendix 13. Quality appraisals for the RCTs that were not included in the statistical analyses (described in Section 4.10) are provided in Appendix 6.

MM-002

MM-002, was an open-label, randomised Phase I/II study assessing the maximum tolerated dose (MTD) of POM and the safety and efficacy of POM±LoDEX in patients who had received two or more previous therapies including BOR and LEN and who had progressed within 60 days of the most recent therapy.[19] The MTD was determined from the Phase I part of this study, to be 4mg daily, based on the dose-limiting toxicity of neutropenia.[114] For the Phase II part of the study, 221 patients (median of five previous therapies [range 1-13]), were randomised to POM+LoDEX (n=113) or POM (n=108). With a median follow-up of 14.2 months.Median PFS was 4.2 and 2.7 months (HR=0.68 [95% CI: 0.51-0.90]; *p*=0.003), ORRs were 33% and 18% (odds ratio: 2.28 [95% CI: 1.21-4.29]; *p*=0.013), median response duration was 8.3 and 10.7 months in patients with at least a partial response, and median OS was 16.5 and 13.6 months (HR=0.94 [95% CI: 0.70-1.28]; p=0.709), for POM+LoDEX and POM patients, respectively. The outcomes confirmed the improved efficacy of using POM combined with LoDEX compared with the single agent POM in patients with RRMM who have exhausted multiple prior therapies, including BOR and LEN and suggested there was no cross-resistance of POM+LoDEX with previous therapies.

IFM-2009-02 and Baz, 2016

These studies were supportive of the findings of MM-003 and MM-002, in that they demonstrated POM+LoDEX to be effective and well tolerated in the treatment of RRMM, especially in a heavily pretreated patient population including patients refractory to LEN and BOR.

4.11.2 Efficacy evidence from other supporting non RCTs and real world evidence for POM

A list of all the relevant supporting non-RCT studies for POM is provided in Appendix 14. Summaries for key non-RCT studies are provided below.

STRATUS Study (MM-010)

Study design

The MM-010 study is a multicentre, single-arm, open-label, European Phase IIIb study, which evaluated the safety and efficacy of POM+LoDEX in patients with RRMM.[18] Patients (≥18 years) were included if they were refractory to last prior therapy, had received ≥2 prior therapies (including ≥2 consecutive cycles of LEN and BOR, alone or in combination and adequate prior alkylator therapy) and had previous BOR and LEN treatment failure (defined as progressive disease on or within 60 days of treatment [refractory], progressive disease ≤ 6 months after achieving a PR [relapsed], or intolerance to BOR). Exclusion criteria included prior POM therapy, hypersensitivity to THAL, LEN or DEX, Grade ≥2 peripheral neuropathy, and substantial cardiac disease.

Patients received POM 4mg on Days 1-21 with LoDEX 40mg (20mg for patients aged >75 years) on Days 1, 8, 15 and 22 every 28 days until progressive disease or unacceptable toxicity. All patients received thromboprophylaxis with low dose aspirin, low-molecular-weight heparin or equivalent. The primary endpoint was safety; secondary endpoints included POM exposure, investigator-assessed ORR (≥PR), DOR, TTP, PFS and OS.

Patient demographics

A total of 682 patients with RRMM (ITT population) were recruited between November 2012 and December 2014; six patients (0.9%) did not receive study drug. At data cut-off (4 May 2015; median follow-up 16.8 months) 15.2% of patients remained on treatment while 83.9% had discontinued. Primary reasons for treatment discontinuation were progressive disease (62.2%) and death (7.9%).

The median age of study patients was 66 years (range, 37–88 years) with a median time from initial diagnosis of 5.3 years. Patients had received a median of five

(range, 2-18) prior treatment regimens with most refractory to LEN (95.9%) and BOR (83.7%). In total 80.2% of patients were refractory to both treatments.

Baseline characteristics for the ITT population are shown in Table 35.

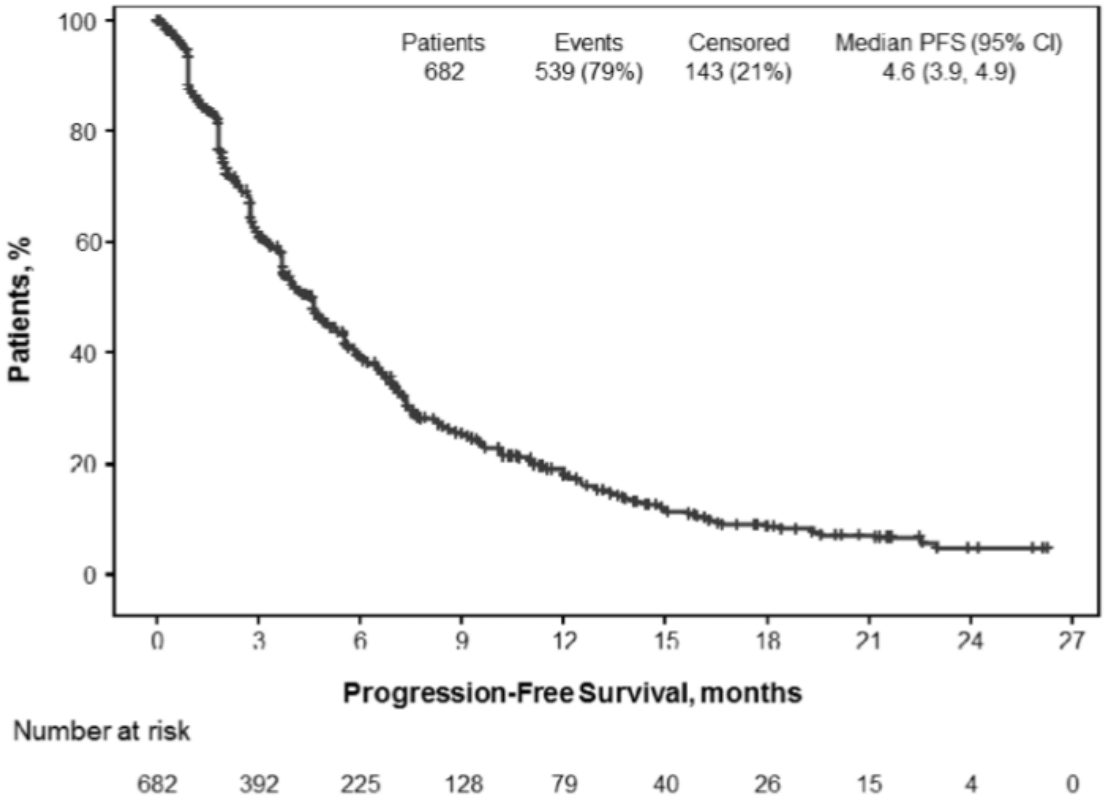
Table 35: Baseline characteristics in MM-010: ITT population (n=682)

Characteristic	Number of patients
Median (range) age, years	66 (37–88)
Median (range) time since initial diagnosis, years	5.3 (0.6–28.2)
ECOG PS, n (%)	
0–1	614 (90.0)
2–3	68 (10.0)
ISS stage, n (%)	
I–II	414 (60.7)
III	236 (34.6)
Missing	32 (4.7)
CrCl < 60 mL/min, n (%)	237 (34.8)
Median (range) prior regimens, n	5 (2–18)
>2 prior regimens, n (%)	367 (93.4)
Prior therapy, n (%)	
Lenalidomide	682 (100.0)
Bortezomib	682 (100.0)
Dexamethasone	666 (97.7)
Thalidomide	372 (54.5)
Carfilzomib	24 (3.5)
Stem cell transplant	451 (66.1)
Treatment-refractory, n (%)	
Lenalidomide	654 (95.9)
Bortezomib	571 (83.7)
Lenalidomide and bortezomib	547 (80.2)
Key: CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance score; ISS, International Staging System; ITT, intention to treat.	

Efficacy results

Median PFS was 4.6 months (95% CI: 3.9, 4.9) in the ITT population (Figure 28). Similar results (median PFS [95% CI]) were observed for patients refractory to LEN (4.6 [3.8, 4.9]), BOR (4.2 [3.8, 4.8]) and to both LEN and BOR (4.2 [3.8, 4.7]). Median PFS was also similar regardless of the number of prior lines of therapy (≤3 prior lines: 3.9 months [95% CI: 3.7, 5.1]; vs >3 prior lines: 4.6 months [95% CI: 4.0, 5.3]).

Figure 28: KM curve of PFS in the ITT population (n=682; data cut-off, 4 May 2015)

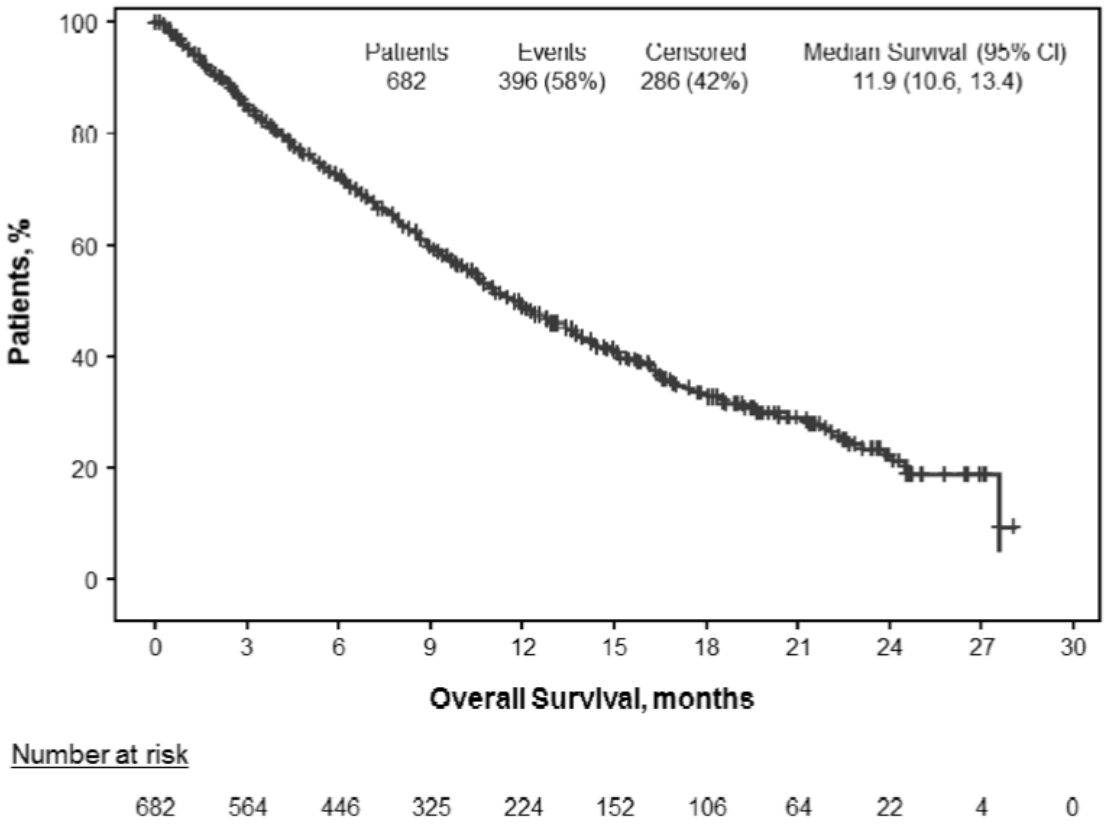


Key: CI, confidence interval; KM, Kaplan-Meier; PFS, progression-free survival; ITT, intention to treat.

In the ITT population, median OS was 11.9 months (95% CI: 10.6, 13.4) (Figure 29). Median OS was also 11.9 months (95% CI: 10.6, 13.4) in each of the three treatment groups (LEN-, BOR- and both LEN and BOR-, refractory patients). Survival (median

OS [95% CI]) was also similar, irrespective of the number of prior lines of therapy (≤3 versus >3: 12.8 [8.9, 18.4] vs 11.9 [10.6, 13.0]).

Figure 29: KM curve of OS in the ITT population (n=682; data cut-off, 4 May 2015)



Key: CI, confidence interval; KM, Kaplan-Meier; OS, overall survival.

In the ITT population, the ORR was 32.6% (95% CI: 29.0, 36.2), with 0.6% of patients achieving a CR, 7.6% having a VGPR, and 24.3% achieving a PR. Median TTR was 1.9 (range, 0.5–17.5) months, median DOR was 7.4 months (95% CI: 6.5, 8.7) and stable disease was achieved by 49.7% of patients.

Conclusion

The MM-010 study is the largest study conducted to date with POM+LoDEX in a heavily pre-treated RRMM patient population. The findings of this large study support the previous studies with POM+LoDEX in demonstrating that the combination is an

effective treatment for heavily pre-treated patients with RRMM who have exhausted currently available treatment options. In the 80% of patients who were refractory to both LEN and BOR clinical benefits were similar to the overall population, supporting the sequential use of these treatment regimens.

UK real world evidence

Evidence for 117 heavily pre-treated patients (median prior therapy lines: 3-4) from two retrospective studies indicated consistent outcomes with POM+DEX in UK clinical practice compared to the trial data.[27, 28] The OS in these two studies ranged from 10.9 to 13.7 months, PFS ranged from 3.4 to 4.3 months and ORR ranged from 39% to 53%.

Celgene real world evidence project

Celgene conducted a retrospective real world data collection project on prescribing of BEN, BOR retreatment and POM+LoDEX at third line onwards with the aim of increasing the comparator evidence available to NICE.[135]

Eligible patients (n=150) were included from 17 UK centres (13 in England, 2 in Wales, and 2 in Northern Ireland), and must have received at least 2 prior treatments (including ≥2 consecutive cycles of LEN and BOR [alone or in combination]), progressed on BOR and LEN, and have been prescribed and progressed on BEN (n=58), BOR retreatment (n=38) or POM+LoDEX (n=54) at 3rd line onwards. Inclusion/exclusion criteria are presented in Table 36.

Table 36: Inclusion/exclusion criteria for UK RWE

Inclusion criteria	Exclusion criteria
All patients must have received at least 2 prior treatments • ≥ 2 consecutive cycles of LEN and BOR (alone or in combination) • Adequate prior alkylator treatment (SCT or ≥6 cycles or PD after ≥2 cycles) All patients must have progressed on BOR and LEN All patient should have been prescribed and progressed on one of the following at 3rd line onwards • BEN • BOR (retreatment) • POM+LoDEX	BEN+BOR (in combination) BEN or BOR retreatment patients who have received POM as part of the treatment pathway POM: any indication outside of the licensed indication
Key: BEN, bendamustine; BOR, bortezomib; LEN, lenalidomide; LoDEX, low-dose dexamethasone; PD, progressive disease; POM, pomalidomide; SCT, stem cell therapy. **Source:** Schey et al., 2016: UK RWE.[135]	

Unfortunately this data collection exercise failed to supply information adequate to inform quantitative comparison. Substantial protocol deviations occurred, primarily: the receipt of subsequent POM for patients who received BEN (29.3%) or BOR retreatment (39.5%). In addition, there were major differences between treatment groups in:

- Proportion of older patients (aged >70 years): 44.4% for POM+LoDEX; 24.1% for BEN; 28.9% for BOR
- Median number of prior treatments: 4 for POM+LoDEX vs 3 with BOR and with BEN.
- Amount of subsequent treatment received: 44.4% for POM+LoDEX; 62.1% for BEN, and 81.6% for BOR

Patient demographics and characteristics at baseline are presented in Table 37.

Table 37: Patient characteristics at T0 in UK RWE study

Characteristic	POM+LoDEX (n=54)	BEN Combo (n=58)	BOR Combo (n=38)
Median age, years (range)	69 (47 - 84)	65 (46 - 76)	67 (39 - 86)
Age category			
>70 yrs	24 (44.4)	14 (24.1)	11 (28.9)
>75 yrs	10 (18.5)	1 (1.7)	4 (10.5)
Median time from diagnosis, years (range)	5.1 (0.9 - 15.5)	4.8 (0.9 - 16.4)	4.5 (1.7 - 12.7)
ISS stage, n (%)			
I	1 (1.9)	3 (5.2)	1 (2.6)
II	2 (3.7)	4 (6.9)	0 (0.0)
III	4 (7.4)	4 (6.9)	1 (2.6)
Missing	47 (87.0)	47 (81.0)	36 (94.7)
ECOG-PS, n (%)			
0	4 (7.4)	4 (6.9)	1 (2.6)
I	7 (13.0)	9 (15.5)	5 (13.2)
II	2 (3.7)	9 (15.5)	0 (0.0)
III	0 (0.0)	0 (0.0)	1 (2.6)
IV	1 (1.9)	1 (1.7)	1 (2.6)
Missing	40 (74.1)	35 (60.3)	30 (78.9)
CrCL, n (%), < 60 mL/min	4 (7.4)	4 (6.9)	3 (7.9)
Cytogenetic risk, n (%): Missing	54 (100)	58 (100)	38 (100)
Median (range) number of previous treatments	4 (2 -9)	3 (2 -9)	3 (2 -7)

Previous treatments			
DEX	54 (100)	58 (100)	38 (100)
THAL	44 (81.5)	43 (74.1)	30 (78.9)
LEN	54 (100)	58 (100)	38 (100)
BOR	54 (100)	58 (100)	38 (100)
BEN	12 (22)	0 (0)	5 (13)
Previous SCT, n (%)	35 (64.8)	30 (51.7)	23 (60.5)
Refractory to LEN*, n (%)	47 (87)	52 (89.7)	34 (89.5)
Refractory to BOR*, n (%)	37 (68.5)	36 (62.1)	12 (31.6)
Refractory to LEN & BOR*, n (%)	32 (59.3)	33 (56.9)	12 (31.6)

*Refractory progressed on or within 60 days of treatment in real world clinical practice.

Key: BEN, bendamustine; BOR, bortezomib; DEX, dexamethasone; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; ISS, International Staging System; LEN, lenalidomide; POM+LoDEX, pomalidomide plus low-dose dexamethasone; SCT, stem cell transplant; T0, time when treatment of interest was initiated; THAL, thalidomide.

Source: Schey et al., 2016: UK RWE.[135]

Results of the study in terms of PFS, OS and ORR are presented in Table 38. POM+LoDEX delivered the longest median PFS, compared with BOR and BEN, while median OS was shorter. As stated in Section 4.10, there were several issues with this data collection exercise, which may have biased the results, and led to a lack of comparability with other POM+LoDEX trials.

Table 38: PFS, OS and ORR by treatment in the Celgene UK RWE collection exercise

	POM+LODEX (UK-RWE)	BEN (UK-RWE)	BOR (UK-RWE)
Median PFS (months)	8.0	5.5	6.3
Median OS (months)	8.6	13.2	14.4
ORR (≥PR)	42.6%	36.2%	47.4%

Key: BEN, bendamustine; BOR, bortezomib; LoDEX, low-dose dexamethasone; ORR, overall response rate; PFS, progression-free survival; POM, pomalidomide; PR, partial response; UK-RWE, United Kingdom real world evidence.
Sources: Schey et al., 2016: UK RWE[135].

4.11.3 Studies of comparators in UK current care

A list of all the relevant supporting RCT and non-RCT studies for the comparators is provided in Appendix 15. Tabulated summaries of study design, baseline characteristics and results for all the supporting comparator studies not included in the statistical analyses (described in Section 4.10) are also presented. The following information is a summary of comparator efficacy evidence (please see section 4.12.5 for comparator safety evidence.)

BEN

Bendamustine does not currently have a marketing authorisation in the UK for refractory and relapsed/refractory MM, has not been appraised by NICE. Currently, BEN is only available in the UK via the CDF, and has a licence in newly-diagnosed multiple myeloma only.[1, 12]

The SLR (as described in Section 4.1) identified a total of six relevant studies investigating BEN-containing regimens in patients with RRMM who had previously received treatment with at least two regimens including LEN and BOR (≥75% of

patients had received both LEN and BOR as per the SLR inclusion criteria). The studies included one RCT, namely the MUK-one study which compared two different regimens of BTD,[16] and five non-RCT studies investigating BEN+steroid±THAL regimens.[39, 136-139]

The Phase II MUK-one study (n=95) is the largest published study looking at the combination of BTD in UK clinical practice with the aim of identifying an optimally active and deliverable dose of BEN in combination with THAL and DEX in patients with RRMM.[16] Patients received either BEN 60mg/m^2 or 100mg/m^2 IV on Days 1 and 8 of a 28-day cycle with THAL and DEX. The total MUK-one study population (n=95) had less advanced disease than patients entering the pivotal POM+LoDEX study MM-003. Patients in MUK-one had only received a median of 3 prior treatments (range 1-5) and only 66% of patients had received prior LEN and BOR, respectively. In addition, only 22% of patients were refractory to their last therapy. Response and survival outcomes are heavily influenced by the amount of previous treatment received and level of refractoriness to previous treatments.[30] Under the circumstances, a better response, DOR & survival outcome with a triple drug combination in earlier lines of treatment would be expected. Despite this, the BEN 60mg/m^2 combination only delivered a median PFS and OS of 6.5 and 10.6 months, respectively in the treated population. The BEN 100mg/m^2 IV dose in combination with THAL+DEX was deemed to be undeliverable and this arm of the study was closed early.

In general, it is challenging to try and draw efficacy comparisons between the BEN studies identified in the SLR and the data for POM+LoDEX as the BEN studies are all conducted in a less advanced and less refractory population.[16-18, 39, 136-139]

In addition, most of these studies identified, except for the MUK-one RCT, are single-arm, uncontrolled trials or retrospective, observational studies, conducted in only small numbers of patients (n=18 to 110), limiting the robustness of the data. Across all the BEN studies identified, the median OS ranged from 7.2 to 13.0 months.[16, 39, 136, 137]

During a recent advisory board meeting, clinical advisors stated that patients often struggle to continue to take treatment with BEN and that durable responses are

uncommon.[9] In addition, clinical advisors commented on the need for additional clinic visits compared with POM for administration of the drug.[9] The NCCN rated the effectiveness of BEN as 3/5 compared to 4/5 for POM+LoDEX.[104]

PANO+BOR+DEX

PANO+BOR+DEX is available to patients in the UK as per the recent NICE recommendation in patients who have received at least two prior regimens including BOR and an immunomodulatory agent.[93] Only one relevant study of PANO+BOR+DEX was included in the SLR (as described in Section 4.1), according to the current inclusion/exclusion criteria (in particular that ≥75% of patients must have received both LEN and BOR), namely the PANORAMA 2.[35] PANORAMA 2 is a Phase II, two-stage, single-arm, open-label multicentre study of PANO+BOR+DEX in patients with relapsed and BOR-refractory multiple myeloma (i.e., received ≥2 prior lines of therapy, including an immunomodulatory drug, and patients who had progressed on or within 60 days of the last BOR-based therapy). A total of 55 patients were included (median age: 61 years; 52.7% males) with a median of 54.8 months since diagnosis, and receipt of a median of 4 prior treatments. Median exposure to treatment was 4.6 months. Although 98.2% received prior LEN, data were not presented on proportion of patients refractory to LEN.[35]

The overall response rate (assessed by EBMT criteria) was 34.5%, and DOR among the responders was 6 months. Median PFS and OS were 5.4 months and 17.5 months, respectively.[35, 140]

In contrast to the data in PANORAMA 2, patients who received POM+LoDEX in studies MM-003 & MM-010 tended to be older and have more advanced disease. The advanced disease is reflected in: a higher percentage of patients being classified as ISS stage III, having received more prior treatments and patients being classified as refractory to LEN (75% in MM-003 and 80% in MM-010).[17, 18] In this more challenging patient population, POM+LoDEX has demonstrated improvements in OS, PFS and response. These outcomes were also independent of age.[141]

Clinical advisors have stated that they would be more likely to use PANO+BOR+DEX at fourth-line rather than third-line, with some advisors commenting that they would prefer an entirely oral regimen at third-line.[9]The NCCN

rated the effectiveness of PANO+BOR+DEX as 3/5 compared to 4/5 for POM+LoDEX.[104]

Conventional chemotherapy

No papers presenting information on conventional chemotherapy were included in the SLR according to the current inclusion/exclusion criteria, because no studies had been conducted in a patient population relevant to this submission. Information available from patient level data sources is presented in Section 4.10 and indicates that outcomes may reasonably be considered as comparable to HiDEX.

Clinical advisors stated that conventional chemotherapy regimens are sometimes used as a bridge to a second transplant or as a bridge whilst waiting for other treatments to become available.[9] Clinical experts consulted at the recent daratumumab scoping meeting (21 March, 2016) advised that there is no real efficacy data at fourth and fifth line,[11] and the UK Myeloma Forum and Myeloma UK also stated that conventional chemotherapy agents (e.g., melphalan and cyclophosphamide) are generally used as a final option.[11]

4.12 Adverse reactions

This section reviews the available evidence regarding the safety of POM+LoDEX in patients with refractory and relapsed/refractory multiple myeloma with a key focus on the safety data from the pivotal MM-003 study in which POM+LoDEX was compared with HiDEX. Safety data reported for the MM-003 study are from the last full CSR to a data cut-off of 01 March 2013 unless otherwise stated.[17]

4.12.1 MM-003 study

- Discontinuation of POM+LoDEX because of an AE was uncommon (8.6% versus 10.5% in the HiDEX group) suggesting that with dose modifications and supportive care the safety profile was predictable, manageable and generally well tolerated.[17]
- The most common Grade 3/4 haematological AEs in the POM+LoDEX and HiDEX arms were: neutropenia (48.3% versus 15.3%), anaemia (32.7% versus 38.7%) and thrombocytopenia (22.0% versus 26.0%).[17]

- Grade 3/4 non-haematological AEs in the POM+LoDEX and HiDEX arms included infections and infestations (30.0% versus 24.0%), pneumonia (12.7% versus 8.0%), bone pain (7.3% versus 4.7%) and fatigue (5.3% versus 6.0%). AEs such as muscular weakness (0.7% versus 3.3%), myopathy (0.3% versus 3.3%) and hyperglycaemia (3.7% versus 7.3%) were less frequent with POM+LoDEX than HiDEX.[17]
- There were 11 (4%) treatment-related deaths in the POM+LoDEX arm: eight cases of infections and infestations, two cases of multi-organ failure or sudden death and one nervous system disorder: There were seven (5%) in the HiDEX arm due to infections and infestations.[110]
- Due to structural similarities between POM and THAL, a risk minimisation plan has been established to reduce risk of foetal exposure to POM.[4]

Treatment emergent adverse events

Treatment emergent adverse events (TEAEs) were consistent with the known safety profiles of POM and HiDEX. The AE profile suggests that POM+LoDEX is generally well-tolerated, with a predictable and manageable side effect profile.[17, 41, 110, 142] The data presented were obtained from analysis of the safety population, which included patients who had received at least one dose of study medication (POM+LoDEX, n=300; HiDEX, n=150).

In the MM-003 study, AEs were more likely to occur shortly after treatment initiation (within the first two cycles) and decreased in frequency thereafter. Almost all patients in each treatment group had a TEAE (99% in the POM+LoDEX group and 99.3% in the HiDEX group).

Appendix 10 contains an overview of TEAEs. A summary of all TEAEs and Grade 3/4 TEAEs occuring in >10% of patients is presented in Table 39. Drug-related AEs can also be found in Appendix 10.

Grade 3/4 treatment-emergent adverse events

Similar percentages of subjects in each treatment arm had at least one Grade 3/4 AE (86.3% for POM+LoDEX and 84.7% for HiDEX) and many of these events occurred in similar proportions of subjects in the two treatment groups.

Haematological AEs were the most common Grade 3/4 AEs (67.7% for POM+LoDEX and 56.0% for HiDEX).

Grade 3/4 events that occurred more frequently in the POM+LoDEX arm than in the HiDEX arm included: neutropenia (48.3% versus 15.3%); febrile neutropenia (9.3% versus 0%); pneumonia (12.7% versus 8.0%); bone pain (7.3% versus 4.7%); decreased neutrophil count (4.7% versus 0.7%); and leukopenia (9.0% versus 3.3%).[17]

Grade 3/4 events that occurred less frequently in the POM+LoDEX arm than in the HiDEX arm included: asthenia (3.7% versus 6.7%); hyperglycaemia (3.7% versus 7.3%); myopathy (0.3% versus 3.3%); muscular weakness (0.7% versus 3.3%); and insomnia (1.0% versus 3.3%).[17]

Table 39: TEAEs that occurred in ≥10% of patients of any grade in either treatment group by system organ class and preferred term (safety population) and corresponding Grade 3/4 TEAEs

	POM+LoDEX (n=300)	HiDEX[b] (n=150)	POM+LoDEX (n=300)	HiDEX[b] (n=150)
System organ preferred class[a]	**Total**	**Total**	**Grade 3/4**	**Grade 3/4**
Number of patients with at least one AE	297 (99.0)	149 (99.3)	259 (86.3)	127 (84.7)
Blood and lymphatic system disorders	**229 (76.3)**	**99 (66.0)**	**203 (67.7)**	**84 (56.0)**
Anaemia	156 (52.0)	77 (51.3)	98 (32.7)	58 (38.7)
Neutropenia	154 (51.3)	30 (20.0)	145 (48.3)	23 (15.3)
Febrile neutropenia	28 (9.3)	0 (0.0)	28 (9.3)	0 (0.0)
Thrombocytopenia	89 (29.7)	44 (29.3)	66 (22.0)	39 (26.0)
Leukopenia	38 (12.7)	8 (5.3)	27 (9.0)	5 (3.3)
General disorders and administration site conditions	**224 (74.7)**	**95 (63.3)**	**62 (20.7)**	**37 (24.7)**
Fatigue	101 (33.7)	41 (27.3)	16 (5.3)	9 (6.0)
Pyrexia	80 (26.7)	35 (23.3)	9 (3.0)	7 (4.7)
Oedema peripheral	52 (17.3)	17 (11.3)	4 (1.3)	3 (2.0)
Asthenia	50 (16.7)	27 (18.0)	11 (3.7)	10 (6.7)
General physical health deterioration	35 (11.7)	16 (10.7)	24 (8.0)	12 (8.0)
Infections and infestations	**203 (67.7)**	**79 (52.7)**	**90 (30.0)**	**36 (24.0)**
Upper respiratory tract	48 (16.0)	11 (7.3)	5 (1.7)	1 (0.7)

	POM+LoDEX (n=300)	HiDEX[b] (n=150)	POM+LoDEX (n=300)	HiDEX[b] (n=150)
infection				
Pneumonia	45 (15.0)	16 (10.7)	38 (12.7)	12 (8.0)
Bronchitis	30 (10.0)	8 (5.3)	4 (1.3)	0 (0.0)
Gastrointestinal disorders	**178 (59.3)**	**62 (41.3)**	**24 (8.0)**	**10 (6.7)**
Diarrhoea	66 (22.0)	28 (18.7)	3 (1.0)	2 (1.3)
Constipation	65 (21.7)	22 (14.7)	7 (2.3)	0 (0.0)
Nausea	45 (15.0)	16 (10.7)	3 (1.0)	2 (1.3)
Musculoskeletal and connective tissue disorders	**162 (54.0)**	**83 (55.3)**	**49 (16.3)**	**30 (20.0)**
Back pain	59 (19.7)	24 (16.0)	15 (5.0)	6 (4.0)
Bone pain	54 (18.0)	21 (14.0)	22 (7.3)	7 (4.7)
Muscle spasms	46 (15.3)	11 (7.3)	1 (0.3)	1 (0.7)
Muscular weakness	9 (3.0)	19 (12.7)	2 (0.7)	5 (3.3)
Respiratory, thoracic and mediastinal disorders	**151 (50.3)**	**49 (32.7)**	**36 (12.0)**	**13 (8.7)**
Cough	60 (20.0)	15 (10.0)	2 (0.7)	1 (0.7)
Dyspnoea	59 (19.7)	22 (14.7)	15 (5.0)	7 (4.7)
Epistaxis	28 (9.3)	15 (10.0)	3 (1.0)	3 (2.0)
Nervous system disorders	**129 (43.0)**	**54 (36.0)**	**30 (10.0)**	**18 (12.0)**
Dizziness	37 (12.3)	14 (9.3)	4 (1.3)	2 (1.3)
Metabolism and nutrition disorders	**117 (39.0)**	**64 (42.7)**	**58 (19.3)**	**33 (22.0)**
Decreased appetite	38 (12.7)	11 (7.3)	3 (1.0)	2 (1.3)
Hypercalcaemia	21 (7.0)	16 (10.7)	13 (4.3)	7 (4.7)
Skin and subcutaneous tissue disorders	**94 (31.3)**	**26 (17.3)**	**9 (3.0)**	**1 (0.7)**
Psychiatric disorders	**88 (29.3)**	**56 (37.3)**	**17 (5.7)**	**15 (10.0)**
Insomnia	32 (10.7)	32 (21.3)	3 (1.0)	5 (3.3)
Investigations	**86 (28.7)**	**30 (20.0)**	**40 (13.3)**	**12 (8.0)**
Renal and urinary disorders	**52 (17.3)**	**24 (16.0)**	**22 (7.3)**	**8 (5.3)**

Key: AE, adverse event; DEX, dexamethasone; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide; TEAEs, treatment-emergent adverse events.
Notes: TEAEs are defined as any AE occurring or worsening on or after the first treatment of the study medication and within 30 days after the end date of study drug; [a], System organ classes and preferred terms are coded using the MedDRA dictionary version 14.0. System organ classes and preferred terms are listed in descending order of frequency of POM+LoDEX group. A patient with multiple occurrences of an AE is counted only once in the AE category; [b], Data are before crossover to POM+LoDEX.
Source: CSR.[17] Date cut-off: 01 March 2013.

Key adverse events in MM-003 (01 March 2013 data cut-off)

Neutropenia

High levels of neutropenia and the presence of febrile neutropenia in the POM+LoDEX compared with the HiDEX group (51.3% versus 20.0% for neutropenia and 9.3% versus 0% for febrile neutropenia) were of particular interest, occurring mainly in the first few cycles of therapy. However, few neutropenic events were serious, only one patient discontinued therapy and no patients died due to neutropenia. Furthermore, in the group of patients that experienced neutropenia of Grade 3 and above, the majority of patients had no concurrent infection.

Thrombocytopenia

Thrombocytopenia levels were similar in both groups (29.7% for POM+LoDEX and 29.3% for HiDEX). However, only 1% of patients discontinued due to thrombocytopenia. No patients died due to thrombocytopenia. Among patients with at least one occurrence of thrombocytopenia, 26.5% of POM+LoDEX and 25.5% of HiDEX patients had concurrent haemorrhage or bleeding. Haemorrhage was the cause of death for two patients in the POM+LoDEX group and one patient in the HiDEX group.

Infection

Levels of infection were high in both treatment groups (67.7% for POM+LoDEX and 52.7% HiDEX). The most frequent infection was upper respiratory tract infection (16.0%) for POM+LoDEX and pneumonia (10.7%) for HiDEX. Patients in the POM+LoDEX group had a lower death rate from infections compared to those in the HiDEX group (4.7% versus 11.3%), due to lower proportions of septic shock (0% versus 4.0%, respectively).

Peripheral neuropathy

In the POM+LoDEX group, 19.0% of patients had at least one occurrence of peripheral neuropathy compared with 14.0% in the HiDEX group. The most frequently occurring peripheral neuropathy events included peripheral sensory neuropathy (24 patients in the POM+LoDEX group [8.0%] and four in the HiDEX

group [2.7%]) and paraesthesia (ten patients in the POM+LoDEX group [3.3%] and six in the HiDEX group [4.0%]). However, Grade 3/4 peripheral neuropathy was uncommon in both treatment groups (1.7% for POM+LoDEX and 1.3% for HiDEX), and there were no serious peripheral neuropathy-related TEAEs. Only one patient in the POM+LoDEX group and no patients in the HiDEX group discontinued treatment due to peripheral neuropathy. Furthermore, in patients with at least one occurrence of peripheral neuropathy, 50.9% of POM+LoDEX-treated patients and 57.1% of HiDEX-treated patients had neuropathy at baseline.

Thromboembolic events

Venous (VTEs) and arterial (ATEs) embolic and thrombotic events occurred infrequently in both treatment groups and none of these events resulted in death.

In total, 12 (4.0%) patients in the POM+LoDEX group and three (2.0%) patients in the HiDEX group experienced at least one VTE. At least one Grade 3/4 VTE occurred in three (1.0%) patients in the POM+LoDEX arm and in no patients in the HiDEX arm. Serious VTEs occurred in six (2.0%) patients in the POM+LoDEX arm and in no patients in the HiDEX arm. No VTE led to treatment discontinuation in either treatment arm. No specific VTE occurred in >2% of patients in either treatment arm. Deep vein thrombosis and venous thrombosis occurred in similar proportions of patients in both treatment arms. Pulmonary embolism occurred in three (1.0%) patients in the POM+LoDEX arm and in no patients in the HiDEX arm.

ATEs occurred in five (1.7%) patients in the POM+LoDEX arm and in no patients in the HiDEX arm. In the POM+LoDEX arm, these events included embolism, ischaemic cerebral infarction and myocardial infarction, each occurring in two patients. None of these ATEs resulted in treatment discontinuation.

Treatment emergent adverse events by subgroup

The pattern of AEs was generally similar across subgroups based on gender, race, baseline ECOG status, disease population subgroups and key stratification subgroups: age, disease population and number of prior anti-myeloma therapies, where sample size was adequate to allow analysis.

In the three baseline renal function subgroups (≥60mL/min, ≥45mL/min and <60mL/min, and <45mL/min), in both treatment arms, the occurrence of Grade 3/4 TEAEs increased as baseline creatinine clearance decreased.

Serious adverse events

All treatment-emergent serious AEs that occurred in ≥2% of patients in either treatment arm of study MM-003 are summarised in Appendix 10.

In total, 183 (61.0%) patients in the POM+LoDEX arm and 80 (53.3%) patients in the HiDEX arm experienced at least one serious AE. The most frequently occurring serious AEs in both treatment arms were pneumonia (13.0% in the POM+LoDEX arm and 8.7% in the HiDEX arm) and general physical health deterioration (8.7% and 8.0%, respectively).

Deaths

As of 01 March 2013, a lower proportion of patients in the POM+LoDEX group had died (146/300 [48.7%]) than in the HiDEX group (84/150 [56.0%]). As expected, the most common cause of death in both treatment groups was multiple myeloma: 100 patients (33.3%) in the POM+LoDEX group and 52 patients (34.7%) in the HiDEX group.[17] The second most common cause of death was infection, which occurred less frequently in the POM+LoDEX group (14 of 300 patients [4.7%]) than in the HiDEX group (17 of 150 patients [11.3%]). The third most common cause of death was general disorders, accounting for 6.0% patients in either group; general physical health deterioration was the most frequently reported TEAE leading to death for these patients. Other general disorders resulting in death included disease progression, multi-organ failure and sudden death.

There were 11 (4%) treatment-related deaths in the POM+LoDEX group: eight cases of infections and infestations, two cases of multi-organ failure or sudden death and one nervous system disorder. There were seven (5%) in the HiDEX group: all infections and infestations.[17] A table of causes of patient deaths can be found in Appendix 10.

Treatment discontinuations, dose reductions and dose interruptions

The majority of patients in MM-003 study discontinued treatment due to progressive disease (54.0% [163/302] of POM+LoDEX versus 60.1% [92/153] of HiDEX-treated patients; *p* value not reported; ITT population). Few patients discontinued treatment because of AEs (8.6% of patients in the POM+LoDEX group and 10.5% in the HiDEX group). Thrombocytopenia was the most common reason for POM discontinuation (in 3/300 [1.0%] patients).

Dose interruptions were more common than dose reductions in both treatment groups: 27.3% of patients experienced at least one POM dose reduction; 67.0% experienced at least one POM dose interruption; median of two POM dose interruptions; 32.7% of patients experienced a HiDEX dose reduction; 30.0% experienced at least one HiDEX dose interruption; median of two HiDEX dose interruptions. Neutropenia and thrombocytopenia were the most common reasons for dose interruptions and reductions of POM in the POM+LoDEX arm. Hyperglycaemia and myopathy were the most common reasons for DEX dose reductions in the POM+LoDEX and HiDEX groups. A table of TEAEs leading to discontinuations can be found in Appendix 10.

Supportive care

A greater proportion of patients in the POM+LoDEX group than in the HiDEX group required granulocyte colony stimulating factor for the treatment of neutropenia (43% versus 10%). Other supportive measures were comparable between the two treatment groups: anti-infectives (antibiotics, antifungal drugs and antiviral drugs) were used to treat infections in 86% and 79% of patients in the POM+LoDEX and HiDEX groups, respectively; RBC transfusions were given to treat anaemia in 50% of POM+LoDEX patients and 54% of HiDEX patients; and platelet transfusions were given to address low platelet levels in 20% and 21% of patients in the POM+LoDEX and HiDEX groups, respectively (see Table 8 in Section 2.4.5).

Summary of later published safety data on MM-003: 01 September 2013 data cut-off:

Limited safety data are available from the 01 September 2013 data cut.[119] Overall, with the extended follow-up, the safety profile was consistent with that reported in the original publication[110] and the CSR.[17]

4.12.2 Supporting safety data

Safety data from other POM trials support the evidence presented from study MM-003, and show a similar safety profile for POM+LoDEX.[2, 18, 19]

MM-010 STRATUS study

Additional supportive safety data on POM in refractory & relapsed refractory multiple myeloma are available from the MM-010 study.[18] Data for 676 patients who received at least one dose of study drug were included in the safety analyses and are reported here to a data cut-off date of May 4, 2015 (median follow-up of 16.8 months).

At this data cut-off, 104 (15.2%) patients remained on study while 572 (83.9%) patients had discontinued for the following reasons: disease progression (62.2%), death (7.9%), AEs (5.9%), consent withdrawal (2.9%), other (4.8%; including clinical progression without confirmed IMWG-defined PD, and transition to commercial POM), and patients lost to follow-up (<1%).

The most common Grade 3/4 haematological TEAEs included neutropenia (49.7%), anaemia (33.0%), thrombocytopenia (24.1%); Grade 3/4 febrile neutropenia was reported in 5.3% of patients. The occurrence of neutropenia did not seem to affect the incidence of infections as over half of all grade infections occurred in the absence of neutropenia. Grade 3/4 non-haematological TEAEs included infections (28.1%, including pneumonia [11%]), and fatigue (5.9%). Grade 3/4 VTE and peripheral neuropathy both occurred in 1.6% of patients.

Dose reductions, interruptions and discontinuations of POM resulting from TEAEs were required in 22.0%, 66.3% and 5.9% of patients, respectively. Common AEs leading to dose reductions were neutropenia (5.9%), thrombocytopenia (4.3%),

fatigue (2.5%), and pneumonia (2.4%). Common AEs leading to dose interruptions were neutropenia (22.6%), thrombocytopenia (11.1%), and pneumonia (10.2%).

AEs were predominately managed through dose reductions and interruptions; however, concomitant medications were also used, mainly: G-CSF for 56.4% of patients with infections and 75.4% of patients with neutropenia; anti-infectives in 95.5% of patients with infections; and red blood cell transfusions and platelet transfusions in 48.4% and 16.1% of the entire patient population, respectively.

Second primary malignancies (SPM) were reported in 15 patients (5 patients had invasive solid tumors, and 10 patients had non-invasive skin cancers). The incidence rate of developing an invasive solid tumor SPM was 0.90 per 100 person years (95% CI: 0.37, 2.16).

In summary, POM+LoDEX was generally well tolerated, and the safety profile in this large patient population was consistent with the profile observed in other pivotal studies of POM+LoDEX;[17, 19] no new safety signals were identified in this study.

MM-002 study

POM+LoDEX was generally well tolerated in Phase II studies.[19, 26] In MM-002, Grade 3/4 neutropenia occurred in 41% of POM+LoDEX patients; no Grade 3/4 peripheral neuropathy was reported, and the incidence of any grade deep vein thrombosis was low (2%).[19]

4.12.3 Additional safety considerations

Teratogenic potential

POM is structurally related to THAL, which is a known human teratogenic substance that causes severe, life-threatening birth defects. A pregnancy prevention programme has been developed to inform patients of the potential teratogenic risk of POM and to restrict its use in women of childbearing potential. Full details of the pregnancy prevention programme are provided in the UK SmPC for POM.[4]

4.12.4 Summary of pomalidomide safety

The AE profile for POM+LoDEX obtained from the pivotal Phase III study MM-003 suggests that it is reasonably well tolerated, with a predictable and manageable side

effect profile.[110] Discontinuations due to TEAEs were 8.6% for POM+LoDEX versus 10.5% for HiDEX.[17]

Grade 3/4 muscle weakness, asthenia, myopathy, hyperglycaemia and insomnia occurred less frequently in the POM+LoDEX arm than in the HiDEX arm, whereas Grade 3/4 neutropenia, febrile neutropenia, pneumonia, bone pain, decreased neutrophil count, and leukopenia occurred more frequently with POM+LoDEX arm compared with HiDEX.

In MM-003, myelosuppression with POM+LoDEX was predominately managed through dose interruptions, reductions and supportive care when required.[17, 110] Safety data from the other POM studies (including MM-002 and the STRATUS study [MM-010]) highlight a safety profile which is consistent with MM-003. Importantly, the AEs appeared to occur early after initiation of treatment, during the first cycles, and tend to decrease over time.[2]

4.12.5 Comparator safety

BEN

The SLR (see Section 4.1) identified a total of six relevant studies investigating BEN-containing regimens in patients with RRMM who had previously received treatment with at least two regimens including prior LEN and BOR. The studies included MUK-one,[16] and five non-RCT studies investigating BEN+steroid±THAL regimens.[39, 136-139]

As highlighted in the comparator efficacy section (Section 4.11.3), the Phase II MUK-one study (n=95) is the largest published studies looking at the combination of BTD in UK clinical practice.[16] This study aimed to find an optimally active and deliverable dose of BEN in combination with THAL and DEX in patients with RRMM. Unlicensed treatment with BTD in this study (in a less advanced patient population than MM-003) was explored for two doses of BEN (60mg/m^2 or 100mg/m^2 IV) with THAL and DEX, the BEN 100mg/m^2 arm of the study was discontinued due to excessive cytopenias; Grade 3/4 neutropenia, thrombocytopenia and anaemia were experienced in 64%, 43% and 36% patients respectively. Patients who received BEN at 60mg/m^2 with THAL and DEX were reported to experience Grade 3/4 neutropenia, thrombocytopenia and anaemia in 33%, 31% and 22% respectively. Despite these

lower rates of Grade 3/4 AEs, only 40% of patients received all 36 weeks of treatment with no dose reductions or delays and 21% of patients still discontinued treatment due to toxicity (compared with 8.6% discontinuation for POM+LoDEX in study MM-003 and 5.9% in MM-010).

As discussed previously, it is challenging to try and draw comparisons between the BEN studies identified in the SLR and the data for POM+LoDEX as the BEN studies are primarily small uncontrolled, observational studies conducted in a less advanced and less refractory patient population.[16-18, 39, 136-139] The largest study of 110 patients who received BEN± steroid did not report AEs.[137]

Across all the BEN studies identified in the SLR, where reported, rates of Grade 3/4 neutropenia ranged between 30 and 64%,[16, 39, 136] Grade 3/4 thrombocytopenia between 22 and 34%,[16, 39, 136] anaemia between 35 and 36%[16, 39] and Grade 3/4 neuropathy between 0 and 5%.[16, 39, 136] In two smaller studies with limited patient numbers Grade 3/4 haematological toxicity was reported in 22-50% of patients.[138, 139]

During a recent advisory board meeting, clinical advisors echoed these clinical study findings, commenting that patients struggle with side effects, including cytopenias, fatigue and infection and, as a result, often stop treatment after only a few cycles[9] The advisors also felt that the haematological AEs require careful management, and that the toxicity of BEN tends to be cumulative, limiting its long-term use.[9] When clinicians were asked to rate safety of BEN out of ten (10=best; 1=worst), they gave a mean score of 4.8, compared with 7.4 for POM.[9] The NCCN rate the safety of BEN as 3/5 compared with 4/5 for POM+LoDEX.[104]

PANO+BOR+DEX

Only one relevant study of PANO+BOR+DEX was included in the SLR (see Section 4.1), according to the current inclusion/exclusion criteria; this was the PANORAMA 2 study.[35]

As highlighted in the comparator efficacy section (Section 4.11.3), PANORAMA 2 is a Phase II, two-stage, single-arm, open-label multicentre study of PANO+BOR+DEX in patients with relapsed and BOR-refractory MM. In total, 55 patients (less heavily pre-treated than patient populations in MM-003 & MM-010) were enrolled into the trial & were evaluable in the safety population. With a median duration of treatment

of 4.6 months, the most common AEs of any grade included diarrhoea (70.9%), fatigue (69.1%), thrombocytopenia (65.5%), nausea (60.0%), anaemia (47.3%) and treatment emergent peripheral neuropathy (27.3%). Grade 3/4 AEs included thrombocytopenia (63.6%), diarrhoea (20.0%), fatigue (20.0), anaemia (14.5%), neutropenia (14.5%) and pneumonia (14.5%). In total, 10 patients (18.2%) discontinued treatment due to an AE compared with 8.6% discontinuation for POM+LoDEX in study MM-003 and 5.9% in MM-010.

The PANORAMA 1 study provides more information on the safety profile of PANO+BOR+DEX (n=758, Safety population) in an even less advanced patient population (PANO+BOR+DEX arm: 1-3 prior treatments, 44% prior BOR and 19% prior LEN).[53] This pivotal study which led to the licensing of PANO+BOR+DEX in a subgroup of patients who have received ≥2 prior regimens including BOR and an IMiD[10] reported Grade 3/4 AEs in 364 patients (96%) in the PANO group, including thrombocytopenia (68.0%), lymphopenia (54%), neutropenia (35.0%), diarrhoea (25.0%), asthenia or fatigue (24.0), peripheral neuropathy (18.0%) and pneumonia (13.0%). The median duration of treatment in the PANO group was only 5 months, with 34% patients discontinuing due to an AE, 24% of which were attributed to study drug in the PANO group.[53]

In the PANORAMA 1 study patient reported outcomes were assessed by EORTC QLQ-C30, QLQ-MY20 and FACT/GOG-NTX, PAN + BTZ + DEX was associated with significant worsening in quality of life during the treatment period.[10] As a reflection of the data & toxicity profile in PANORAMA 1, PANO+BOR+DEX use is limited to a fixed treatment duration of 48 weeks.[13]

During a recent advisory board meeting, clinical advisors commented that PANO adds to the toxicity profile of BOR and results in a poorer profile particularly in terms of fatigue, high-grade thrombocytopenia and diarrhoea, and is not appropriate for patients with neuropathy.[9] When advisors were asked to rate safety of PANO+BOR+DEX out of ten (10=best; 1=worst), they gave a very low mean score of 3.8, compared with 7.4 for POM.[9] Additionally, during the NICE appraisal of PANO (TA380), the Committee noted statements from a patient and carer group, which highlighted patients' concerns that the worsened toxicity profile may lead to

increased hospitalisation.[93] The NCCN rate the safety of PANO+BOR+DEX as 2/5 compared with 4/5 for POM+LoDEX.[104]

Conventional chemotherapy

No safety data was available from literature or the CONNECT MM registry on safety of conventional chemotherapy at this line of therapy. However, clinical expert opinion on the safety of conventional chemotherapy has been elicited. Clinical experts consulted at the recent daratumumab scoping meeting (21 March, 2016) advised that they use BEN rather than conventional chemotherapies as the toxicity of the latter tends to be unacceptably high.[11] In further support of this, when clinicians were asked to rate safety of conventional chemotherapy out of ten (10=best; 1=worst), they gave a mean score of 4.3, compared with 7.4 for POM.[9]

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 Summary of benefits and harms of pomalidomide

Current treatment options for patients with RRMM who have progressed on LEN and BOR include PANO+BOR+DEX, along with unlicensed combinations of BEN in combination with THAL+DEX or steroid alone and conventional chemotherapy, which tends to be a last option in clinical practice.[1, 9] All these treatments have limited data in patients refractory to both LEN and BOR, and in addition, their use is confined to shorter treatment durations due to associated toxicities.[12-16, 22] In this setting there is a high unmet need for alternative oral treatment combinations like POM+LoDEX, with a different mechanism of action and toxicity profile allowing for continuous treatment to suppress residual disease, which may be particularly important for patients refractory to both BOR and LEN.

POM+LoDEX is the first licensed treatment available with Phase III evidence for patients, the majority of which, have previously received and become refractory to both BOR and LEN.[4, 18, 110, 143]

POM+LoDEX Efficacy

In the Phase III study MM-003, POM+LoDEX demonstrated significant improvement compared to HiDEX (which can be considered similar in its effectiveness to conventional chemotherapy)[29] across a number of outcome measures:

- POM+LoDEX demonstrated a significant improvement in PFS compared with HiDEX. [17, 119]
  - POM+LoDEX demonstrated a significant improvement in OS compared with HiDEX despite 56% of patients crossing over from HiDEX to POM. [119]
  - POM+LoDEX median OS 13.1 vs HiDEX 8.1 months; HR=0.72 [*p*<0.009], data cut –off, 01 September 2013, Investigator review.
  - After adjustment for crossover the median OS in the HiDEX arm reduced to 5.7 months.[126]
- POM+LoDEX produced a significant higher ORR (≥PR) compared with HiDEX. [20, 120]
  - POM+LoDEX demonstrated a significant longer TTP and DOR compared with HiDEX (Median TTP 4.7 vs HiDEX 2.1 months);. [120]
  - Regardless of refractoriness to selected anti-myeloma therapies median PFS & OS were consistent with the consistent with the overall ITT population.[17]

The efficacy seen with POM may partly be attributed to its mechanism of action; in binding directly with cereblon (a component of the E3 ubiquitin-ligase complex), POM inhibits the proliferation of LEN-resistant multiple myeloma cell lines and therefore minimises the refractoriness to LEN. This, coupled with the immunomodulatory activity of POM results in enhanced anti-tumour effects.[21, 31, 32] In addition, its toxicity profile, unlike comparator treatments, allows it to be given continuously until disease progression.[4]

Suppression of disease through continuous treatment in responding patients has been shown to produce durable responses leading to long-term survival (median OS

19.9 months).[20] In responders, the lack of cumulative toxicity and immunomodulatory activity of POM resulting in enhanced anti-tumour effects mediated by T and natural killer (NK) cells,[21, 41, 57, 58] may not only prolong remissions but lead to patients being more able to benefit from subsequent therapy.[128]

Efficacy data from the MM-002 and MM-010 trials were supportive of study MM-003 with OS of 16.5 and 11.9 months, respectively. [18, 114] Similar outcomes were seen in observational studies reporting POM+LoDEX outcomes in UK clinical practice.[27, 28] Available evidence outside of the Phase III trial indicates that longer survival can be expected with POM+LoDEX in less refractory patients.[114]

POM+LoDEX Safety

POM+LoDEX is a well-tolerated treatment, which is of critical importance for a continuous treatment. In study MM-003, the most frequent TEAEs initially reported were haematological in nature: the most common Grade 3/4 haematological AEs for POM+LoDEX and HiDEX were neutropenia (48.3% versus 15.3%), anaemia (32.7% versus 38.7%) and thrombocytopenia (22.0% versus 26.0%).[17] Discontinuation of POM+LoDEX because of an AE was, however, uncommon (8.6% versus 10.5% in the HiDEX group) suggesting that with dose modifications and supportive care the safety profile was predictable, manageable and generally well tolerated.[17, 110] After extended follow up (median 15.4 months) the safety profile of POM+LoDEX was consistent with initial reports.[119] Safety data from the MM-002, MM-010 and UK clinical practice were also consistent with study MM-003.[18, 27, 28].

POM+LoDEX Quality of Life

Multiple myeloma causes deterioration in HRQL which decreases as the burden of illness increases over time with progression of the disease,[56] therefore improvement or maintenance of quality of life is an important goal of treatment.[8] In study MM-003, the improvement in PFS did not come at the expense of QoL. HRQL was shown to be improved compared to HiDEX through cross-sectional and longitudinal analysis across a number of preselected domains.[33] In addition, mixed-model analysis of the EQ-5D utility index score showed that there was a significant effect for treatment (p=0.005) on utility.[127] Significant improvements in HRQL on the EQ-5D have not been previously demonstrated in RRMM and are difficult to demonstrate in clinical

trials in general providing a good indication of the scale of HRQL benefit experienced by patients receiving POM+LoDEX.

Clinical benefit of POM+LoDEX relative to current comparator treatments

It is challenging to draw efficacy comparisons between POM+LoDEX and comparator studies which are all conducted in less advanced and less refractory patient populations.[16, 35, 39, 53, 136-139] In terms of toxicity, HRQL and convenience, POM+LoDEX offers considerable advantages over existing treatments.[16, 17, 35, 39, 53, 136-139]

Comparative toxicity & HRQL

All relevant comparators (PANO+BOR+DEX, BEN Combinations and conventional chemotherapy) are limited to shorter treatment durations due to associated toxicities.[12-16, 22] In the MUK-one study, BEN given at 100mg/m2 was discontinued due to excessive cytopenias and in the 60mg/m2 arm only 40% of patients received all 36 weeks of planned treatment with 21% of patients discontinuing treatment due to toxicity. In key studies of PANO+BOR+DEX despite a short median duration of treatment (4.6 to 5 months) patients presented with grade 3 / 4 thrombocytopenia (64-68%), diarrhoea (20-25%), fatigue (20-24%) and peripheral neuropathy (18%) and between 18 and 34% of patients discontinued due to an AE.[35, 53] In addition, in the PANORAMA 1 study, PANO+BOR+DEX was associated with significant worsening in quality of life during the treatment period.[10] As highlighted previously, despite evidence in a more advanced and refractory patient population POM+LoDEX has a manageable and predictable side effect profile. It is associated with a low rate of discontinuation due to AEs (2 to 9%) and a low rates of grade 3/4 peripheral neuropathy (0 to 1.7%).[17, 18, 114] In addition, improvement in PFS does not come at the expense of QoL.[33, 56] POM+LoDEX is also not associated with all the side effects of conventional chemotherapy such as hair loss.[15, 144]

POM+LoDEX as an oral therapy

As an oral therapy POM+LoDEX can be self-administered by patients at home. This is expected to be more convenient and less distressing for most patients then treatment with PANO+BOR+DEX or BEN combinations, which require patients to attend hospital (either in a day case or outpatient setting) to receive SC or IV

administration.[12-14] This benefit is particularly important for elderly, frail individuals and their carers, along with those patients and carers who live far away from hospital. The use of an oral agent such as POM provides patients with a greater sense of control over their disease and less interruption of their daily (including work) compared to IV and SC treatments.[23, 87]

Clinical expert opinion

Clinical experts were questioned as to their experience using POM and their opinion on its removal from the CDF. The experts felt that in delisting, both patients and clinicians had "lost a very effective drug, primarily for the following reasons[9]:

- Substantial efficacy benefits, with several of the experts reporting a durable response with POM in those patients that do respond;
- Safety and tolerability;advisors consider POM to be a well-tolerated treatment if administered by a haematologist; and
- Convenience, with experts describing POM as being more easy to use and reducing resource use requirements due to its oral nature.

This was further supported by a scoring exercise, in which the experts were asked to provide a score out of ten (ten being the best) for efficacy and for safety and tolerability of POM+LoDEX and each of the comparators as fourth-line options. POM was rated as the most efficacious (mean: 4.9), with BEN (mean: 4) and PANO (mean: 3.3) having lower efficacy and being, in turn, better than conventional chemotherapy (mean: 2.7). For safety and tolerability, POM was considered the best option by far (mean: 7.4), followed by BEN (mean: 4.8), conventional chemotherapy (mean: 4.3), and PANO+BOR+DEX (mean: 3.8). Full details of the scores provided for each advisor (anonymised) within the advisory board report itself.[9]

4.13.2 Strengths and limitations of the evidence base

Strengths

A large body of evidence now exists to demonstrate the safety and efficacy of POM+LoDEX in a particularly hard to treat group of patients with refractory and relapsed refractory MM. In total, 1,097 patients were enrolled into MM-002, MM-003

and MM-010 studies.[17, 18, 114] These studies are supported by a number of other Phase II studies and observational studies relevant to UK clinical practice.[24-28]

The Phase III MM-003 trial is one of the largest RCT studies to date showing activity in disease refractory to both BOR and LEN. The EMA considered the study to be adequately designed to demonstrate the efficacy of POM+LoDEX against an appropriate comparator (HiDEX).[2] The EMA stated the inclusion criteria of the study corresponded to the criteria by the IMWG of primary refractory and relapsed-and-refractory multiple myeloma and the choice of endpoints and statistical methods were considered appropriate.[2]

To ensure an unbiased assessment of the data, an IRAC reviewed all efficacy data in a blinded manner (independent of investigator-reported response), and determined the response to therapy and the time to progressive disease for each patient. Although the study was open-label, the sponsor's study team was blinded to the study treatment code prior to the final analysis of PFS.[17] Primary and key secondary outcomes were assessed based on the international standard for the assessment of response in multiple myeloma studies (IMWG criteria).

As secondary analysis, outcomes were evaluated by IRAC using EBMT criteria and by investigator using IMWG criteria.[82, 83] PFS, OS and myeloma response outcomes were consistent using the different analysis, supporting the robustness of the data.[17] Finally, the MM-003 dataset is also now mature, with 84% of patients on the POM+LoDEX arm having experienced a progression and 58% of patients having died.[120] This data maturity allows greater certainty around long-term outcomes of treatment. In comparison to the 2014 NICE submission for POM+LoDEX[34], this submission provides substantially more evidence and consistent outcomes for PFS, OS and response for POM+LoDEX in refractory and relapsed refractory MM.[17, 18, 114] In addition, these data are supported by UK observational studies highlighting that outcomes achieved in clinical trials can be expected in clinical practice.[27, 28] In total, 96 UK patients enrolled in MM-003 and MM-010 studies and 117 patients were reported in UK observational studies.[27, 28] Efficacy and safety outcomes are also consistent across subgroups; in particular in the hardest to treat refractory patient

population and in older age groups, demonstrating the ability of POM+LoDEX to meet the needs of a broad patient population.[17]

Limitations

When the MM-003 study was originally devised, HiDEX was selected in agreement with the EMA and FDA as the comparator arm as it has been widely used in previous published studies for evaluating novel agents prior to their approval in RRMM.[115-117] As reflected in the final NICE scope, HiDEX is no longer viewed as optimal treatment in this setting in the UK and is given at a lower dose mostly with palliative intent.

The lack of a relevant comparator in the Phase III MM-003 study makes comparison to the comparators listed in the decision problem difficult. This problem is compounded by the lack of high quality evidence available for all three comparators in the relevant patient population. While a substantial body of evidence is available to support the clinical effectiveness of POM+LoDEX in patients who have received treatment with both BOR and LEN and have become refractory to both agents, the same cannot be said for treatments used in current clinical practice.

The ability to produce a valid estimation of comparative effectiveness is hindered by the strict inclusion/exclusion criteria applied within the Phase III and Phase IIIb studies for POM+LoDEX. Within these studies, patients not only had to be refractory to their last therapy, they also have to have failed treatment with both BOR and LEN by having progressed on or within 60 days of their treatment or, if they previously achieved at least a PR, they must have progressed within 6 months.[17, 18] In the MM-003 and MM-010 studies, just over 80% of patients fell into the category of progressing on or within 60 days of their previous treatment with BOR and LEN, meaning that this trial recruited a highly refractory patient population likely to have a poor prognosis, with a reduced ability to benefit from subsequent treatment.

Evidence available for comparator treatments is generally only available in less heavily pre-treated and less refractory patients and formal indirect comparison methods could not be applied (due to lack of RCT evidence / lack of common comparators to form a network) meaning that non-randomised comparisons had to be made. The ability of techniques such as MAIC and covariate-adjustment to

account for differences in patient populations is limited by the size of the datasets available for comparators and the quality of reporting within comparator trials.

The challenges of providing an evidence base for comparative effectiveness within this disease area are numerous and can be highlighted through review of the RWE evidence gathering project initiated by Celgene which unfortunately failed to deliver the comparative effectiveness data hoped to inform this submission. Challenges include:

- Considerable use of off-label and unlicensed treatments
- Individualisation of treatment which leads to considerable selection bias within observational datasets
- Constant evolution of the treatment pathway leading to relevant comparators at study initiation no longer being considered relevant at the time of reporting
- Use of POM as a palliative treatment by many centres rather than earlier in the pathway (like BEN) because of lack of availability of POM leading to difficulties in comparing treatments
- Lack of collection of data from patients who did not complete treatment (as per protocol); this eliminated responders with a durable response, which likely biased against POM+LoDEX
- Issues with the use of subsequent therapy impacting the ability to interpret longer term outcomes – particularly given that for a substantial proportion of later-line patients clinical practice involves enrolment into clinical trials. Since the start date and duration of subsequent treatment were not recorded, adjustment was not possible.
- Inconsistency in the recording of data and measurement of key outcomes such as progression across centres and clinical trials, leading to many missing data and imbalanced covariates, as well as limiting comparability of studies

4.13.3 Relevance of evidence to the decision problem

Evidence from the MM-003 study, supported by the Phase II MM-002 and Phase IIIb MM-010 studies are highly relevant to the decision problem as in clinical practice there are a number of patients who will have progressed on or become refractory to prior treatment with BOR and LEN. At this stage of the disease patients want to receive an active treatment rather than palliative care.[9, 37] This is reflected in the fact that 96 UK patients enrolled in MM-003 and MM-010 studies. These patients may not be suitable for, or able to tolerate, PANO+BOR+DEX, BEN combinations or conventional chemotherapy.[16, 35, 39, 53, 136-139]

The Phase III study MM-003 demonstrates activity in disease refractory to both BOR and LEN. The clinical endpoints of PFS and OS are the primary measures of survival efficacy in cancer therapy, and have been defined as the most important outcomes.[145] EQ-5D, used as a measure in the trial for HQRL, is a standardised instrument and a well-recognised measure for health outcome.

The average age of patients in study MM-003 was approximately 64 years; slightly younger than patients expected to be treated in clinical practice.[106] However, in study MM-003, PFS, OS, myeloma response rate, and DOR were similar for patients aged ≤65 years and those aged >65 years, as well as for those aged >75 years.[17] Additionally, there were no obvious differences between the TEAE profile of patients aged >75 years and that of patients aged ≤75 years in the study.[17] This was further supported in a pooled analysis of 1,097 patients who received POM+LoDEX in MM-003, MM-002 and MM-010, which showed similar efficacy and safety outcomes, irrespective of age group.[141] The clinical effectiveness and safety of POM is therefore demonstrated across age groups relevant to clinical practice.

As mentioned previously, MM-003 and MM-010 trials were conducted in an advanced and highly refractory patient population likely to have a poor prognosis, with a reduced ability to benefit from subsequent treatment.[17, 18] In clinical practice, POM+LoDEX is expected to be used earlier in the treatment pathway at either third or fourth line where patient outcomes may be better than those reported in the MM-003 and MM-010 studies.[9, 106] This is supported by the largest UK observational dataset published by Maciocia et al, which highlights that in patients who receive four

prior lines of treatment (compared to five in MM-003) the ORR (≥PR) was 53% with an associated median PFS and OS of 4.3 and 13.7 months, respectively.[28]

4.13.4 Ability of POM+LoDEX to meet end-of-life criteria

POM+LoDEX was considered to meet end-of-life criteria; in the FAD issued in the previous NICE review (TA338).

The median OS of patients with RRMM previously treated with BOR and LEN is considerably shorter than 24 months and ranged from 3 to 9 months (8.1 months in the control group of MM-003 without adjustment for crossover;[17] 5.7 months when crossover is accounted for).[126]

In the MM-003 trial, the difference in median OS between POM+LoDEX and HiDEX was 5 months (unadjusted for crossover),[17] and 6 to 7 months when adjusted for crossover.[126] This evidence is considered translatable to expected outcomes with conventional chemotherapy as detailed in Section 4.10.

Based upon covariate-adjusted comparison to BEN (see Section 4.10) the medians are 16.6 months (95% CI [12.6, 21.3]) and 10.5 months (95% CI [5.8, 14.8]) for POM+LoDEX and BEN, respectively, indicating a 6.1 month difference. Unadjusted median OS times are 16.5 months (95% CI [12.6, 19.8]) and 8.1 months (95% CI [5.3, 15.5]) for POM+LoDEX and BEN, respectively, indicating an 8.4 month difference.

Evidence for end of life is less compelling in the comparison to PANO+BOR+DEX as no improvement was demonstrated in median outcomes for OS; difficulties in comparing to PANO+BOR+DEX are, however, considerable given the limited evidence available and lack of patient level data to correct for differences in patient population.

Table 40: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS is 3-9 months.[36-40]
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 BEN: 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
The treatment is licensed or otherwise indicated for small patient populations	The eligible patient population is expected to be 620 patients

4.14 Ongoing studies

Table 41 presents details of all POM studies which are likely to report data within the next 12 months.

Table 41: List of POM studies that are due to report data within the next 12 months

Trial no. (Acronym) Phase	Study design	Population	Interventions	Status	Expected reporting date	Primary reference
MM-008 (NCT01575925)	A Phase I, multicentre, open-label trial to assess the pharmacokinetics and safety of POM+LoDEX in RRMM patients with normal or impaired renal function.	Patients (estimated enrolment n=30) with RRMM and impaired renal function. Patients must have measurable disease (serum M-protein ≥ 0.5g/dL or urine M-protein ≥ 200 mg/24 hours)	Patients with creatinine clearance ≥60mL/min: POM 4mg on Days 1-21 of a 28-day cycle plus LoDEX 40mg (≤75 years) or 20mg (>75 years) on Days 1, 8, 15, 22 Patients with creatinine clearance <30mL/min: POM 2mg or 4mg on Days 1-21 of a 28-day cycle plus LoDEX 40mg (≤75 years) or 20mg (>75 years) on Days 1, 8, 15, 22	Ongoing	Estimated study completion: February 2022	www.clinicaltrials.gov
MM-013 (NCT02045017)	A Phase II Multicentre, Open-label Study With POM in Combination With Low-Dose Dexamethasone to Determine the Safety and Efficacy in Subjects With Relapsed or Refractory Multiple Myeloma and Moderate or Severe Renal Impairment including Subjects Undergoing Haemodialysis	Patients with RRMM (n=80) and renal impairment (estimated glomerular filtration rate [eGFR] of < 45 mL/min/1.73 m^2) across 3 cohorts: Cohort A (moderate RI [eGFR = 30 to < 45 mL/min/1.73 m^2], n = 33) Cohort B (severe RI without dialysis [eGFR < 30 mL/min/1.73 m^2], n = 33) Cohort C (severe RI requiring dialysis, n = 14)	POM 4mg is administered on Days 1-21 of a 28-day cycle and LoDEX 40mg/day (20mg for pts aged > 75 yrs) on Days 1, 8, 15, and 22 until progressive disease (PD) or unacceptable toxicity	Ongoing	Estimated Primary Completion Date: September 2017 (final data collection date for primary outcome) Estimated study completion: June 2021	www.clinicaltrials.gov

Key: POM, pomalidomide; LoDEX, low-dose dexamethasone; RI, renal impairment; GFR, Glomerular filtration rate

5 Cost effectiveness

5.1 Published cost-effectiveness studies

Identification of studies

An extensive systematic literature review (SLR) of cost-effectiveness studies was conducted for the previous NICE review (TA338) in December 2013.[146] This has been updated to provide the evidence base for this resubmission. The details of the search strategy and inclusion/exclusion criteria are provided in Appendix 17. Updated searches were carried out from 1 December 2013 through 3 March 2016 to ensure that the latest available evidence is presented in the resubmission. Prior to 1 December 2013, only additional studies adding to the TA338 SLR that met the pre-specified inclusion/exclusion criteria were included.

The SLR was performed to identify and summarise the relevant economic evidence for adult patients with RRMM previously treated with LEN and BOR reporting outcomes for POM+LoDEX versus relevant comparators. Studies reporting cost effectiveness were not filtered by study design. Included studies were full economic evaluations that provided costs, life years gained (LYG), quality-adjusted life years (QALYs) and incremental cost-effectiveness ratio (ICER) with sufficient detail regarding methods and results. Primary screening of abstracts and secondary screening of full-texts were conducted by two independent reviewers. Data extraction from the included full-text of articles was also performed independently by two reviewers to ensure that everything was captured.

Description of identified studies

454 studies were identified; systematic database searches identified 451 records and three health technology assessments (HTAs). Screening of titles and abstracts against the pre-specified inclusion and exclusion criteria (as presented in Appendix 17) was performed for 450 records after removing four duplicates. After screening, only the three HTAs were included for data extraction (Appendix 17).

These included the original NICE appraisal (TA338) for POM+LoDEX and the equivalent submissions for Scotland and Wales. Data were extracted from each appraisal, but as the limitations raised by the AWMSG and SMC formed a subset of those raised by NICE

as part of the original submission, only the key issues raised by the ERG and the Appraisal Committee during the original NICE appraisal (TA338) were extracted in order to show how each issue has been addressed in the resubmission. Table 42 provides this information as a summary.

Table 42: Issues raised from the original TA338 appraisal

	Issues	How this submission addresses this
Comparative effectiveness data	The Committee considered that all data available at the time had been included in the submission; however, very few data were identified for current care, which left the Committee unable to fully assess the cost-effectiveness of POM+LoDEX vs its comparators	Additional evidence has been sourced via a wide spanning data collection exercise (see Section 4.10) Clinical SLRs have been refined to improve the robustness and validity of the search results. However, filters were not removed as this would have resulted in an infeasible number of hits to no additional benefit. Updated data for POM+LoDEX have been included from the Phase III, Phase II and Phase IIIb trials to increase certainty around outcomes
Assumptions regarding equivalence of comparators	Disagreed with the manufacturer's assumption, the comparators have equal effectiveness with regard to OS, PFS and TTF, which the ERG found unjustified by the evidence	Comparison is now presented for 2 of the 3 relevant comparators using comparator specific data now available
Relative benefit of current care vs HiDEX	There were concerns that predictions for current care estimated lower survival than for HiDEX, which was considered sub-optimal treatment	This unexpected result is no longer seen with the new evidence identified for BEN
Adjustment of trials to provide comparable estimates	Differences in patient characteristics meant that the populations in the studies included for analysis were not considered comparable The ability to adjust for differences in patient characteristics was questionable due to the limited sample size available	Adjustment for differences in patient characteristics has been conducted based upon a thorough covariate selection process (Section 4.10). It should be noted, however, that the ability to adjust is still limited by the comparator data available, but the direction of bias in comparisons to both PANO+BOR+DEX and BEN is very much against POM+LoDEX due to the highly refractory and heavily pre-treated population included in the POM+LoDEX trials relative to available comparator evidence.

AEs	The Committee considered that the cut-off point to include disutility values only for AEs that occurred in more than 2% of patients on the POM+LoDEX arm to be arbitrary. Error in modelling: the impact of AEs on HRQL, leading to an underestimation of the utility decrement of AEs and subsequently an underestimation of the ICER for POM+LoDEX versus its comparators.	The 2% cut off is considered for the MM-003 trial as this is the most granular and consistent data available – data associated with a 5% cut off are inconsistently presented in the literature for the comparators. A 2% cut-off was selected for clinical trial reporting (and therefore also for modelling). Methodology for including AE rates has been updated in line with clinical advice Coding error in the implementation of AEs on HRQL has been corrected
Dosing	Assumption that unused tablets of POM+LoDEX due to non-protocol interruptions were fully recovered by the NHS was not justified properly and it may not hold in clinical practice	It is now assumed that unused tablets are not recovered by the NHS. Only dose interruptions that would result in an entire pack not being used are assumed not to incur costs
Key: AE, adverse event; BEN, bendamustine; HiDEX. high-dose dexamethasone; HRQL, health related quality of life; OS, overall survival; PANO+BOR+DEX, panobinostat+bortezomib+dexamethasone; POM, pomalidomide; LoDEX, low-dose dexamethasone.		

5.2 De novo analysis

5.2.1 Patient population

POM+LoDEX has a marketing authorisation in the UK 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 last therapy'. The economic evaluation considers the role of POM+LoDEX for this population - consistent with the decision problem for this technology appraisal (Section 1).

This population reflects the licensed indication discussed and is similar to patients included in the MM-003, MM-002 and MM-010 trials (discussed in Sections 4.5 and 4.11). As discussed in Section 4.13 there is some mismatch between the clinical evidence available for POM+LoDEX and the expected positioning in UK clinical practice (primarily fourth line).

Baseline patient characteristics are presented in Table 43 and were obtained from two studies considering the real world outcomes of POM across a number of UK centres where possible.[27, 28] These studies reflect the expected positioning of POM+LoDEX in clinical practice, and therefore the patient characteristics associated with these data are more appropriate to use when predicting outcomes relevant to

clinical practice than the heavily pre-treated clinical trial populations in the POM+LoDEX trials (3.7 vs 5 prior treatment lines for the real world and clinical trial data, respectively). Where the data were unavailable, available estimates from MM-003, MM-002 and MM-010 trials relevant to each comparator were considered. Patient characteristics are used in the utility regression equations and the covariate analysis in the model.

Table 43: Baseline patient characteristics

Patient characteristic	POM+LoDEX vs BTD	POM+LoDEX vs PANO+BOR+DEX	POM+LoDEX vs CTD	Source
Mean age	67.6			Maciocia et al. (2015) and Miles and Wells (2015)[27, 28]
Proportion male	54.87%[a]	56.88%[b]	59.93%[c]	[a]MM-002 [b]Weighted average across MM-003, MM-002 and MM-010 [c]MM-003 [d]Weighted average across MM-003 and MM-002 (not reported in MM-010) [e]Weighted average across MM-003 and MM-010 (not reported in MM-002) [f]MM-003 (not reported in MM-002 or MM-010)
Mean patient height (cm)	167.13[a]	167.32[b]	168.67[c]	
Mean patient weight (kg)	79.36[a]	73.58[b]	74.89[c]	
Baseline ECOG status: 0	28.32%[a]	40.02%[b]	37.09%[c]	
Baseline ECOG status: 1	59.29%[a]	47.77%[b]	45.70%[c]	
Baseline ECOG status: 2/3	12.39%[a]	12.22%[b]	17.22%[c]	
Baseline Durie Salmon stage: 1	7.08%[a]	6.99%[d]	6.95%[c]	
Baseline Durie Salmon stage: 2	25.66%[a]	29.64%[d]	31.13%[c]	
Baseline Durie Salmon stage: 3	67.26%[a]	63.37%[d]	61.92%[c]	
Baseline ISS stage: 1	23.07%[e]		26.82%[c]	
Baseline ISS stage: 2	39.02%[e]		38.41%[c]	
Baseline ISS stage: 3	37.91%[e]		34.77%[c]	
Proportion of patients refractory to lenalidomide	77.88%[a]	93.71%[b]	94.70%[c]	
RBC level (10^12/L)	3.1[f]			
Proportion of patients having received prior thalidomide	84%			Maciocia et al. (2015)
Mean prior treatment lines (range)	3.7 (1.6-7.7)			Maciocia et al. (2015) and Miles and Wells (2015)
Proportion European	100%			NICE Reference Case[147]

Key: BOR, bortezomib; BTD, bendamustine + thalidomide + dexamethasone; CTD, cyclophosphamide + thalidomide + dexamethasone; DEX, dexamethasone; LoDEX, low-dose dexamethasone; NICE, National Institute for Health and Care Excellence' PANO, panobinostat; POM, pomalidomide; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; RBC, red blood cell.

Comparators

In line with the decision problem outlined in the scope, the model compares POM+LoDEX with BTD, PANO+BOR+DEX and conventional chemotherapy. It is noted that the scope requests comparisons to be made:

- At third line versus PANO+BOR+DEX
- At fourth line onwards versus all comparators

Evidence available for POM+LoDEX use specifically at third line is limited (n=61 patients across MM-002, MM-003 and MM-010; the vast majority of whom are refractory to prior treatment due to the stringent inclusion/exclusion criteria within these trials). Available evidence does not indicate a differential treatment effect according to number of prior lines received (see Figure 11, Section 4.8) although a difference in absolute outcomes may be expected with less refractory and less heavily pre-treated patients who are expected to experience longer survival. Comparison is therefore presented in line with the available clinical trial data in all patients rather than specifically by line of therapy.

5.2.2 Model structure

Based upon the models identified within the economic literature it was decided to adapt the economic model submitted within the original submission to NICE for TA338 rather than constructing a new *de novo* economic model.

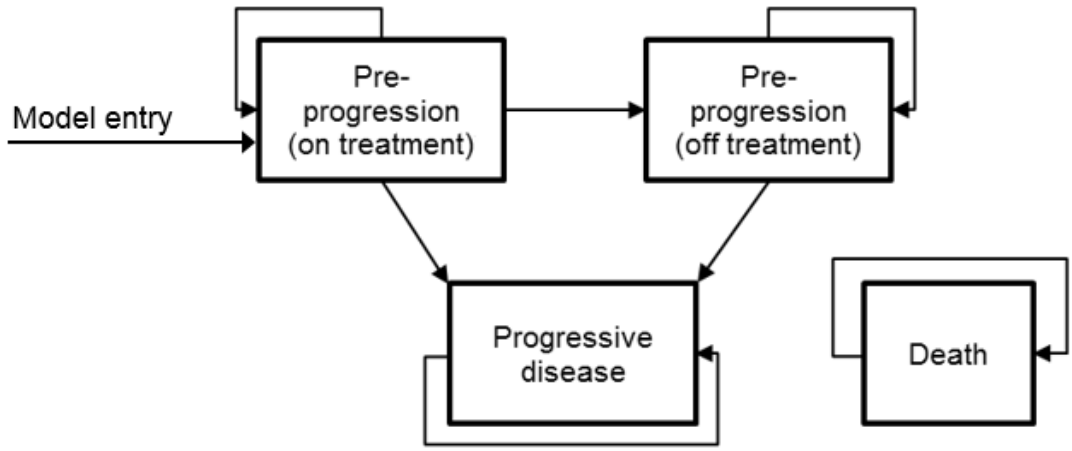
This model was developed in Microsoft® Excel 2010 using a semi-Markov partitioned survival structure. Similar Markov models have been previously used in multiple myeloma HTA submissions; Markov models lend themselves to disease areas in which patients progress through distinct stages, such as multiple myeloma which is characterised by a sequence of relapses (see Section 2).[90] The ERG deemed this model structure acceptable within the original submission to NICE.[148]

The four model health states comprise a pre-progressive state (split into on treatment and off treatment), a post-progression state (progressive disease), and

death (Figure 30). Health states were defined in relation to disease progression and whether or not patients were receiving treatment prior to progression. Disease progression was based on IMWG (2013) uniform response criteria assessed by investigator review:

- IMWG criteria were selected as these were used within the primary endpoints across the POM+LoDEX trials (MM-003, MM-002 and MM-010). Little difference was seen between IMWG and EBMT assessment in either MM-003 or MM-002.[17, 111] EBMT assessment was not conducted in MM-010.
- Investigator assessment was chosen as central review data were not available for the most recent data cut in the MM-003 trial nor in MM-010; consistent with the evidence available for comparator treatments. Little difference was seen between investigator assessment and central review in either MM-003 or MM-002.

Figure 30: Model Diagram



The four model health states are designed to capture the factors most important to multiple myeloma patients at this stage of disease (Section 3), including:

- Whether or not the patient is pre-progression (responding to treatment or maintaining stable disease) or post-progression: with impacts on quality of life and the costs of managing the disease

- Whether the patient is receiving treatment or not
- Survival

A cycle length of 1 week was considered sufficient to capture the rapid progression of RRMM. In the base case, a half cycle correction was applied. However, given the short cycle length this had little impact on the results. Table 44 summaries the key features of this economic analysis.

Table 44: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Life time (15 years)	Sufficiently long to be considered a lifetime horizon for at least third-line RRMM patients based on a patient starting age of 67.6 years.
Were health effects measured in QALYs; if not, what was used?	QALYs	NICE reference case[147]
Discount of 3.5% for utilities and costs	3.5% for utilities and costs	NICE reference case
Perspective (NHS/PSS)	To meet the requirements for submission to NICE	NICE reference case
Key: NHS, National Health Service; PSS, Personal social services; QALYs, Quality-adjusted life years.		

5.2.3 Intervention technology and comparators

The doses of the intervention and comparator treatments were implemented as per their marketing authorisation (where marketing authorisation exists). For treatments that are not licensed for this indication, such as BEN and THAL, dosing was taken from the MUK-One trial described in Section 5.5.

5.3 Clinical parameters and variables

The evidence used within the economic model is in line with evidence presented to inform comparative effectiveness in Section 4.10.

In the previous NICE review (TA338), the ERG stated that the main limitation of the evidence submitted was the lack of clinical-effectiveness data for the comparators listed in the scope.[148] Following this feedback, real world data were collected and the previous systematic review has been refined and updated to ensure all relevant clinical data are included. Unfortunately, the real world data cannot be utilised within the model due to the heterogeneity between these data and the clinical trial data and confounding of key outcomes (see Sections 4.10 and 4.11). However, the evidence gathering process conducted to enable this resubmission has provided substantially more data than the previous submission (MM-003, Gooding et al. and Tarant et al.) and incorporates the more recent datasets from MM-003, MM-002, MM-010, MUK-One and PANORAMA-2 as sources of clinical data.

5.3.1 Data used for POM+LoDEX

Key model inputs related to POM+LODEX have been obtained from MM-003, MM-002 and MM-010 trials. The latest available data cut has been used for each of the trials: the September 2013 data cut from MM-003, June 2014 data cut from MM-002 and May 2015 data cut from MM-010.

For the comparison of POM+LoDEX with BTD, clinical data for POM+LoDEX were sourced from the MM-002 trial (refractoriness to LEN and BOR in the BTD data: 20% and 6.7% compared with 78% and 71% in the MM-002 trial; n=113). The MM-003 and MM-010 trials were not considered as appropriate for comparison with the BTD data due to being conducted within an extremely refractory population (refractoriness to LEN and BOR: 95% and 79% in the MM-003 trial and: 96%, 84% in the MM-010 trial).

For the comparison of POM+LoDEX with PANO+BOR+DEX, clinical data for POM+LoDEX were sourced from pooled estimates across MM-003, MM-002 and MM-010 trials. These comprise the totality of the trial information available for POM+LoDEX that Celgene has access to.

For the comparison of POM+LoDEX with conventional chemotherapy, clinical data for POM+LoDEX were sourced from the MM-003 trial – this comparison represents a

within trial comparison where the efficacy of conventional chemotherapy is estimated using the HiDEX arm from the MM-003 trial as a proxy (see Section 4.10 for rationale for appropriateness of this proxy).

5.3.2 Data used for BTD

The previous submission identified KM data from Gooding et al. and median estimates from the observational study described in Tarant et al. for which the patient level data were submitted in response to the appraisal consultation document for the original submission (TA338).[37, 38] In addition to these data, the clinical SLR identified a UK trial, MUK-One, for which patient level data are now available.[16] These studies are specific to UK practice and contain data for the relevant patient population (all patients with RRMM having received both previous LEN and BOR). The comparison was undertaken using patient level data for both POM and BTD.

5.3.3 Data used for PANO+BOR+DEX

In the absence of direct comparisons between POM+LoDEX and PANO+BOR+DEX a MAIC was conducted to inform the efficacy inputs within the model (see Section 4.10).[130] The MAIC matched using reported baseline summary statistics across MM-003, MM-002 and MM-010 and the PANORAMA-2 trial. As detailed in Section 4.10, the PANORAMA-2 trial was identified as the only viable source of data based upon comparison of the patient characteristics and inclusion/exclusion criteria for this trial and the POM+LoDEX trials. In order to match the POM+LoDEX patients to the PANORAMA-2 trial, only patients in MM-003, MM-002 and MM-010 that were refractory to prior BOR and were not primary refractory were included in the Cox regression analysis. Full details of the MAIC conducted and rationale for study selection are provided in Section 4.10.

5.3.4 Data used for conventional chemotherapy

No sources of data considering treatment of RRMM with conventional chemotherapy within the relevant patient population were identified in the clinical SLR (see Section 4.1). Instead HiDEX data have been used as a proxy for other conventional

chemotherapy regimens. Similar to conventional chemotherapy regimens; HiDEX at the dosing regimen used within the MM-003 trial, is effective for a limited number of patients (response rate, PR or better, of 11% in the MM-003 trial) but with a significant toxicity. Full rationale for the clinical appropriateness of this comparison is provided in Section 4.10. HiDEX outcomes are similar to those in the few available datasets reporting conventional chemotherapy outcomes (albeit with limited numbers of patients), and available literature does not indicate a significant difference in HiDEX outcomes versus conventional chemotherapy.

In line with the previous submission to NICE (TA338), data for HiDEX have been included within the model using the two-stage method to adjust for crossover to POM post progression based upon the results of the published crossover analysis.[126]

In using HiDEX as a proxy, we assume that the efficacy and safety results observed in the MM-003 study for POM+LODEX versus HiDEX are equivalent for all conventional chemotherapies. For costing purposes we have included the cost of CTD within the model as this is representative of the type of chemotherapy received by frail patients and cheaper than MPT (the other most frequently used regimen).

5.3.5 Covariate adjustment

In the previous NICE submission (TA338), the ERG concluded that differences in patient characteristics meant that the populations included across the clinical data were not comparable.[148] In this resubmission, due to differences between the characteristics of patient populations within the datasets available to estimate comparative effectiveness, covariate adjusted comparisons have been conducted (see Section 4.10) and are used within the economic model. These are implemented within the economic model using the corrected group prognosis (CGP) method in the base-case analysis, and the mean of covariates method in a scenario analysis.[149] CGP estimates the OS for every possible combination of covariates found in the dataset and then calculates a weighted OS curve using the proportion of patients with each combination of covariates. The sources of data and covariates included in the base case economic model are presented in Table 45.

Table 45: Base case analyses: source and covariate data

	POM+LODEX vs BTD	POM+LODEX vs PANO+BOR+DEX	Conventional chemotherapy
Source	MM-002 Gooding et al. Tarant et al. MUK-One	MM-003 MM-002 MM-010 PANORAMA-2	MM-003
Covariates	Age Prior lines of therapy Refractory to LEN Receipt of prior THAL[a]	Age Prior lines of therapy Receipt of prior THAL ECOG stage[b]	Not required – within trial comparison

Key: BOR, bortezomib; BTD, bendamustine, thalidomide and dexamethasone; DEX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; LEN, lenalidomide; LoDEX, low-dose dexamethasone; PANO, panobinostat; POM, pomalidomide; THAL, thalidomide

[a]ISS stage at baseline was not included due to data limitations in the MM-002 and Gooding et al. data, other covariates considered potentially prognostic (including refractory to BOR) could not be included due to data limitations in the evidence for BEN

[b]Refractoriness to LEN and ISS stage were not included due to data limitations in the PANORAMA-2 and MM-002 trials. Refractory to BOR is not a covariate because 100% of the PANORAMA-2 population is refractory to BOR and the subset of POM data that was refractory to BOR was used.

5.3.6 Sensitivity analyses conducted around included datasets

As discussed within Section 4.10 three sensitivity analyses were conducted using the patient level data available for comparison to BTD. The first analysis considers the comparison of POM+LoDEX with BTD using MM-002, MM-003 and MM-010. This analysis is presented in the economic model as a scenario analysis. The second and third analyses evaluated the impact of including or excluding ISS stage from the analysis using only datasets where ISS stage at baseline was available. Neither of these analyses were included in the economic model as it was not considered appropriate to reduce the comparability of the datasets even further in favour of BEN by comparing to the more refractory MM-003 and MM-010 datasets only. The results of the analysis indicated that including ISS stage in the analysis using the same datasets increased the estimated treatment effect of POM+LoDEX.

Therefore, the lack of ability to include ISS stage in the analysis comparing to MM-002 is most likely to bias against POM+LoDEX.

It should be noted that it is highly likely that the differences in inclusion/exclusion criteria cannot be fully adjusted for using the covariates available for the clinical trials. Therefore, it was considered reasonable to present analyses using the most comparable dataset to the BEN data for POM+LoDEX (MM-002) in the base case; particularly given that the lack of inclusion of ISS stage as a covariate is only expected to bias outcomes against POM+LoDEX. Even when using the most comparable dataset, the inclusion/exclusion criteria applied in the MUK-One dataset used for BTD are considered highly likely to bias outcomes in favour of BTD because only fitter patients are included in the analysis.

5.3.7 Survival analysis summary

In line with NICE Decision Support Unit (DSU) guidance the applicability of a single parametric model or a Cox proportional hazards model was determined using visual inspection of the KM curves, the log cumulative hazard plots (LCHP) and the Q-Q curves. LCHPs were assessed to determine the suitability of using a single parametric model for the two treatment arms in terms of the underlying hazard and in assessing the suitability of projecting using exponential, Weibull and Gompertz curves. Q-Q plots were assessed to determine the suitability of the use of accelerated failure time (AFT) models.[125]

Six parametric distributions (exponential, log-normal, log-logistic, Gompertz, gamma and Weibull) were examined for each clinical outcome (OS, PFS and TTF), in line with the NICE DSU guidance.[125] The fit of each parametric model to the covariate adjusted survival data was explored using visual inspection, LCHPs, Q-Q plots, Akaike information criterion (AIC) and Bayesian information criterion (BIC) goodness of fit statistics and clinical plausibility. AIC and BIC provide an estimated relative fit of the alternative parametric models to the observed trial data. All curves were fitted using statistical software package R.

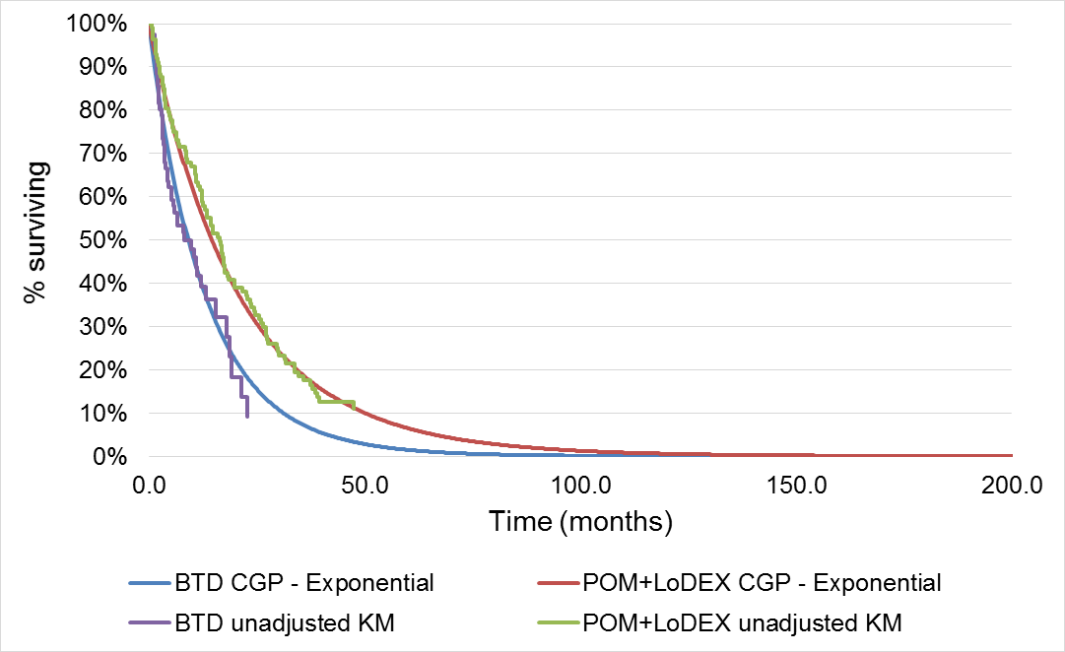
5.3.8 POM+LoDEX vs BTD - Overall survival

Appendix 18 presents the LCHP, the Q-Q plots, visual inspection and AIC and BIC estimates for OS associated with POM+LoDEX. These methods suggested that the exponential curve provides the most appropriate choice of model as this curve had the lowest AIC/BIC and provided a good fit to the observed dataset (Figure 31). Interpreting the AIC/BIC the log-logistic and lognormal curves provided a poor fit to the observed dataset and Q-Q plots confirmed the inappropriateness of using an AFT model. The generalised gamma, Weibull and Gompertz curves provided plausible estimates and good visual fit and are therefore also considered to be appropriate for prediction.

After 5 years, 6.6% of patients are expected to still be alive on the POM+LoDEX arm, 0.1% at 10 years and 0.01% at the model time horizon of 15 years. This is clinically valid as RRMM is a heterogeneous disease, and while the majority of patients have poor prognosis (median OS 3-9 months), a small proportion of patients can experience relatively long survival.[37, 38]

The applicability of using unstratified models for the comparison of POM+LoDEX with BTD was determined using visual inspection of the KM curves, the LCHPs and the Q-Q curves. In the short term the LCHPs are shown to cross; however, in the long term the LCHPs are parallel, and proportional hazards can reasonably be assumed. Therefore, a treatment effect was estimated for BTD compared with POM+LoDEX and applied to the POM+LoDEX fitted exponential OS curve. A comparison of the modelled BTD curve with the original BTD OS data indicates a good fit and validates this method of modelling BTD efficacy estimates (Figure 31).

Figure 31: Comparison of fitted OS curves (exponential) with unadjusted KM curves for POM+LoDEX and BTD



Key: BTD, bendamustine, thalidomide and dexamethasone; CGP, corrected group prognosis; LoDEX, low-dose dexamethasone; KM, Kaplan-Meier; OS, overall survival; POM, pomalidomide.

The impact on model results of selecting different parametric curves was tested in scenario analyses. Additionally, to characterise uncertainty in model inputs a probabilistic sensitivity analysis (PSA) was conducted, this selects the choice of OS curve by sampling from the probability that each parametric model is the best of the fitted parametric models using the AIC estimates.[150]

The individual AIC values are first transformed:

$$\Delta_i = AIC_i - AIC_{min}$$

Where AIC_{min} is the minimum across the AIC values – this transformation allows for meaningful interpretation without the unknown scaling constants and sample size issues that enter into non-transformed AIC values. Δ_i represents the information loss experienced if the model uses an alternative parametric model rather than the best fitted parametric model (as shown by the lowest AIC estimate, Appendix 18). The

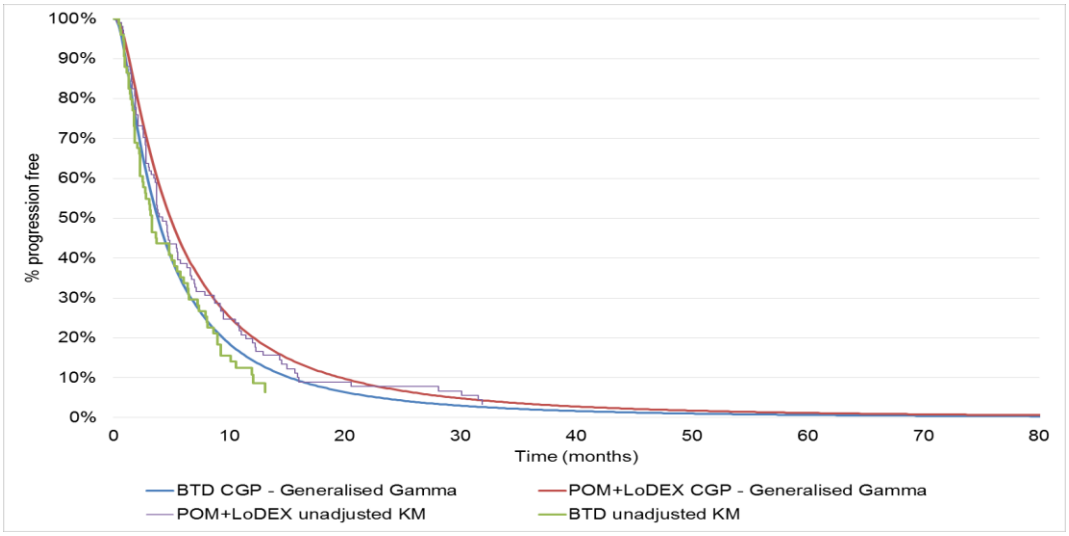
model likelihoods can then be estimated and normalised to provide the probability of each parametric model being the best fitted parametric model. The PSA selects the type of OS curve based upon sampling from the probability that each parametric model is the best fitted parametric model, and therefore incorporates uncertainty around the choice of parametric curve.

Appendix 18 presents the comparison of parametric curve fits with the patient level data when the mean of covariates method is used to adjust for covariates for POM+LoDEX and BTD.

5.3.9 POM+LoDEX vs BTD - Progression-free survival

Appendix 19 presents the LCHP, the Q-Q plots, visual inspection and AIC and BIC estimates for PFS associated with POM+LoDEX. These methods suggested that the Gompertz, Weibull and generalised gamma curves provide appropriate choices of model. The Q-Q plot indicated the inappropriateness of using an AFT model. The generalised gamma curve was selected in the base case (Figure 32) as this appears to provide the better visual fit.

Figure 32: Comparison of fitted PFS curves (generalised gamma) with unadjusted KM curves for POM+LoDEX and BTD



Key: BTD, bendamustine, thalidomide and dexamethasone; CGP, corrected group prognosis; LoDEX, low-dose dexamethasone; KM, Kaplan-Meier; OS, overall survival; POM, pomalidomide.

The same as the analysis conducted for OS, the impact on model results of selecting different parametric curves for PFS was tested in scenario analyses and the choice of PFS curve was sampled from the probability that each parametric model is the best of the fitted parametric models using the AIC estimates in PSA (Appendix 19).[150]

The applicability of the using unstratified models for the comparison of POM+LoDEX with BTD for PFS was determined using visual inspection of the KM curves, the LCHPs and the Q-Q curves. Visually assessing the LCHP for PFS indicates that, although in the short term the LCHPs are shown to cross, in the long term the LCHPs are parallel, and proportional hazards can reasonably be assumed. Therefore, a treatment effect was estimated for BTD compared with POM+LoDEX and applied to the POM+LoDEX fitted generalised gamma PFS curve. A comparison of the modelled BTD curve with the original BTD PFS data indicates a good fit and validates this method of modelling BTD PFS estimates. Appendix 19 presents the comparison of parametric curve fits with the patient level data when the mean of covariates method is used to adjust for covariates for POM+LoDEX and BTD.

Within the model, the potential for the PFS curve to cross the OS curve was curtailed by applying the minimum of PFS and OS if PFS was greater than OS at a given time point. This was apparent in only early model cycles and was adjusted in order to attain clinical validity.

5.3.10 POM+LoDEX vs BTD - Time to treatment failure

TTF was used to determine treatment discontinuation, allowing for potential treatment discontinuation prior to disease progression to be included in the analysis. TTF was defined within the POM clinical trials as the earliest of disease progression, treatment discontinuation, death or initiation of another anti-myeloma therapy.

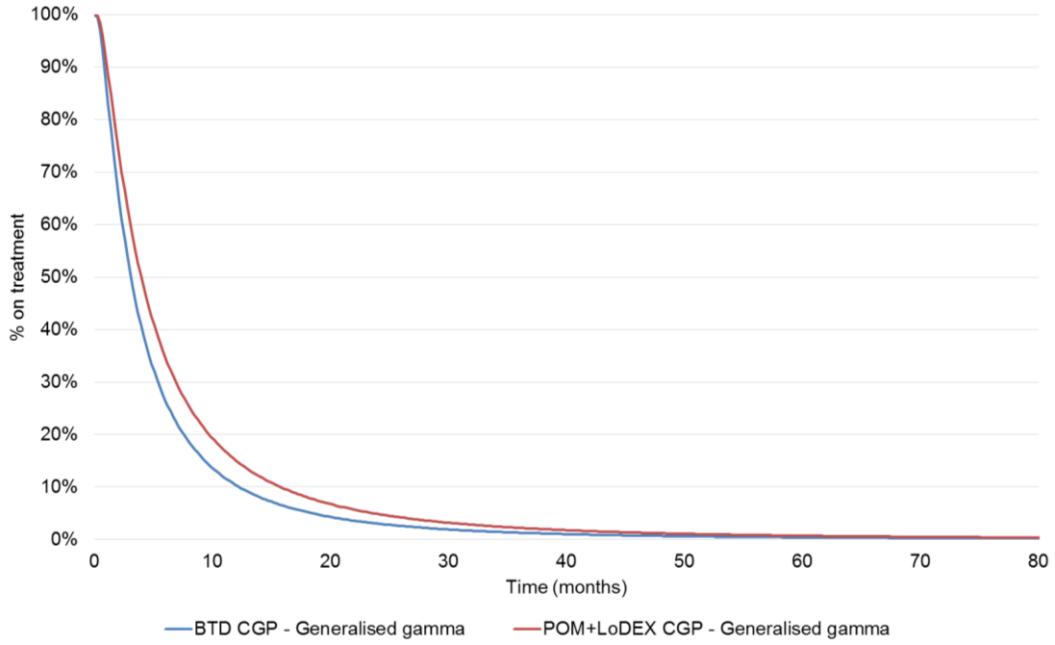
Complete TTF data were only available for POM+LoDEX. The feasibility of using standard parametric models as for OS and PFS was assessed. However, using standard parametric survival curves suggested that the TTF was greater than the PFS at a number of time points, which by definition of TTF (defined as the earliest of

progression, treatment discontinuation, death or initiation of another anti-myeloma therapy) is not a valid interpretation. This issue occurred even when the same functional form was selected as for PFS.

Within the model, the potential for the TTF curve to cross the PFS curve was therefore avoided by estimating TTF curves as a function of PFS using the common treatment effect approach. Unstratified parametric survival curves were produced for each relevant function specifying treatment arm 1 as PFS and treatment arm 2 as TTF for each individual POM+LoDEX patient (using data from MM-002). From these parametric curve fits, the treatment effect for TTF relative to PFS was estimated (Appendix 20). The estimated treatment effect for TTF relative to PFS was then applied to the corresponding PFS curve (generalised gamma curve in the base case) selected within the economic model to estimate TTF. This method was considered more appropriate than calculating a HR as it can be used for all curve types (including AFT functions).

For the TTF associated with BTD, the same coefficients were used for each of the covariates and the same effect between PFS and TTF as for POM+LoDEX, but the treatment effect for POM+LoDEX was excluded. This assumes that the relationship between TTF and PFS for BTD is the same as for POM+LoDEX. Figure 33 presents the treatment effect for TTF relative to the generalised gamma PFS curve, which is used in the base case model.

Figure 33: Base case TTF curves for POM+LoDEX vs BTD



Key: BTD, bendamustine, thalidomide and dexamethasone; CGP, corrected group prognosis; LoDEX, low-dose dexamethasone; POM, pomalidomide; TTF, time to treatment failure.

5.3.11 POM+LoDEX vs PANO+BOR+DEX - Overall survival

Appendix 18 presents the LCHP, the Q-Q plots, visual inspection and AIC and BIC estimates for OS associated with POM+LoDEX compared with PANO+BOR+DEX, using all data from MM-003, MM-002 and MM-010. These methods suggest that the generalised gamma curve provides the most appropriate choice of model as this curve had the lowest AIC/BIC and provided a good fit to the observed dataset (Figure 34). Interpreting the AIC/BIC, the log-logistic and log-normal curves provide a poor fit to the observed dataset, the Q-Q plots confirmed the inappropriateness of using an AFT model. The exponential, Weibull and Gompertz curves provided equally plausible estimates and good visual fit and are therefore also considered to be appropriate for prediction.

To determine the appropriateness of fitting a Cox regression model to the POM+LoDEX and PANO+BOR+DEX data, patient level data for the subgroup of patients who were refractory to BOR but were not primary refractory were obtained

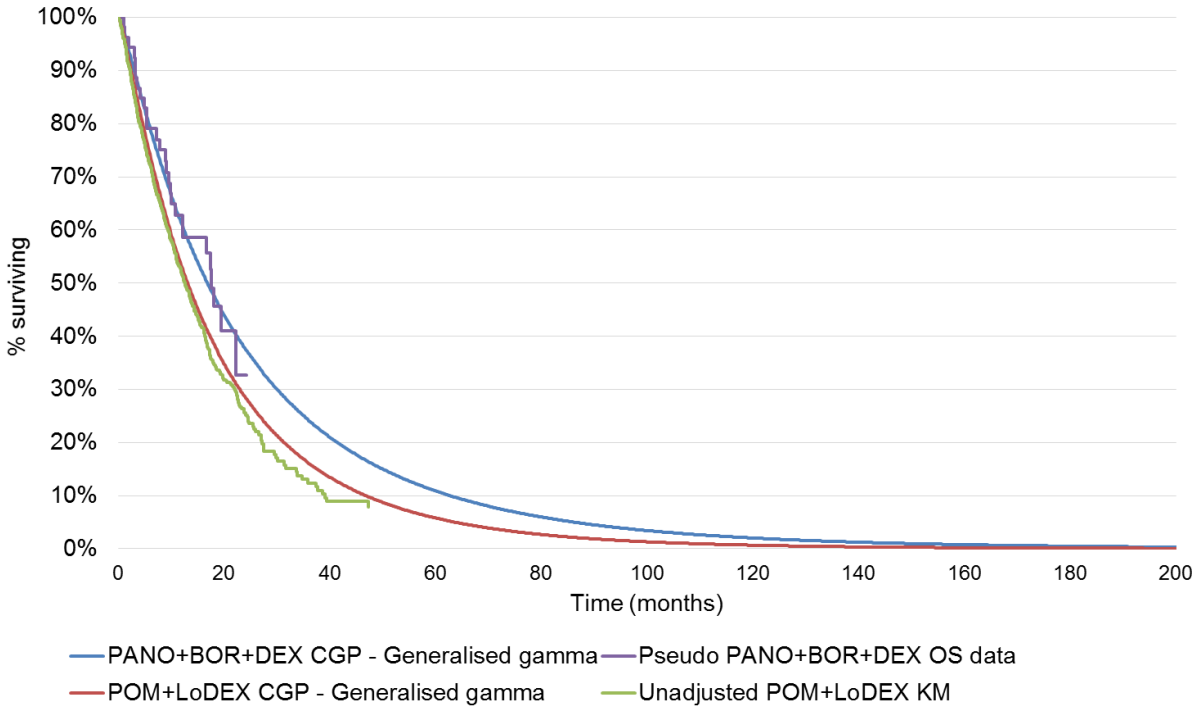
from MM-003, MM-002 and MM-010 and compared with the pseudo patient level data from PANORAMA-2. Propensity weights were calculated for the POM+LoDEX data based on the observed baseline characteristics in PANORAMA-2 with respect to age, prior lines of therapy, receipt of prior THAL and ECOG. Appendix 18 presents the weighted/unweighted patient level data for POM+LoDEX, the pseudo patient level data for PANO+BOR+DEX, the LCHPs and the Q-Q curves for this comparison. The LCHPs depict approximately parallel curves and so confirm the appropriateness of fitting the Cox proportional hazards model. Similarly, as the Q-Q plot for OS approximates to a straight line, an assumption of a constant relative AF is supported.

The weighted patient level data for POM+LoDEX and pseudo patient level data for PANO+BOR+DEX were included in a Cox proportional hazards model to calculate a MAIC HR between PANO+BOR+DEX and POM+LoDEX (see Section 4.10). The model estimated a HR of 0.778 [95% CI: 0.555 – 1.090] for PANO+BOR+DEX compared with a matched POM+LoDEX population. This HR was applied to the parametric curves fitted to the full POM+LoDEX trial datasets (MM-003, MM-002 and MM-010).

The impact of the uncertainty associated with this estimate on the model results is investigated in the PSA. For each iteration the HR is randomly sampled from its assigned log-normal distribution.[151]

A comparison of the modelled PANO+BOR+DEX curve with the pseudo PANO+BOR+DEX OS data indicates a good fit and validates this method of modelling PANO+BOR+DEX efficacy estimates (Figure 34).

Figure 34: Comparison of fitted curves (generalised gamma) for OS with unadjusted POM+LoDEX KM data (including MM-003, MM-002 and MM-010) and pseudo patient level data for PANO+BOR+DEX



Key: BOR, bortezomib; CGP, corrected group prognosis; DEX, dexamethasone; KM, Kaplan-Meier; LoDEX, low-dose dexamethasone; OS, overall survival; PANO, panobinostat; POM, pomalidomide.

5.3.12 POM+LoDEX vs PANO+BOR+DEX - Progression-free survival

Appendix 19 presents the LCHP, the Q-Q plots, visual inspection and AIC and BIC estimates for PFS associated with POM+LoDEX compared with PANO+BOR+DEX, using all data from MM-003, MM-002 and MM-010. These methods suggest that the Gompertz, Weibull, exponential and generalised gamma curves provide the most appropriate choice of model as these curves have the lowest AIC/BIC. The generalised gamma curve was selected for the base case as this provided a good fit to the observed dataset and is consistent with the curve choice for OS (Figure 35). Interpreting the AIC/BIC, the log-logistic and log-normal curves provide a poor fit to the observed dataset, the Q-Q plots confirmed the inappropriateness of using an AFT model.

Appendix 19 presents the weighted/unweighted patient level data for POM+LoDEX, the pseudo patient level data for PANO+BOR+DEX, the LCHPs and the Q-Q curves used to assess the validity of fitting a Cox regression model to the POM+LoDEX and PANO+BOR+DEX data.

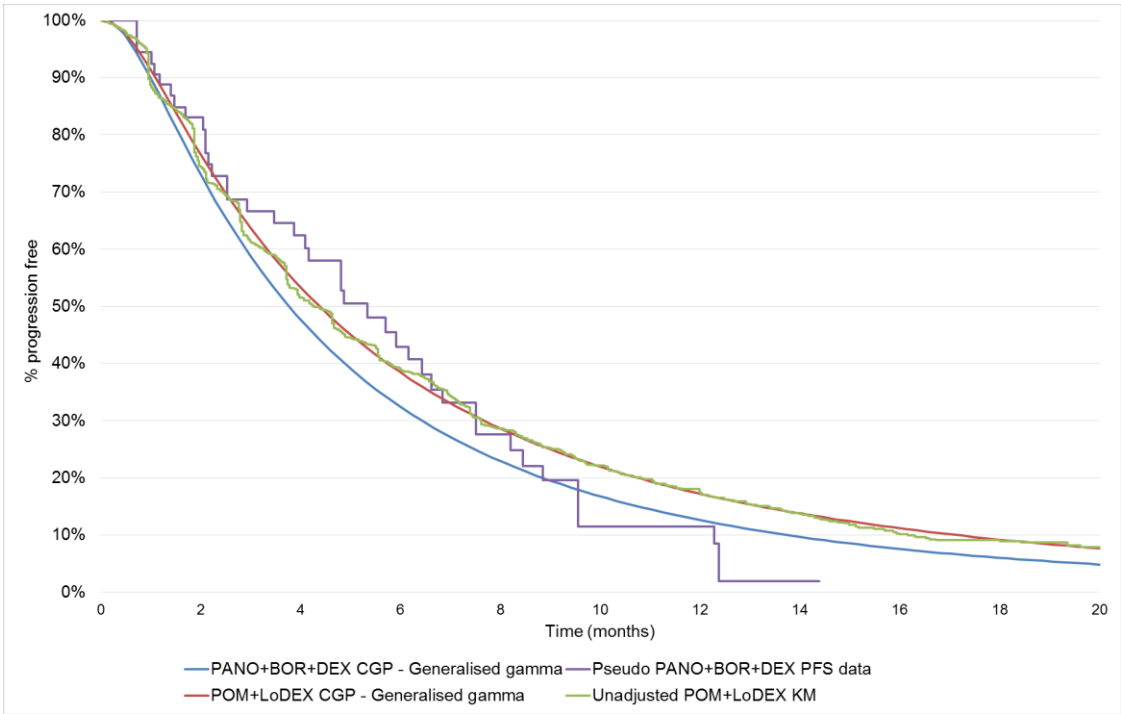
The lines for each treatment for PFS do not look parallel indicating a lack of proportionality of hazards between PANO+BOR+DEX and the weighted POM+LoDEX curve. This is not unexpected given the crossing of KM curves between the treatments, and the fact that full PFS follow-up is reached for PANO+BOR+DEX. The Q-Q plot for OS approximates to a straight line. Therefore, an assumption of a constant relative acceleration factor (for accelerated failure time models) is supported. However, a constant relative acceleration factor for PFS is not supported given the lack of linearity. Minimal extrapolation is required for PFS in the economic model, and therefore these curves provide enough evidence to support the Cox proportional hazards model. The direction of bias in assuming proportional hazards is potentially against POM+LoDEX as the PFS curves are diverging at the point of last observation for PANO+BOR+DEX (patients still remain progression free on POM+LoDEX compared to complete follow-up with PANO+BOR+DEX).

The weighted patient level data for POM+LoDEX and pseudo patient level data for panobinostat were included in a Cox proportional hazards model to calculate a MAIC HR between PANO+BOR+DEX and POM+LoDEX (see Section 4.10). The model estimated a HR of 1.178 (95% CI: 0.893 – 1.555) for PANO+BOR+DEX compared with a matched POM+LoDEX population.

This HR is applied to parametric curves fitted to the full POM+LoDEX trial datasets with the underlying functional form (generalised gamma for PFS in the base case) of the curve fit. The impact of the uncertainty associated with this estimate on the model results is investigated in the PSA. For each iteration the HR is randomly sampled from its assigned log-normal distribution.

A comparison of the modelled PANO+BOR+DEX curve with the original PANO+BOR+DEX KM PFS data indicates a good fit and validates this method of modelling PANO+BOR+DEX efficacy estimates (Figure 35).

Figure 35: Comparison of fitted curves (generalised gamma) for PFS with unadjusted POM+LoDEX KM data (including MM-003, MM-002 and MM-010) and pseudo patient level data for PANO+BOR+DEX



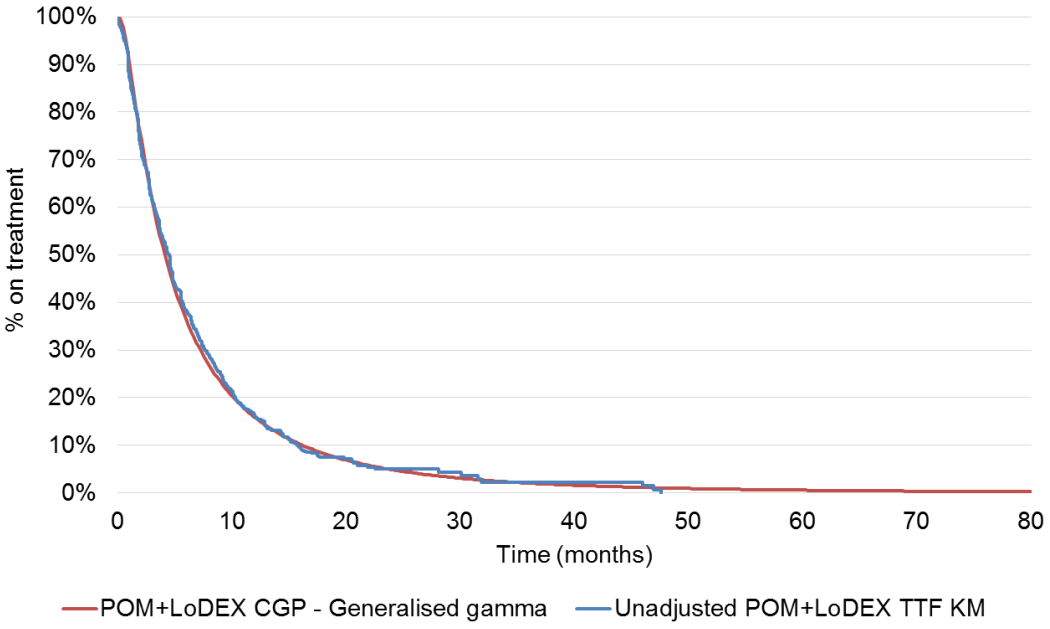
Key: BOR, bortezomib; CGP, corrected group prognosis; DEX, dexamethasone; KM, Kaplan–Meier; LoDEX, low-dose dexamethasone; MM, multiple myeloma; NHS, National Health Service; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; POM, pomalidomide.

5.3.13 POM+LoDEX vs PANO+BOR+DEX - Time to treatment failure

The feasibility of using standard parametric models for OS and PFS was assessed. However, using standard parametric survival curves suggested that the TTF was greater than the PFS at a number of time points, which by definition of TTF (defined as the earliest of progression, treatment discontinuation, death or initiation of another anti-myeloma therapy) is not a valid interpretation. This issue occurred even when the same functional form was selected as for PFS.

As with the comparison of POM+LoDEX with BTD, the potential for the TTF curve to cross the PFS curve was avoided by estimating TTF curves as a function of PFS using the common treatment effect approach. Unstratified parametric survival curves were produced for each relevant function specifying treatment arm 1 as PFS and treatment arm 2 as TTF for each individual POM+LoDEX patient (using all data from MM-003, MM-002 and MM-010). From these parametric curve fits, the treatment effect for TTF relative to PFS was estimated (Appendix 20). The estimated treatment effect for TTF relative to PFS was then applied to the corresponding PFS curve (generalised gamma curve in the base case) selected within the economic model to estimate TTF. This method was considered more appropriate than calculating a HR as the method can be used for all curve types (including AFT functions). Figure 36 presents the treatment effect for TTF relative to the generalised gamma PFS curve used in the base case model.

Figure 36: Base case TTF curves for POM+LoDEX (including MM-003, MM-002 and MM-010)



Key: BOR, bortezomib; CGP, corrected group prognosis; DEX, dexamethasone; KM, Kaplan-Meier; LoDEX, low-dose dexamethasone; PANO, panobinostat; TTF , time to treatment failure.

PANO+BOR+DEX is a fixed dose regimen, and therefore treatment does not exceed 42 cycles within the model (14 treatment cycles consisting of 21 days). As a conservative assumption the model considers that all patients are treated until the first of either progression or this fixed dose. This is in line with the NICE submission for PANO (TA380).[93] The dose intensity assumed for patients receiving PANO+BOR+DEX is discussed in Section 5.5.

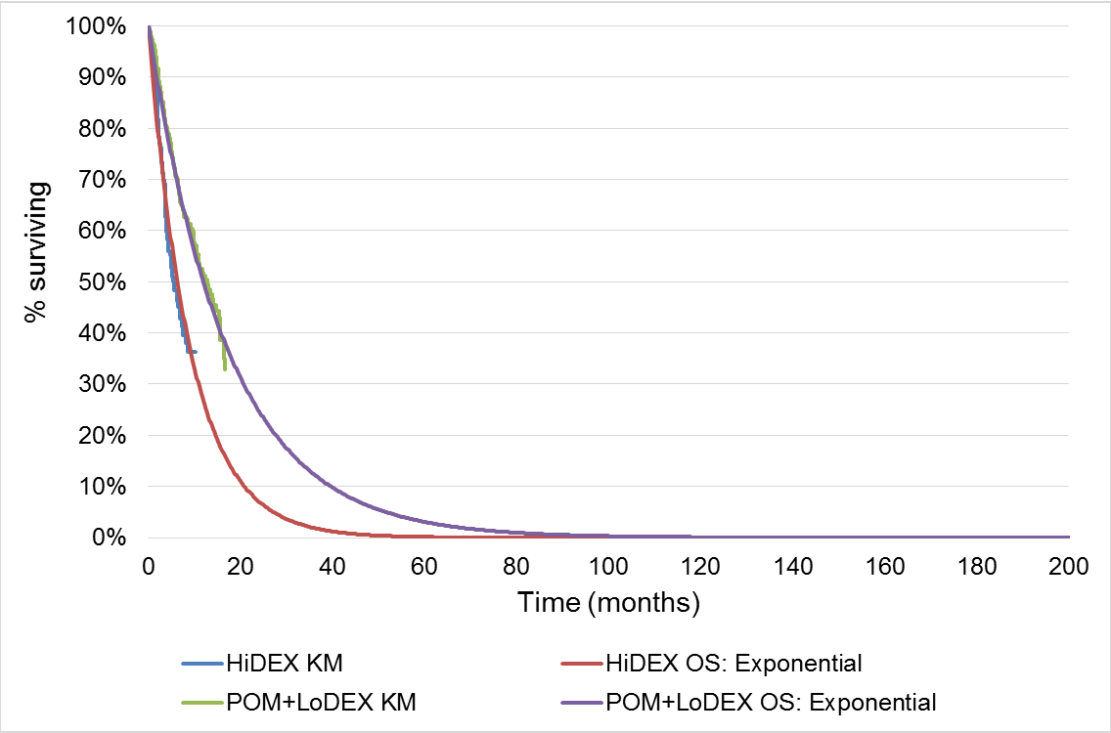
5.3.14 POM+LoDEX vs conventional chemotherapy

Comparative data were available for POM+LoDEX and HiDEX from the MM-003 trial, and therefore comparative efficacy considers a within-trial comparison. The original NICE submission provides OS estimates for the exponential, log-normal, log-logistic and Weibull curves for the HiDEX data, used as a proxy for conventional chemotherapy.[146] Two methods were used to account for treatment switching within the MM-003 trial; the two-stage method and the rank preserving structure failure time model (RPSFTM) approach. PFS and TTF were fitted using these curves and also the extreme value curve (the extreme value curve was not fitted to OS data due to convergence issues).

This resubmission estimates parameters for the generalised gamma and Gompertz curves in addition to the original curves provided, using both the two-stage and RPSFTM methods. AIC and BIC statistics are presented in Appendices 18 - 20.

Visual inspection of fitted and KM curves as well as AIC and BIC statistics indicated that the exponential adjusted using the two stage Weibull approach provided the best fit for the OS data (Figure 37). The Weibull curve adjusted using the two stage approach was also shown to be a valid option for curve choice. Previously the log-logistic curve was selected, but in light of updated data, the long-term survival predicted by this curve is no longer considered clinically plausible.

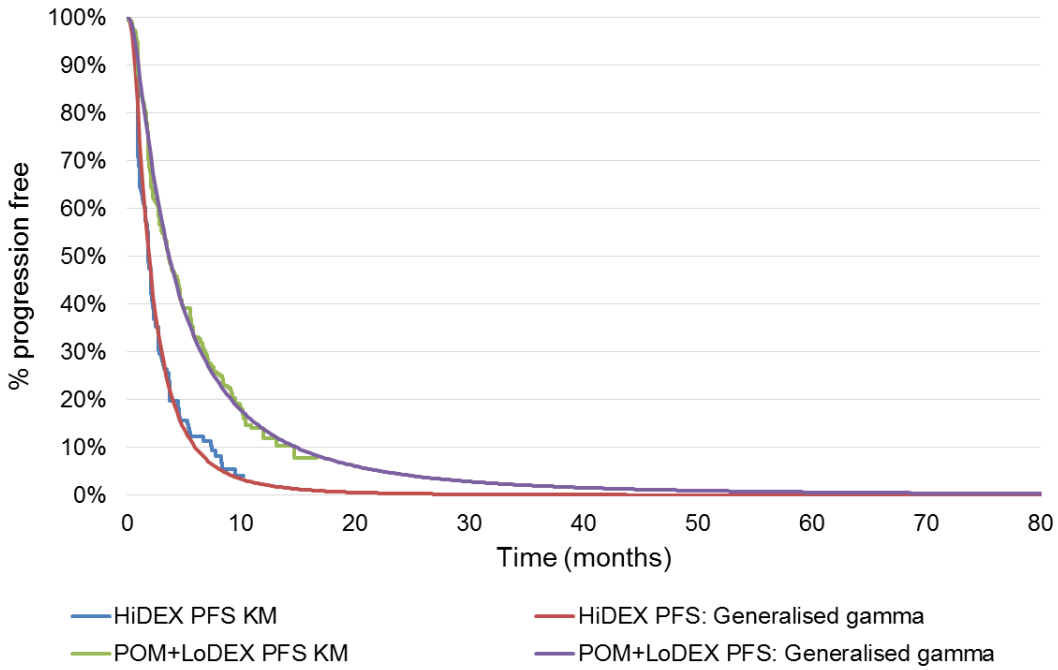
Figure 37: Comparison of fitted curves (exponential) for OS with POM+LoDEX and HiDEX KM data



Key: HiDEX, high-dose dexamethasone; KM, Kaplan-Meier; LoDEX, low-dose dexamethasone; OS, overall survival; POM, pomalidomide.

The generalised gamma curve was selected as the base case cure for PFS based upon visual inspection of fitted and KM curves as well as AIC and BIC statistics (Figure 38). Whilst the log-normal and log-logistic curves appear to have a good fit according to AIC and BIC statistics Q-Q plots demonstrated that the AFT assumption was not appropriate.

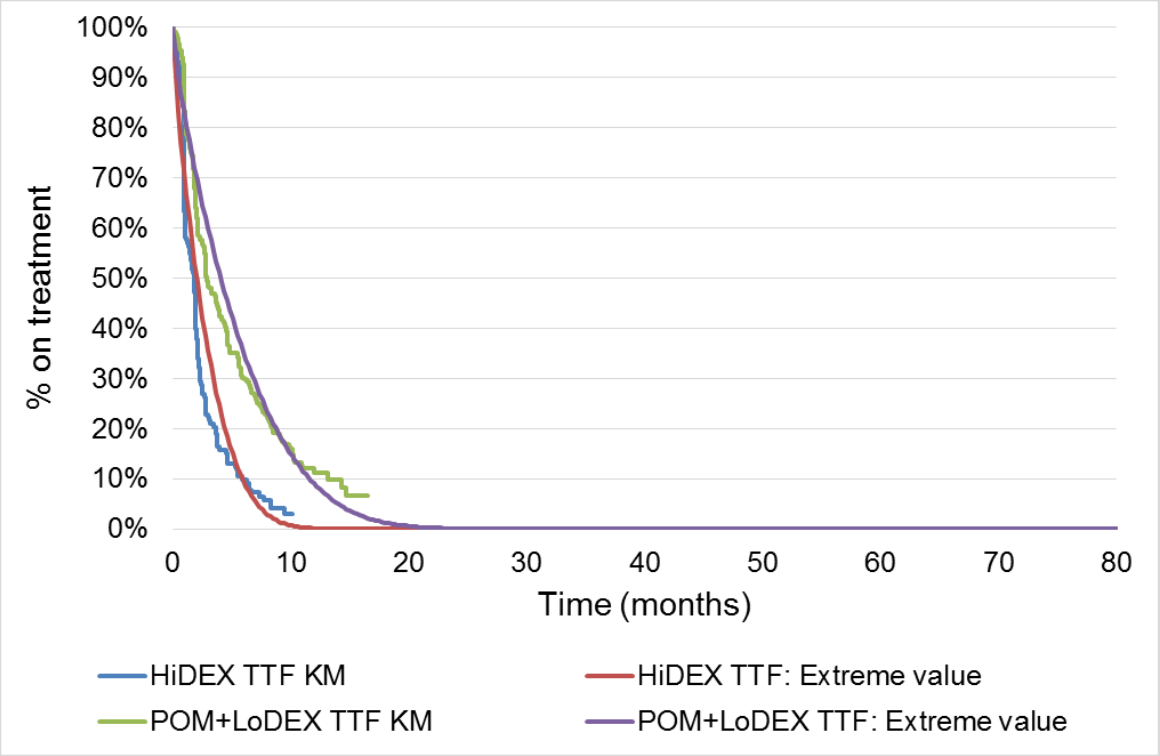
Figure 38: Comparison of fitted curves (generalised gamma) for PFS with POM+LoDEX and HiDEX KM data



Key: HiDEX, high-dose dexamethasone; KM, Kaplan-Meier; LoDEX, low-dose dexamethasone; PFS, progression-free survival; POM, pomalidomide.

Consistent with the previous submission visual inspection of fitted and KM curves as well as AIC and BIC statistics indicated that the extreme value curve provided a good fit for the TTF data (Figure 39). The exponential and Weibull curves were also shown to be valid options for curve choice.

Figure 39: Comparison of fitted curves (extreme value) for TTF with POM+LoDEX and HiDEX KM data



Key: HiDEX, high-dose dexamethasone; KM, Kaplan-Meier; LoDEX, low-dose dexamethasone; POM, pomalidomide; TTF, time to treatment failure.

5.3.15 Validation of OS and PFS

In the previous NICE submission (TA338), the Appraisal Committee and the ERG commented that the ratio of OS to PFS predicted in the economic analysis were different from the 2.45 month increase in OS for each month of median PFS reported by Felix et al., and therefore the face validity of the comparative efficacy was uncertain.[148, 152] This statement was later revised within the FAD to indicate that higher ratios can be expected in later line treatments, such as POM+LoDEX.

In this resubmission the ratio for POM+LoDEX (including data from MM-002 only) is 3.93 months (median OS = 16.5 months, median PFS = 4.2 months). If the larger dataset for POM+LoDEX is considered, the ratio of OS to PFS for POM+LoDEX (including data from MM-003, MM-002 and MM-010) is 3.02 months (median OS =

12.4 months, median PFS = 4.1 months). The ratio for BTD (including data from Tarant et al., Gooding et al. and MUK-One) in this resubmission is 2.49 months (median OS = 8.2 months, median PFS = 3.3 months). The ratio for PANO+BOR+DEX (based upon data from PANORAMA-2) in this resubmission is 3.24 months (median OS = 17.5 months, median PFS = 5.4 months). The ratio for conventional chemotherapies (using HiDEX as a proxy) in this resubmission is 3.06 (median OS = 5.7 months, median PFS = 1.86 months).[17, 35, 153]

When looking at the all trials comparison, the difference in the ratio of PFS to OS between POM+LoDEX and BTD is considerably smaller than that projected within the original submission to NICE. There are various factors thought to be at play here:

- BTD is more effective than some of the other regimens included in previous analysis (such as conventional chemotherapy) that were previously assumed to represent the efficacy of BTD
- The patient population from the BTD trials included in the current analysis is less refractory to previous treatment and less heavily pretreated than the patient population in the combined POM+LoDEX trial dataset; this enables these patients to obtain greater benefit from subsequent therapies. It is unlikely that simply applying covariate adjustment can account for all differences in patient characteristics, and the small coefficient size assigned to number of previous treatments in the regression equations is an indicator of this difficulty. Additionally, lack of subsequent therapy data for patients receiving BTD means that we cannot compare what treatments were received by patients between the trials.

The difference in the ratio of PFS to OS between POM+LoDEX and PANO+BOR+DEX is also small. However, the HRs for OS and PFS associated with PANO+BOR+DEX compared with POM+LoDEX (0.778 and 1.178 for OS and PFS, respectively) are in the opposite directions. This indicates that there is likely major confounding from subsequent therapy use; lack of subsequent therapy data for

patients receiving PANO+BOR+DEX means that we cannot compare what treatments were received by patients between the trials.

We therefore consider the comparative effectiveness estimates versus BTD presented using the all trials comparison to be extremely conservative. This is particularly the case as there are reasons related to mode of action (see Section 2.5) to expect longer PPS with POM+LoDEX relative to BTD. This is why MM-002 only has been selected for the base case.

Table 46: Comparison of OS:PFS ratio with those observed in other multiple myeloma trials

Study	Patients	Median OS	Median PFS	OS:PFS ratio
Present analysis	POM+LoDEX (MM-003, MM-002 and MM-010)	12.4 months	4.1 months	3.02
	POM+LoDEX (MM-002)	16.5 months	4.2 months	3.93
	BTD	8.2 months	3.3 months	2.49
	PANO+BOR+DEX	17.5 months	5.3 months	3.30
	Conventional chemotherapy	5.7 months	1.86 months	3.06
MM-009 & MM-010 trials for lenalidomide[154]	One prior therapy	42.0 months	14.1 months	2.979
	>1 prior therapy	35.8 months	9.5 months	3.768
PANORAMA-2	>2 prior therapy BOR refractory PANO+BOR+DEX	17.5	5.4	3.24
APEX[110, 155]	BOR	29.8 months	6.2 months*	4.806
	HiDEX	23.7 months	3.5 months*	6.771
VISTA[156]	BOR + melphalan + prednisone	56.4 months	24.0 months*	2.350
	BOR	43.1 months	16.6 months	2.596

Key: BOR, bortezomib; BTD, bendamustine + thalidomide + dexamethasone; DEX, dexamethasone; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; MM, multiple myeloma; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; POM, pomalidomide.
Note: * denotes median TTP.

5.3.16 Adverse events

Treatment emergent adverse events (TEAEs) Grade 3/4 were included in the economic analysis if they occurred in at least 2% of POM+LoDEX patients in the MM-003 trial dataset. This level of granularity was not available for MM-002 and MM-010.

Data available for comparator treatments to assess the impact of toxicity are considerably more limited than the data available to assess impacts for effectiveness, and it is not possible to covariate-adjust these data to improve comparability. HiDEX data sourced from the MM-003 trial could potentially be used as a proxy to model AE rates for conventional chemotherapy, but are unlikely to be fully representative. Furthermore, reporting of AEs for comparator treatments even at earlier lines of therapy is exceedingly sparse.

Therefore, two approaches were taken to estimate the impact of AEs on patients:

1. Use of the proportion of patients that discontinued due to a TEAE, reported consistently across all datasets, relative to the proportion of patients discontinuing in the POM+LoDEX arm of the MM-003 trial. This provides a relative increase or decrease in the proportion of TEAEs occurring in at least 2% of patients.
2. Use of relative safety estimates provided by the advisory board (March 2016).[9]

Use of the proportion of patients discontinuing due to TEAEs

In the base case the proportion of patients from each dataset discontinuing due to TEAEs was recorded and a proportion change relative to the complete data available for the POM+LoDEX arm in the MM-003 trial was calculated. This method estimates a relative decrease in TEAEs for the POM+LoDEX arms in MM-002 and all POM+LoDEX trials (17.77% and 27.89% decrease, respectively), and a relative

increase in TEAEs for BTD and PANO+BOR+DEX (93.59% and 111.19% increase, respectively).

To be consistent with the other comparators in the model, this method is used for conventional chemotherapy in the base case; this results in a relative increase of 21.47% compared to the POM+LoDEX arm in the MM-003 trial.

The annual TEAE event rates for POM+LoDEX were calculated based upon the reported number of occurrences of each event and the total number of patient years over the duration for which the TEAEs were monitored:

- POM+LoDEX: 250 patient years; based on follow-up time over 10 months and data on AEs available for 300 patients[17]

Annual event rates were converted to rates per week – these allow for the number of events occurring per week on each arm to be applied in the model. The weekly TEAE rate was then multiplied by the relevant proportional increase or decrease to estimate the weekly TEAE event rate for each comparator.

Appendix 21 presents the TEAEs recorded in the MM-003 trial and the estimated weekly probability of Grade 3/4 events occurring while on treatment applied in the economic analysis.

Use of clinician estimates in sensitivity analysis

In a scenario analysis, TEAE rates are estimated by applying the relative safety scores provided by clinicians during an advisory board to the POM+LoDEX data sourced from MM-003 (Section 5.3). This method estimates a relative increase in TEAEs compared with POM+LoDEX for BTD, PANO+BOR+DEX and conventional chemotherapy; 36.5%, 47.3% and 41.9% decrease, respectively.

The weekly TEAE rate for POM+LoDEX, calculated using MM-003 data, was multiplied by the relevant proportional decrease in tolerability to provide the weekly TEAE event rate for each comparator. Appendix 21 presents the estimated weekly probability of Grade 3/4 events occurring while on treatment applied in this scenario analysis.

Additional information on the tolerability profile of POM+LoDEX

Clinicians advised that patients experiencing an AE whilst on treatment with POM+LoDEX are most likely to experience the AE in the initial few weeks and so estimating an AE rate over a short time period does not take into account the long term safety profile of POM+LoDEX.

An additional analysis was conducted to investigate the long term safety profile associated with POM+LoDEX relative to HiDEX. The analysis used AE data from the MM-003 trial and compared the proportion of patients not experiencing an AE after three treatment cycles (84 days) between the POM+LoDEX and HiDEX arms (Appendix 22). This comparison was also conducted for the following subgroups: responders, stable disease and progressive disease patients.

The data indicate that, after the initial three treatment cycles, a greater proportion of patients on the POM+LoDEX arm remain AE free – this is in line with the feedback provided at the advisory board (where POM was considered to have the best safety profile in UK clinical practice).[9] This pattern can be observed in the responders, stable disease and progressive disease subgroups. Therefore, the AE rate applied for POM+LoDEX within the economic model is likely an overestimate of what would be observed with longer-term use in clinical practice.

5.3.17 Clinician validation

Celgene Ltd conducted an advisory board with 10 clinical experts on 23 March 2016 to share data and seek advice on the importance of POM in UK clinical practice. The panel reviewed the comparators listed by NICE in the scope for the POM resubmission, data from key clinical trials of POM and three real world studies (Section 4), and some of the methods and assumptions under consideration for use in the health economic model for the resubmission of POM to NICE. Full details of the validation process and its opinions are provided in the reference supplied.[9]

Model results show POM+LoDEX to have superior efficacy to BTD and conventional chemotherapy, in line with advisors' comments; POM+LoDEX is associated with 1.19

life years (MM-002 data), 1.09 life years (MM-003, MM-002 and MM-010 data) and 0.98 life years (MM-003 data), compared with 0.75 and 0.52 life years for BTD and conventional chemotherapy. However, the model estimates more life years for patients receiving PANO+BOR+DEX – this is likely due to significant confounding associated with subsequent therapies. Model results show POM+LoDEX to have superior PFS to PANO+BOR+DEX; 0.66 pre-progression life years for POM+LoDEX and 0.54 for PANO+BOR+DEX.

The information on comparative safety has been used in a scenario analysis within the model.

5.4 Measurement and valuation of health effects

Section 3.1 and section 3.2 provide an overview of MM and its impact.In addition to the physical symptoms multiple myeloma patients can suffer considerably from fear of recurrence and uncertainty about the future due to the relapsing nature of the disease. Additionaly, the complexity, the difficulty of treatment and frustration with the limited treatment options available can combine to lead to patients feeling a loss of independence and inability to plan for the future.[157]

5.4.1 Health-related quality-of-life data from clinical trials

The MM-003 clinical study used three questionnaires to measure HRQL; the EQ-5D-3L and two EORTC questionnaires (the EORTC QLQ-MY20 and the EORTC QLQ-C30). HRQL data were not included in either the MM-002 or MM-010 studies. The EORTC QLQ-C30 assesses the quality of life of cancer patients and the EORTC QLQ-MY20 focuses specifically on patients with multiple myeloma. These questionnaires were provided in electronic format to each patient to complete on the first day of every cycle, including Cycle 1, and at study discontinuation and treatment phase discontinuation visits.

The EORTC QLQ-C30 and EORTC QLQ-MY20 cannot be used directly in economic evaluation as they do not incorporate preference information.

Quality of life analysis used within the model base case was the same as that used within the original submission for POM as no further data beyond the original March data cut were available from the MM-003 trial.

The EQ-5D UK tariff was applied to the data obtained from the EQ-5D in the MM-003 trial.[158]

Multivariate analysis was then conducted to determine the most significant predictors of HRQL over all time points, using a 5% significance level. A multiple regression model was used, fitting a mixed effect model that allowed for non-linear relationships. The model also allowed for polynomial terms, such as age, which may have a non-linear effect, and as such, this variable was included as both a linear and quadratic variable. The model includes a random-effect term for patients, which is appropriate when there are clustered data (i.e. observations taken over time on the same individual), as the majority of patients' utility scores (both EQ-5D and EORTC-8D) were measured at more than one time point.

Explanatory variables included in the analysis were determined to be potential influencers of HRQL in consultation with UK clinicians.[159] A separate analysis was employed converting the EORTC QLQ-C30 to utilities using the EORTC-8D algorithm by Rowen et al.[160]

Both regression analyses were conducted using three different methods: stepwise selection, backward selection and forward selection. In the base case stepwise selection method was used. The stepwise selection method yielded identical results to backward selection, and the forward selection method was discarded due to its inflexible nature resulting in the possibility of including non-significant explanatory variables in the final model.[161]

All variables identified by the stepwise selection method were included in the utility calculation (Table 47), as stepwise selection identifies a subset of predictor variables that need to be included in the model for the model to have good predictive ability. Utility values were calculated by summing each coefficient multiplied by the number of events for that explanatory variable.

The results from this regression show that baseline ECOG status and best overall response have the greatest effect on utility. The ECOG performance status is a scale from 0 to 5 representing varying levels of performance and ability; the higher the ECOG status, the lower the level of performance and the greater detriment on utility, and hence HRQL.

Table 47: Utility regression coefficients for parameters obtained using EQ-5D from the MM-003 trial

Explanatory variable	Utility coefficient	
	Stepwise and backwards selection (p value)	Forward selection (p value)
Intercept	0.727	-0.046
Disease progression	-0.037 (0.109)	-0.036 (0.119)
Best overall response after 12 weeks: stable disease (relative to response)	-0.095 (0.003)	-0.096 (0.003)
Best overall response after 12 weeks: progressive disease (relative to response)	-0.139 (0.009)	-0.138 (0.009)
Age (decades)	No coefficient	0.267 (0.090)
Age^2 (decades)	No coefficient	-0.022 (0.081)
Hospitalised[a]	-0.138 (0.001)	-0.138 (0.001)
Adverse event(s)[b]	-0.076 (0.001)	-0.077 (0.001)
Gender: male	0.074 (0.006)	0.073 (0.007)
Baseline ECOG = 1 (relative to 0)	-0.134 (<0.001)	-0.133 (<0.001)
Baseline ECOG = 2 or 3 (relative to 0)	-0.332 (<0.001)	-0.333 (<0.001)
Baseline Durie Salmon stage = 1 (relative to 3)	0.030 (0.543)	0.036 (0.469)
Baseline Durie Salmon stage = 2 (relative to 3)	0.071 (0.019)	0.075 (0.013)
Log(number of prior lines of therapy)	No coefficient	-0.012 (0.726)
RBC level (10^{12}/L)	0.049 (0.013)	0.048 (0.015)
Location: Europe	-0.069 (0.079)	-0.061 (0.130)

Explanatory variable	Utility coefficient	
	Stepwise and backwards selection (p value)	Forward selection (p value)
Key: BORR, best overall response rate; ECOG, European Cooperative Oncology Group; RBC, red blood cell. **Note:** *Not all variables included within the original list have an associated coefficient from stepwise selection method as they were deemed statistically insignificant through this process. a, Having matched the date of HRQL assessments with the occurrence of any hospitalisations. b, Having matched the date of HRQL assessments with the occurrence of any adverse events. The impact of different types of adverse events could not be easily or reliably explored to limited data that would be matched with a HRQL assessment.		

The average (mean) and standard error of the observed and estimated utility scores for patients was used to estimate the multivariate model for all patients combined and for subgroups stratified using the variables included in the multivariate model (Appendix 23). As noted by the ERG as part of the previous NICE review (TA338), although differences are shown between the observed utility scores and those predicted by the regression model, it is not likely that these differences would have a large impact on the cost-effectiveness results.[148]

The regression model includes both the occurrence of AEs and hospitalisation as covariates. This is appropriate as, although these measures are likely correlated, it allows changes in HRQL to be picked up for AEs that do not result in hospitalisation as well as those that do.

The coefficients obtained from the EORTC-8D are presented in Appendix 23. A high correlation was found between the EQ-5D and EORTC-8D outcomes, (correlation coefficient 0.66).

The results of residual diagnostic tests are also provided in Appendix 23. These suggest statistical preference for the model based upon EORTC-8D values, since the data better satisfy the underlying multivariate model assumption of normality of the outcome variable (utility). However, in accordance with the NICE reference case, the EQ-5D model is applied for the base case cost-effectiveness evaluation. Use of the disease-specific EORTC-8D model is explored in a scenario analysis.

Determinants of utility model inputs

Best overall response rates

Investigator-assessed best overall response rates (BORRs) were measured at Week 12 in the POM+LoDEX and comparator clinical data. As BORRs were measured at Week 12 across the clinical data, it was assumed that before 12 weeks all patients were in the pre-progression state and achieving a best overall response of stable disease, relative to response. Based on available data, BORRs were weighted and normalised across the trials for use in the utility regression equation for POM+LoDEX patients (Table 48).

For BTD, BORRs were obtained as a weighted response across the MUK-One, Gooding et al. and Tarant et al. datasets.[37, 38, 162] For PANO+BOR+DEX, BORRs were sourced from PANORAMA-2.[35] For conventional chemotherapy, BORRs were sourced from the HiDEX arm in the MM-003 trial (used as a proxy for conventional chemotherapies).[17]

As per the previous NICE submission (TA338), patients with a non-evaluable response were assumed to have PD. The overall utility effect of BORR is modelled as a weighted average of the regression coefficients by the proportion of patients achieving each level of BORR presented in Table 48.

Table 48: BORR by treatment arm

Best overall response	POM+LoDEX[17] (MM-003, MM-002 and MM-010)	POM+LoDEX (MM-002)	POM+LoDEX (MM-003)	BTD[162]	PANO+BOR+DEX[35]	Conventional chemotherapies[17d]
Response to therapy	33.09[a]	33.00%	31.10%	40.91%	34.50%	10.37%
Stable disease	48.22[b]	37.00%	50.70%	23.62%	36.40%	59.26%
Progressive disease	18.69[c]	30.00%	18.20%	35.47%	29.10%	30.37%

Key: BOR, bortezomib; BORR, best overall response rate; BTD, bendamustine, thalidomide and dexamethasone; DEX, dexamethasone; LoDEX, low-dose dexamethasone; PANO, panobinostat; POM, pomalidomide.

Note: a, Weighted proportion across MM-003, MM-002 and MM-010. b, Weighted proportion across MM-003 and MM-002 (stable disease not presented for MM-010). c, normalised using data only from MM-003. d, due to lack of data for conventional chemotherapies HiDEX is used as a proxy.

Hospitalisations

Hospitalisations were used in the utility regression analysis, included as a potentially relevant determinant of quality of life; if a patient was hospitalised during the quality of life assessment, we would expect their quality of life to be lower. Hospitalisations were recorded in MM-003 for up to 28 days following treatment discontinuation, excluding hospitalisation that occurred before active treatment had commenced. Per week cycle rates were calculated the same way as AEs, and the hospitalisation rate associated with HiDEX patients was assumed to apply for the comparators. The weekly rates of hospitalisation are:

- POM+LoDEX: 0.055
- HiDEX: 0.064

Hospitalisation rates for the comparator arm were obtained from the MM-003 study control arm as a conservative assumption. Data from the Gooding et al. dataset were

assessed; these showed a similar estimate (0.061 per week); use of these data is considered in a scenario analysis.[37]

Clinical validation of data from the clinical trial

Clinical experts were approached during the original submission to NICE to assess the utility data available from the regression equation fitted to the MM-003 trial data. Parameters included in the HRQL weight regression analysis were considered to be reasonable as potential influences on patient HRQL and the utility results were considered to reasonably characterise RRMM.[146]

5.4.2 Health-related quality-of-life studies

Identification of utility studies

The SLR which formed part of the previous NICE submission (TA338) was updated in order to capture new utility studies for RRMM patients. Literature searches were performed between 1 December 2013 and 3 March 2016. Only studies reporting utilities or data that could be mapped using the publication alone to utilities were included. As little information was identified within the original submission in terms of utility data at the correct line of therapy (post BOR and LEN) outside the MM-003 trial, search criteria were kept broad and all studies reporting outcomes for RRMM were included regardless of whether they were run in the licensed indication for POM or the intervention/comparator discussed. Detailed search strategies, sources search and inclusion/exclusion criteria are provided in Appendix 24.

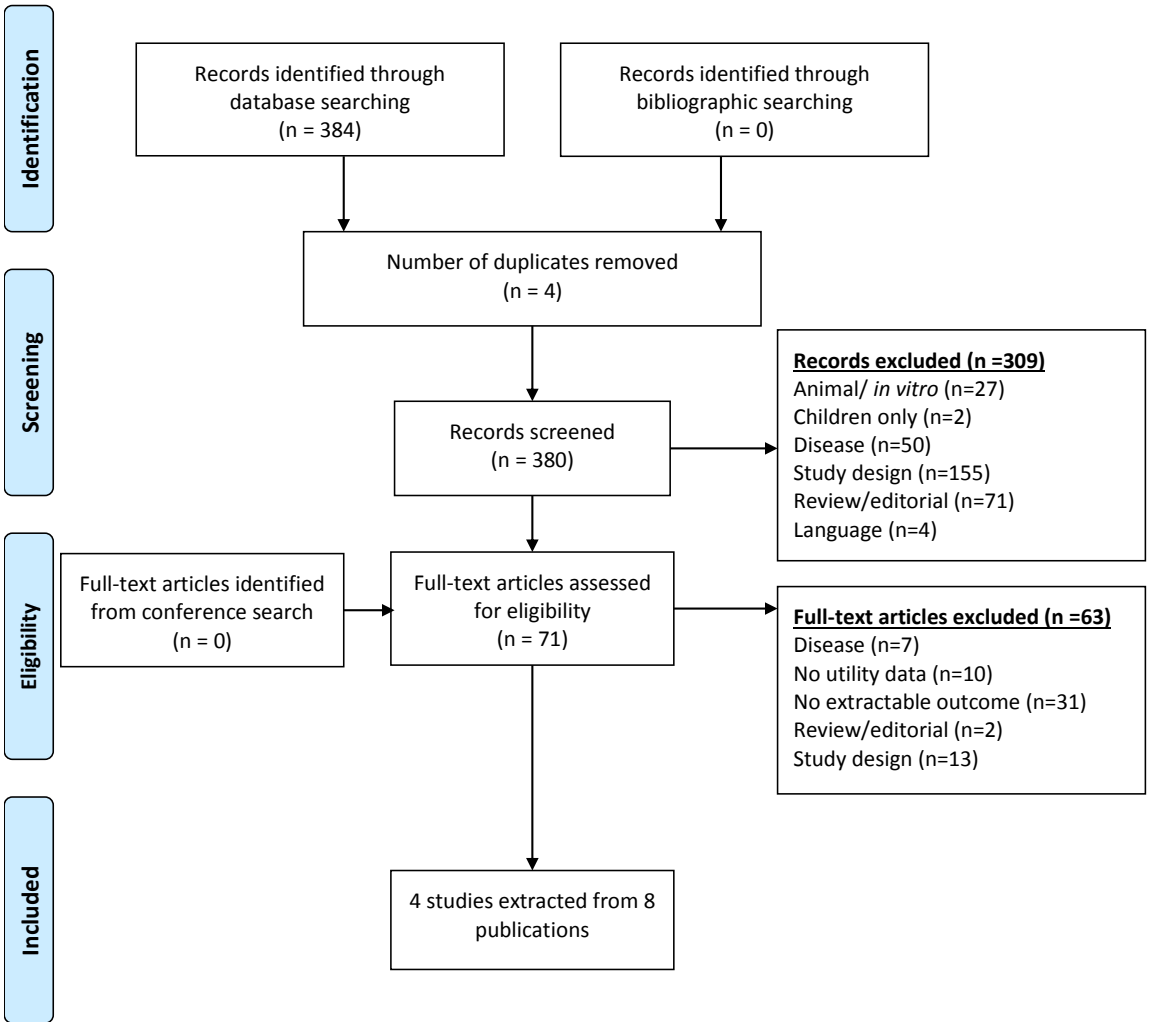
Description of the identified utility studies

Systematic database searches identified 384 records. Preliminary screening of abstracts and titles was performed on 382 records after removing four duplicates. After preliminary screening, 74 records were included. The majority of the records (155) were excluded on the basis of study type. Secondary screening was performed by reading the full texts of these records, after which eight publications were included and relevant data were extracted from four unique studies. Figure 40 presents the flow of studies identified for utility/HRQL review in a PRISMA diagram.

This is in addition to the six studies identified as part of the original SLR. These studies included: Brown et al. (2013), Fragoulakis et al. (2013), Hornberger et al. (2010), Khanna et al. (2006), Moller et al. (2011) and van Agthoven et al. (2004).[163-168]

As part of the ERG comments for the previous NICE submission (TA338), one abstract was highlighted that satisfied the search terms associated with this SLR. However, the study was not identified as it was not indexed in the databases searched. This abstract is included in the resubmission. Consideration of this study indicates that limited information is available, only an overall utility value (n=202, utility=0.65).[169] Furthermore, no differentiation is given pre- and post-progression, which does not allow for any differentiation of the impacts of treatment on utility. The further two studies suggested by the ERG did not satisfy the search terms as these considered a newly-diagnosed multiple myeloma population, which is not relevant for the POM indication.

Figure 40: PRISMA flow diagram for studies identified for utility/HRQL review



Key: NICE, National Institute for Health and Care Excellence; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

Study characteristics and results

A summary of study characteristics including study setting, patient population, cohort size, interventions/comparators, method of elicitation and utility/HRQL values are presented in Table 49. Across the available studies:

- Studies reporting directly obtained EQ-5D values indicated utilities of between 0.65 and 0.81 with the Cella study indicating increased utility with later lines of disease (0.76 for >3 prior lines vs 0.69 for 1 prior line)[168-170]

- Studies reporting mapped utilities reported similar outcomes[171, 172]
- Little impact was seen on utilities for either progressive disease or AEs within the mapped utilities reported in the Quinn study (decrement of <0.03 for both mappings), particularly when compared to the large drop in utility on progression reported in the Van Agthoven study (decrement of 0.155, which, whilst measured in a newly diagnosed population, has previously been used for RRMM modelling)[168, 171]

The patient populations included within the literature based studies is more similar to the available evidence for comparator therapies (i.e. in less refractory patient groups who are less heavily pre-treated) than the evidence that is available for POM+LoDEX.

When compared to the baseline utility of 0.59 reported by Palumbo et al. from the MM-003 study[173]; the utilities reported within the available literature are a clear indicator of how different the patient population in the MM-003 trial is in terms of its refractoriness and frailty to the other studies available in this disease area. This has implications in the interpretation of safety and effectiveness data for comparator therapies (which is only available from trials of less refractory and less frail patients). In particular, comparing safety data from the POM+LoDEX trials to the data available for other therapies which are in a less sick population could underestimate the impact of these therapies on patients (noting that the coefficient for AEs impact is much larger (0.076) in the MM-003 trial compared to the Quinn study (maximum 0.034).[171]

The decline in HRQL uponn disease progression reported in the MM-003 study (0.036 using EQ-5D) is similar in scale to that reported by Quinn et al (<0.03 in both mappings) indicating that progression may not be the factor with the largest impact on quality of life for patients with RRMM.[171] As the only paper reporting direct EQ-5D values in RRMM patients by health state, the values reported in Quinn et al. for progression-free and post progression disease were investigated in a scenario analysis.[171]

Table 49: Characteristics and results of the utilities/HRQL studies identified

<table>
<tr><th>Reference</th><th>Location</th><th>Population</th><th>Cohort size, N</th><th>Intervention and comparators</th><th>Utilities/HRQL included</th></tr>
<tr><td>Majer et al., 2015[172]</td><td>NR</td><td>Non progressing RRMM patients</td><td>686</td><td>PANO+BOR+DEX
BOR+DEX</td><td><u>EQ-5D scores at screening (mapped from EORTC QLQ-C30)</u>
ITT population (n=686) Mean (SD): 0.721 (0.201)
Prior IMiD+BOR+2LOT (n=124)[a] Mean (SD): 0.709 (0.201)</td></tr>
<tr><td>Quinn et al., 2015[171]</td><td>NR</td><td>RRMM patients with PFD and PD as health states</td><td>640</td><td>ELO+LEN+DEX
LEN+DEX</td><td><u>Descriptive summaries of mapped mean EQ-5D scores</u>
<table>
<tr><td colspan="3">Overall</td></tr>
<tr><th>Variables</th><th>Mapped from EORTC QLQ-C30+QLQ-MY20</th><th>Mapped from EORTC QLQ-C30</th></tr>
<tr><td>PFD</td><td>0.733</td><td>0.660</td></tr>
<tr><td>PD</td><td>0.710</td><td>0.652</td></tr>
<tr><td>With response</td><td>0.744</td><td>0.662</td></tr>
<tr><td>No response</td><td>0.704</td><td>0.654</td></tr>
<tr><td>No AE≥ Grade 3</td><td>0.740</td><td>0.664</td></tr>
<tr><td>≥1 AE≥ Grade 3</td><td>0.711</td><td>0.649</td></tr>
</table>
<u>GEE results for mapped mean(95% CI) EQ-5D scores for PFD</u>[b]
• Mapped from EORTC QLQ-C30+QLQ-MY20: 0.603 (0.545-0.661)
• Mapped from EORTC QLQ-C30: 0.649 (0.617-0.680)
<u>Impact of AEs for mapped EQ-5D data for patients who were off-treatment but not in PD</u>
• Utility decrement by direct measurement: 0.029
• Utility decrement by proxy measurement: 0.034</td></tr>
</table>

Reference	Location	Population	Cohort size, N	Intervention and comparators	Utilities/HRQL included
Cella *et al.*, 2015[170]	United states	RRMM patients	273	IMiD PIs IMiD+PIs	**Median EQ-5D scores** • **At baseline**: 0.69 • **At month 6** By lines of prior therapy 1: 0.69, 2: 0.69, >2: 0.76, 3: 0.76, >3: 0.76
Stewart *et al.*, 2015[174]	North America, Europe and the Middle East	Relapsed MM: 1 – 3 prior treatments	792	CFZ+DEX+LEN* DEX+LEN** * CFZ group ** Control group	**Mean (SD) EORTC-8D utility values based on UK tariffs at baseline (cycle1)** • Overall population (n=734): 0.7834 (0.1289) • CFZ group (n=370): 0.7851 (0.1266) • Control group (n=364): 0.7816 (0.1314)

Key: 2LOT, two prior lines of treatment; AE, adverse event; BOR, bortezomib; CFZ, carfilzomib; DEX, dexamethasone; EORTC-8D; EORTC eight dimension questionnaire; EORTC QLQ-C30, EORTC quality of life questionnaire core questionnaire C30; EORTC QLQ-MY20, EORTC multiple myeloma module; EQ-5D, EuroQol five dimensions questionnaire; GEE, generalised estimating equation; HRQL, health related quality of life; IMiD, immunomodulatory drug; ITT, intention to treat; LEN, lenalidomide; MM, multiple myeloma; NR, not reported; PANO, Panobinostat; PD, Progressive disease; PFD, progression-free disease; PIs, protease inhibitors; RRMM, relapsed and/ or refractory multiple myeloma; SD, standard deviation; UK, United Kingdom.

Notes: a Subgroup of patients received prior immunomodulatory drug and a bortezomib-containing regimen and had at least 2 prior lines of treatments. b GEE models provided direct estimation of health state utility values, controlling for confounders. c Percentages of responders defined as ≥10-point improvement from baseline for Global Health Status/QoL at each Cycle and all time points were compared between groups.

HRQL associated with aAEs

In the base case, the regression equation discussed earlier in this section was used to model the HRQL impact associated with AEs. AEs were included as an explanatory variable; this was measured by whether the patient was experiencing an AE at the time of the HRQL assessment, where the date of the HRQL assessments was matched with the occurrence of any AEs. To conduct this analysis the model required the proportion of patients experiencing an AE for each comparator; in the base case this is calculated based on the relative proportion of patients discontinuing due to AEs provided in the literature, the resulting per cycle rates are: 3.7%, 9.6%, 10.5% and 6.2% for POM+LoDEX, BTD, PANO+BOR+DEX and conventional chemotherapy, respectively.

This method was chosen rather than including utility decrements associated with each event reported in MM-003 to make use of the quality of life information reported in the MM-003 dataset and due to the lack of published utility decrements for each AE specific to multiple myeloma patients. It was considered that inclusion of the AE coefficient in the utility regression equation would capture a more realistic and representative impact of AE events on HRQL.

A scenario analysis considered using the utility decrements sourced from the literature applied to each AE event and weighted based on the recorded duration of each event. The duration-weighted decrements were multiplied by the AE rate per year for each event to provide overall AE-related utility decrements per year. The same utility decrements and durations of AEs were assumed for comparator treatments. Appendix 25 presents the duration of each AE reported in the MM-003 trial and the associated utility decrement sourced from published literature.

5.4.3 Health-related quality-of-life data used in cost-effectiveness analysis

Disease related characteristics

Within the model, base case data are taken directly from the MM-003 trial to calculate utilities. This source was selected as the only source reporting utilities within the correct patient population (post both BOR and LEN). A summary table of utilities is provided (Table 50) to show the difference between the utility options.

Table 50: Comparison of utilities by health status

Health status			MM-002: EQ-5D method	All trials: EQ-5D method	MM-003: EQ-5D method	MM-002: EORTC-8D method	All trials: EORTC-8D method	MM-003: EORTC-8D method	Quinn et al.[171]
Best overall response	**Within PD health state?**	**Hospitalisation or adverse event?**							
Response	x	X	0.75	0.77	0.76	0.76	0.77	0.77	0.733
Response	X	Adverse event	0.67	0.69	0.68	0.73	0.74	0.73	0.733
Stable disease	x	X	0.65	0.67	0.66	0.76	0.77	0.77	0.733
Stable disease	X	Adverse event	0.58	0.60	0.59	0.73	0.74	0.73	0.733
Progressive disease	x	X	0.61	0.63	0.62	0.76	0.77	0.77	0.733
Progressive disease	X	Adverse event	0.53	0.56	0.54	0.73	0.74	0.73	0.733
Stable disease	x	Hospitalisation	0.52	0.54	0.53	0.68	0.69	0.69	0.733
Response	✓	X	0.71	0.73	0.72	0.73	0.74	0.73	0.71
Response	✓	Adverse event	0.64	0.66	0.65	0.69	0.70	0.70	0.71
Stable disease	✓	X	0.62	0.64	0.63	0.73	0.74	0.73	0.71
Stable disease	✓	Adverse event	0.54	0.56	0.55	0.69	0.70	0.70	0.71
Progressive disease	✓	X	0.57	0.59	0.58	0.73	0.74	0.73	0.71
Progressive disease	✓	Adverse event	0.50	0.52	0.51	0.69	0.70	0.70	0.71
Stable disease	✓	Hospitalisation	0.48	0.50	0.49	0.65	0.66	0.65	0.71

Key: EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, EuroQoL five dimensions; PD, progressive disease.

Using the base case method (regression analysis) a patient's HRQL is not constant over time. The explanatory variables that change over time are disease progression, age and the number of AEs. The coefficients associated with these variables when using the EQ-5D are shown in Table 51. These demonstrate the effect on HRQL.

Table 51: Explanatory variables that change over time and their coefficients

Explanatory variable	Utility coefficient	
	Stepwise selection	Forward selection
Disease progression	-0.037	-0.036
Age (decades)	No coefficient	0.267
Age^2	No coefficient	-0.022
Adverse event(s)	-0.076	-0.077

As part of the previous NICE submission (TA338), the justification for assuming that the BORRs measured at 12 weeks, and the associated utility benefit, could be extrapolated and held constant for the remaining time in the model was requested.

This resubmission considers that the coefficients associated with BORRs have significant p-values, indicating that response at Week 12 is an important determinant of HRQL.

Assuming this utility benefit is maintained for the duration of the model was deemed to be the best reflection of the data used for the regression modelling. The BORR coefficients were obtained using all HRQL assessments, including when patients had stopped treatment. As such, the coefficients implicitly take into account the possibility of this utility impact changing over time. For example, at Week 12, being a responder might be associated with a utility increase much larger than the coefficient shown. If this benefit was not maintained in responding patients' future HRQL assessments the associated 'final' coefficient (i.e. that used in the regression model for 'response') will be lower accordingly.

In a scenario analysis, the BORRs are assumed equal between POM+LoDEX and the comparators after treatment discontinuation. An alternative scenario, using values obtained from Quinn et al. uses constant utility weights for pre- and post-

progression, and hence the HRQL is the same across all individuals in each health state.

Impact of oral vs non-oral treatments on HRQL

As discussed in Section 2.5, POM is an oral therapy and therefore can be self-administered at home, with only outpatient consultations during the course of treatment. The use of an oral agent such as POM reduces the treatment burden on both patients and carers, relative to IV and SC treatments. This is particularly important for patients with multiple myeloma who are often frail, elderly and have mobility problems related to their condition.[74, 86]

This benefit is unlikely to be fully reflected in the standard QALY measure as, while literature from chemotherapies has been used to include benefits of oral therapies in the cost-effectiveness modelling, the disease area these are taken from does not represent such a frail population.[61, 62] Patients with RRMM are likely to receive more benefit from the availability of oral treatment than previously considered patient populations. During the previous NICE submission (TA338), the patient experts highlighted the importance of having access to oral therapies, given that many current treatment options are given IV or SC. In the previous NICE submission (TA338), the Committee agreed that POM is easy to take and that a patient's HRQL is generally higher with oral therapy than with IV or SC therapy, although the degree of benefit was uncertain.[34]

A reduction in quality of life experienced by patients receiving IV or SC therapy has been included in the model based upon two previous NICE appraisals in small-cell lung cancer.[175, 176] These appraisals estimated a decrement of 0.025. As no multiple myeloma specific information is available, this decrement was included within the economic model while patients are receiving treatment with IV or SC therapies to account for the disruption to usual activities, pain and discomfort associated with non-oral therapies.

This decrement is likely to represent an underestimate of the impact in this population as, due to the frailty of patients with MM, greater disruption and impact to daily living is expected from repeated hospital admissions for administration of therapy. As such a scenario analysis is also explored increasing this decrement to

0.076, which is equal to the blanket AE decrement in the stepwise selection utility regression equation.

5.5 Cost and healthcare resource use identification, measurement and valuation

Appendix 26 presents a table with all cost and resource use parameters used to evaluate the cost-effectiveness of POM+LoDEX.

5.5.1 Resource identification, measurement and valuation studies

Previously, in TA338, resource use associated with haematologist consultations and routine tests and investigations were applied as health state specific frequencies.[90] The cost and resource use SLR conducted as part of this submission did not identify any treatment specific resource use. Monitoring of patients receiving POM+LoDEX was based on the SmPC. Differential resource use for transfusions and concomitant medications were based on the MM-003 trial, where the comparator resource use was assumed equal to the HiDEX arm. Feedback from the advisory board, conducted in March 2016, highlighted that resource use is likely to vary much more between treatments than was captured by the original submission, at the very least due to the differences in mode of administration (IV and SC treatments are associated with more outpatient visits, whereas oral treatments can be taken home). As such, it was considered important to include the differential resource use between treatments in the resubmission.

Advisors agreed to complete a resource use questionnaire to inform the economic model with inputs specific to UK clinical practice for the resubmission of POM+LoDEX in RRMM. The resource use questionnaire was sent to all participants from the advisory board (ten recipients) and six completed questionnaires were received. The blank questionnaire is presented in Appendix 26 alongside the averaged responses. The questionnaire included questions on dosing regimens, treatment specific resource use required per annum pre- and post-progression (on and off treatment) and for routine follow up care, concomitant medications, subsequent therapies and the resource use associated with treating each AE. The average reported across the completed questionnaires for resource use and

concomitant medications were implemented within the economic model. Clinical expert input indicated a drop in resource use requirements beyond administration for POM+LoDEX vs BTD and PANO+BOR+DEX including reductions in requirements for regular monitoring visits, blood transfusions and concomitant medication use.

In the previous NICE submission (TA338) resource use was primarily based on a first-line multiple myeloma population (TA228).[90] Furthermore, the cost and resource use SLR conducted as part of the previous appraisal did not identify any treatment specific or health state specific resource use for the population relevant to POM. Therefore, the inclusion of UK data considering the relevant population for POM is a significant improvement in this resubmission.

5.5.2 Intervention and comparators' costs and resource use

Treatment costs

The unit costs associated with treatment acquisition are shown in

Table 52 at list price. A PAS is in place for POM that reduces the net price from the list price of £8,884 to [redacted]. A PAS is also in place for PANO, but as this is confidential, this has not been included and comparisons are presented at list price.

Table 52: Unit costs associated with treatment acquisition

Therapy	Unit dose (mg)	Pack size	Unit cost including any PAS	Source
POM	1,2,3 or 4	28	[redacted]	MIMs, accessed March 2016. Celgene PAS.
DEX	2	100	£50.31	eMit April 2016 (NPC Code DFN010).
	2	50	£27.76	eMit April 2016 (NPC Code DFN018)
BEN	25	1	£69.45	MIMs accessed March 2016; bendamustine hydrochlor 25mg vial, 5=£347.26
	100	1	£275.81	MIMs accessed March 2016; bendamustine hydrochlor 100mg vial, 5=£1,379.04
THAL	50	28	£298.48	MIMs accessed March 2016; thalidomide, 50mg cap, 28=£298.48
PANO	20	6	£4,656	MIMs accessed April 2016; panobinostat 20mg red cap
BOR	3.5	1	£762.38	MIMs accessed June 2016; 3.5mg powder in vial
CYC	50	100	£139.00	MIMs accessed June 2016; 50mg tab
Subsequent therapies (scenario analysis only)				
Melphalan	2	25	£45.38	MIMs accessed April 2016; melphalan 2mg tab 25=£45.38
Prednisolone	5	28	£0.24	eMIT accessed June 2016; DFC008
CYC	50	1	£9.00	eMIT accessed June 2016
	1000	1	£16.28	
	2000	1	£27.89	

Key: BEN, bendamustine; BOR, bortezomib; DEX, dexamethasone; eMIT, drugs and pharmaceutical electronic market information; MIMs, Monthly Index of Medical Specialties; THAL, thalidomide.

Dosing – POM+LoDEX

Dosing data for POM and LoDEX were obtained from the MM-003, MM-002 and MM-010 patient level data: from MM-002 only in the comparison with BTD, from all trials for the comparison with PANO+BOR+DEX and from MM-003 only in the comparison with conventional chemotherapy.

Analysis of the data identified that some patients experienced non-protocol treatment interruptions due to AEs as specified within the SmPC. Dose interruptions lasting less than 28 days were not considered by the model, as t unused tablets cannot be recovered by the NHS if a patient does not complete a full pack. This is in line with the ERG comments from the previous NICE submission (TA338) and the feedback from the advisory board.

However, a proportion of dose interruptions lasted longer than 28 days, and so a full pack will be saved by the NHS – this cost saving is included within the economic model. In the base case the data indicated that 4.06%, 3.59% and 3.56% of packs would not be distributed to patients due to dose interruptions lasting longer than 28 days for the comparison of POM+LoDEX with BTD, PANO+BOR+DEX and conventional chemotherapy, respectively.

The mean dose of LoDEX per treatment cycle (28 days) was observed to fall over time. To ensure the mean dose each month is a reasonably reliable estimate, for all treatment cycles at which fewer than 10 patients received LoDEX the mean dose for the four prior cycles is applied. Wastage of DEX is not accounted for because its cost was calculated using the average milligram dose per cycle for simplicity. This is not likely to impact model results, due to its negligible acquisition cost.

Dosing - BTD

The dosing regimen for BTD was informed by the MUK-One trial, which provides the largest dataset for the BTD comparison:[162]

- BTD: 60 mg/m^2 BSA on Days 1 and 2 + 100mg thalidomide daily for 21 days in each 28 day cycle + 20mg dexamethasone 4 times per 28 days.

The model assumes that only whole vials of BEN and whole packs of THAL can be dispensed each cycle; therefore the total number of packs/vials required each treatment cycle is rounded up to capture the number of total packs/vials issued.

The dosing requirement for BEN (dosed using vials) were calculated using MM-003, MM-002 and MM-010 weight and height data and the method of moments technique.[177] First a lognormal distribution was derived for the BSAs within the trials based upon the individual trial observations, and this distribution was used to predict what proportion of patients require each number of vials to administer the required dose. This method is substantially more accurate in accounting for wastage than using mean BSAs. It has been assumed that patients only receive whole vials (no vial sharing), in line with clinical practice.

Wastage associated with DEX is not incorporated within the model; the costs of which were calculated using the average milligram dose per week.

Dosing – PANO+BOR+DEX

The dosing regimen for PANO+BOR+DEX was informed by the PANORAMA-2 trial and validated using real world data obtained from resource use questionnaires (see Appendix 26):[35]

- PANO+BOR+DEX: PANO dose of 20mg three times a week for 2 weeks in a 21 day cycle for eight cycles. BOR dose of 1.3 mg/m^2 twice weekly for 2 weeks in a 21 day cycle with 20mg dexamethasone 8 days per 21 days in the first cycle and 1.3 mg/m^2 once weekly for 2 weeks in a 21 day cycle with 20mg dexamethasone 4 days per 21 days for subsequent cycles.

The relative dose intensity (RDI) for each component of PANO+BOR+DEX from PANORAMA-2 was compared with the RDI from MM-003, MM-002 and MM-010 to estimate the relative proportion of whole packs/vials saved, giving an estimate of 4.43%. The dosing regimen and use of RDI to account for dose interruptions matched the NICE submission for PANO+BOR+DEX (TA380).[96] As per the approach for POM, the model assumes that only whole packs of PANO and whole vials of BOR can be dispensed each treatment cycle; therefore the total number of

packs/vials required each treatment cycle are rounded up to capture the number of total packs/vials issued.

The dosing requirement for BOR was calculated using MM-003, MM-002 and MM-010 weight and height data and the method of moments technique.[177]

Wastage associated with DEX is not incorporated within the model; the costs of which were calculated using the average milligram dose per week.

Dosing – conventional chemotherapies

The dosing regimen for conventional chemotherapies was informed by the original TA338 appraisal and validated using real world data obtained from resource use questionnaires (see Appendix 26):[146]

- CTD: CYC dose of 500mg once weekly. THAL dose starting at 100mg daily, increasing to 200mg daily (mean of 167mg daily used in the model). DEX dose of 160mg or 320mg total per cycle.

The model assumes that only whole packs of CYC and THAL can be dispensed each cycle; therefore the total number of packs required each treatment cycle is rounded up to capture the number of total packs issued. Wastage associated with DEX is not incorporated within the model; the costs of which were calculated using the average milligram dose per week.

Dosing – subsequent therapies

The dosing regimen for subsequent therapies was informed by the literature:

- MP: Melphalan dose of 0.25mg/ kg for 4 days, repeated every 4 weeks. PRED dose of 2mg/kg for 4 days, repeated every 4 weeks.[178-180]
- THAL+DEX: THAL dose of 200mg administered, on average, 6 days in a 28 day cycle. DEX dose of 40mg administered, on average, 6 days in a 28 day cycle[180]
- BTD: BEN dose of 60mg/m2 BSA on Days 1 and 2, repeated every 4 weeks. THAL dose of 100mg daily for 21 days, repeated every 4 weeks
- PANO+BOR+DEX: PANO dose of 20mg three times a week for 2 weeks in a 3-week cycle, repeated for 14 cycles. BOR dose of 1.3 mg/m^2 twice weekly for

2 weeks in a 21 day cycle, repeated for 8 cycles. BOR dose of 1.3 mg/m^2 once weekly for 2 weeks in a 21 day cycle for subsequent 6 cycles. DEX dose of 20mg for 8 days per 21 days, repeated for 8 cycles. DEX dose of 20mg dexamethasone 2 days per 21 days for subsequent 6 cycles.

- CYC: 600mg/m^2 for 4 days, repeat every 8 weeks on average[181]
- No active therapy: not applicable

Note that components of the subsequent therapy treatment basket are only included in a scenario analysis.

Administration costs

For treatments administered intravenously or subcutaneously, an administration appointment is required for each administration. In the base case, the costs associated with IV/SC administration visits were obtained from the recently published BOR first-line appraisal (TA311) and uplifted from 2011/12 costs to 2014/15 costs using Curtis and Burns (2015): £222.13 for the first visit and £312.87 for subsequent visits.[89, 182] A scenario analysis costed administration visits using an outpatient clinical haematologist appointment sourced from the NHS reference costs: £154.05.

The cost of a full blood count is also included on top of the administration appointment cost for BOR and BEN. This is to account for the platelet count required prior to each dose.[12, 14]

Medical resource use costs

Resource use was obtained from resource use questionnaires (as described above). The average annual resource use associated with POM+LoDEX, BTD, PANO+BOR+DEX, off active treatment (pre-progression) and off active treatment (post-progression) are shown in Appendix 26. Resource use associated with conventional chemotherapy is assumed equal to BTD. This is a reasonable assumption given the similarities in the component drugs.

The TA228 NICE review provides test specific costs. Where available, medical resource use associated costs were sourced from the TA228 NICE submission, these were uplifted to present values using the 2009/10 and 2014/15 hospital and

community health services inflation indices from Curtis (2015).[182] Remaining costs were sourced from the NHS reference costs 2014/15.[183]

Transfusions

Annual transfusion rates were obtained from the resource use questionnaire for each treatment; and assumed equal to BTD for conventional chemotherapies as a reasonable assumption. Transfusion rates are presented in Appendix 26. Weekly transfusion rates were estimated and multiplied by the cost of transfusions, the following unit costs were used (assumed to include the associated administration cost):

- Unit cost of one RBC unit: £121.85[184]
- Unit cost of a platelet transfusion: £196.96[184]

To accurately calculate the cost of each RBC transfusion, the mean number of transfusions per patient (1.50) and RBC units per patient (2.90) in a randomised UK and Australian study of the use of transfusions in haematological cancers were used.[185] From these values a figure of 1.94 RBC units per transfusion was obtained. This has been applied in the model base case as the number of units per transfusion, resulting in a cost per RBC transfusion of £235.83.

Concomitant medications

The resource use questionnaire provided estimates for annual concomitant medication use associated with POM+LoDEX, BTD, PANO+BOR+DEX, off active treatment (pre-progression) and off active treatment (post-progression). Although differences were observed across the advisors' responses, no difference was observed between treatments or between pre- and post-progression, with the exception of G-CSF use.

Therefore, the base case model considers only the use of G-CSF as it is assumed all other concomitant medication use will be equal across comparator treatments. The average of annual G-CSF use was estimated across the six clinicians for each of the active comparators and for the off active treatment health state (Table 53). Annual G-CSF use was converted into a weekly cycle rate and costed assuming patients

were treated with filgrastim (Neupogen®). Dosing and cost information was sourced from MIMs (accessed June 2016).

Table 53: Concomitant medication use

	POM	BEN	PANO+ BOR+D EX	Off active treatment (pre-progression)	Off active treatment (post-progression)	Cost
Annual G-CSF use	28.25	35.00	33.00	1.60	7.00	£16.81 per dose (MIMs; accessed June 2016)

Key: BEN, bendamustine; BOR, bortezomib; DEX, dexamethasone; G-CSF, granulocyte-colony stimulating factor; PANO, panobinostat; POM, pomalidomide.

Subsequent therapies

Any surviving patient can discontinue treatment. The use of the clinical outcome TTF allows for treatment discontinuation prior to disease progression. In the base case, analysis no subsequent therapies were included following discontinuation, due to the even larger uncertainty of treatments used beyond the POM setting. Furthermore, the efficacy of various subsequent treatment therapies is already included in the OS curves for POM+LoDEX, BTD, PANO+BOR+DEX and HiDEX (used as a proxy for conventional chemotherapy) as subsequent therapies were given in line with local treatment practices in each of these data sources. However, this assumption is explored in a scenario analysis.

The scenario analysis considers two alternate sources of subsequent therapy distribution:

- Fifth-line therapies following second-line BOR and third-line LEN, as per current NICE guidance, are obtained from the Haematological malignancy research network (HMRN) registry and are assumed to represent the typical treatment mix after discontinuation of either POM or comparator treatments.[186]
- Fifth-line therapies following second-line BOR and third-line LEN are based on clinician response to the resource use questionnaires.

Subsequent therapy information was not reported within the MUK-one dataset and progression date was not logged in the Tarant dataset; of the five patients who survived post progression in the Gooding dataset only one patient received subsequent treatment (with BEN).

Subsequent therapies from the HMRN registry

The HMRN registry (2013) provided data regarding treatments given at fifth line following second-line BOR and third-line LEN (as per the current clinical pathway).[9, 186] Treatments included in the HMRN registry included MP, THAL+DEX and no active therapy. Following discontinuation, surviving patients go on to receive a weighted average subsequent therapy. Subsequent therapy lasts for a maximum duration of 17 weeks based upon data on file (HMRN). Patients who survive for longer than this duration are assumed to receive no further therapy; therefore patients incur no treatment costs following 17 weeks of subsequent therapy.

[186]This information was used to cost a subsequent mix of anti-myeloma therapies that patients might receive following the discontinuation of fourth-line treatment (Table 54). Subsequent therapies are costed using a mean cost per week.

Table 54: Subsequent therapy HMRN distribution

Treatment	HMRN distribution of fifth-line treatment
MP	5.9%
No active therapy	76.5%
THAL+DEX	17.6%
Key: DEX, dexamethasone; HMRN, Haematological Malignancy Research Network; MP, melphalan and prednisolone; THAL, thalidomide.	

The dosing regimens for MP and THAL+DEX were obtained from Ludwig et al. (2009). Administration of THAL is associated with daily thromboprophylaxis treatment.[187] No administration costs are included in this weighted average cost because all of the above therapies are oral. It was assumed that no costs are associated with receiving no active treatment. As such the weekly drug cost associated with subsequent treatment in this scenario: is £20.74.

Subsequent therapies obtained from the resource use questionnaire

The resource use questionnaire provided data regarding treatments given at fifth line following second-line BOR and third-line LEN (as per the current clinical pathway) for patients treated with POM+LoDEX, BTD or PANO+BOR+DEX at fourth line (Table 55).[9] Treatments included BTD, PANO+BOR+DEX, THAL-based regimens, CYC-based regimens and no therapy. Within the model following discontinuation, surviving patients go on to a weighted average cost based upon the subsequent therapies indicated by the experts. Subsequent therapy is assumed to last for a maximum duration of 17 weeks based upon data on file (HMRN). Patients who survive for longer than this duration are assumed to receive no further therapy; therefore patients incur no treatment costs following 17 weeks of subsequent therapy. The type of fifth-line treatment associated with conventional chemotherapies was assumed equal to BTD (as these patients also will not have received PANO+BOR+DEX).

Table 55: Subsequent therapy, resource use questionnaire distribution

	After discontinuation of:		
	POM+LoDEX	**BTD**	**PANO+BOR+DEX**
BTD	21.7%	N/A	28.3%
PANO+BOR+DEX	33.3%	35.0%	N/A
THAL-based	1.7%	0%	1.7%
CYC/steroids	3.3%	6.7%	5.0%
No treatment	40.0%	58.3%	65.0%

Key: BOR, bortezomib; BTD, bendamustine + thalidomide + dexamethasone; CYC, cyclophosphamide; DEX, dexamethasone; LoDEX, low-dose dexamethasone; PANO, panobinostat; POM, pomalidomide; THAL, thalidomide.

The dosing regimens used for subsequent treatment with BTD and PANO+BOR+DEX were assumed equal to the dosing regimens used for these treatments as a comparator to POM+LoDEX. THAL-based regimens are costed using THAL+DEX; the dosing regimen for THAL+DEX was obtained from Ludwig et al.[180] The CYC-based regimen is assumed equal to the CYC dose in Lenhard et

al.[181] Administration costs are applied for each administration of IV treatment and the cost of daily thromboprophylaxis associated with THAL is included where relevant. It is assumed that no costs are associated with receiving no active therapy. As such the weekly drug costs associated with subsequent treatment in this scenario are:

- £1,127 per cycle after discontinuation of POM+LoDEX
- £1,068 per cycle after discontinuation of BTD
- £145 per cycle after discontinuation of PANO+BOR+DEX
- £1,068 per cycle after discontinuation of CTD (assumed same as BTD)

Terminal care costs

The base case model considers the impact of using the Kings Fund's estimate of £5,363 as an average cost for the last 8 weeks prior to a patient dying.[188] This is applied in the model as a one off cost when a patient dies.

As a scenario analysis the terminal care usage stated by the advisory board conducted for the previous submission as: 20% of patients use hospital services, 40% use hospice services and 40% use home services is included.[106] Costs per day by setting were obtained from the National Audit Office (2008); these were multiplied by seven in order to obtain weekly costs, then uplifted by the hospital and community health services inflation indices in Curtis (2015) to give the following terminal care unit costs:[182, 189]

- Hospital setting : £1,772.45 per week
- Hospice: £1,057.58 per week
- Community/home: £223.69 per week

The weighted average cost per week was calculated to be £867, which is applied in the model as a one-off cost when a patient dies.

5.5.3 Health-state unit costs and resource use

Table 56 describes each of the costs associated with each health state for POM+LoDEX compared with BTD, PANO+BOR+DEX and conventional

chemotherapies. Resource use requirements per health state from the resource use questionnaires can be found in Appendix 26.

In each health state the model calculates the proportion of patients on therapy. It then applies the appropriate input derived from the MM-003 trial data and resource use questionnaires in order to calculate the proportion of patients undergoing hospitalisation, AEs, medical resource use and costs accordingly. This method is the same for both pre- and post-progression, but costs are weighted differently according to the proportion of patients undergoing each treatment.

The weighted average cost per week of end-of-life care is applied to all patients who enter the death health state as a one-off cost. This is therefore not strictly incurred in the death state, but upon entry into the death state.

Table 56: A breakdown of costs in each health state

Health states	Items	Costs
Pre-progression (typically on treatment)	Technology (cost per cycle)	POM: At list price from £8,565 to £8,884 (dependent on dose interruptions experienced in the cycle) [redacted] DEX: £5.07 to £8.63 (dependent on mg per cycle based on MM-003) BEN: £690.52 every 4 weeks THAL: £596.96 every 4 weeks DEX: £20.17 every 4 weeks PANO: £4,656 every 3 weeks for 14 cycles BOR: £2,287.14 every 3 weeks (first 8 cycles) BOR: £1,524.76 every 3 weeks (subsequent 6 cycles) DEX: £40.34 every 3 weeks (first 8 cycles) DEX: £10.09 every 3 weeks (subsequent 6 cycles) CYC: £139.00 every 4 weeks THAL: £1,193.92 every 4 weeks DEX: £60.52 every 4 weeks

	Monitoring and tests (cost per cycle)	POM+LoDEX: £63.80 per cycle BTD: £150.36 per cycle PANO+BOR+DEX: £185.30 per cycle Pre-progression off treatment: £101.09 per cycle Post-progression off treatment: £142.23 per cycle
	Transfusions (unit cost)	Platelet transfusion: £196.96 RBC Transfusion: £235.83
	Concomitant Medications (cost per cycle)	POM+LoDEX: £71.43 per cycle BTD: £83.50 per cycle PANO+BOR+DEX: £80.08 per cycle Off active treatment (pre-progression): £5.16 per cycle Off active treatment (post-progression): £21.45
	Adverse events (cost per cycle)	POM+LoDEX: £32.16 per cycle BTD: £86.35 per cycle PANO+BOR+DEX: £94.20 per cycle Conventional chemotherapies: £54.18 per cycle
Post-progression (subsequent treatment)	Fifth line treatment	No cost in the base case analysis; £20.74 per week in scenario analysis considering HMRN data and £1,188, £1,171, £95 and £1,171 per week in scenario analysis considering the resource use questionnaire for patients discontinuing POM+LoDEX, BTD, PANO+BOR+DEX and conventional chemotherapies
Death	Terminal Care	£5,363 lump sum applied on death. A scenario analysis considers £867as a lump sum applied on death.
Key: BOR, bortezomib; BTD, bendamustine, thalidomide and dexamethasone; DEX, dexamethasone; LoDEX, low-dose dexamethasone; PANO, panobinostat; PAS, patient access scheme; POM, pomalidomide; RBC, red blood cell.		

5.5.4 Adverse reaction unit costs and resource use

The cost of an AE is assumed to depend on whether the event is actively treated and, if so, on the setting in which care is provided (Appendix 27). These data were obtained from the resource use questionnaires (explained above). Where no data were available, reasonable assumptions were made. The unit cost of an event is the cost of its treatment weighted by the proportion of cases treated and care setting (Appendix 27).

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of base-case de novo analysis inputs

Appendix 28 summarises the variables applied in the economic model and references to the section in the submission where it is explained in more detail.

In line with the NICE reference case, the model considers a UK treatment provider's perspective and discounts costs and QALYs using a 3.5% discount rate. Results are presented over a 15-year time horizon.

Where possible, the totality of clinical trial data is utilised. However, due to significant heterogeneity in the patient populations across the data, it was not appropriate to include all trial data in all comparisons.

For the comparison of POM+LoDEX with BTD, the MM-002 trial was considered to be the most relevant source of clinical data; MM-002 represents the least refractory population of the POM+LoDEX trials. However, patients in this trial are still significantly more refractory to LEN than those in the BTD data (78% vs 20%). Therefore, results are likely to be biased in favour of BTD.

For the comparison of POM+LoDEX with PANO+BOR+DEX, all clinical data associated with POM+LoDEX was utilised. For the comparison of POM+LoDEX with conventional chemotherapies the trial data from MM-003 were utilised, this represents a standalone within trial comparison.

For consistency, for each comparison the relevant clinical data were considered for all inputs in the model; including: dosing and AEs.

5.6.2 Assumptions

Table 57 details the assumptions used in the economic model and provides a justification for each one. Section 5.8 lists the assumptions that are varied in scenario analyses.

Table 57: Base case assumptions

Assumption	Justification	Reference in submission
We assume that the differences in patient characteristics across trials when comparing to BTD and PANO+BOR+DEX can be at least partially accounted for via covariate adjustment	Assumption required in order to enable comparison given that RCT data is not available. Comparison biases in favour of comparator treatments given that the POM+LoDEX trial population is considerably more heavily pre-treated.	Section 4.10
We assume that the efficacy and safety results observed in the MM-003 study for POM+LODEX versus HiDEX are equivalent for comparison to conventional chemotherapy regimens.	Similar to conventional chemotherapy regimens; HiDEX at the dosing regimen used within the MM-003 trial, is effective for a limited number of patients (response rate, PR or better, of 11% in the MM-003 trial) but with a significant toxicity. Available data supports this.	Section 4.10
We assume that the proportional hazards assumption allows for reasonable comparison for BTD and PANO+BOR+DEX compared with POM+LoDEX	Visual assessment of the fitted curves compared to the KM curves provide a good fit. LCHP plots demonstrate that this assumption can be considered reasonable in the majority of comparisons. Impact of assumption is limited and likely biased against POM+LoDEX when looking at PFS curves for comparison to PANO+BOR+DEX	Section 5.3
We assume that all patients receive the fixed dose regimen associated with PANO+BOR+DEX	This is a conservative assumption and is in line with the TA380 NICE appraisal	Section 5.3
We assume that, prior to response being modelled at 12 weeks, that all patients are in the pre-progression health state and have a stable disease relative to response	Response was measured at 12 weeks in the clinical trials. A scenario analysis considers modelling response from Cycle 0.	Section 5.3
We assume that the utility benefit associated with response is maintained for the duration of the model	This was deemed to be the best reflection of the data used for the regression modelling. The BORR coefficients were obtained using all HRQL assessments, including when patients had stopped treatment. As such, the coefficients implicitly take into account the possibility of this utility impact changing over time. For example, at Week 12, being a responder might be associated with a utility increase much larger than the coefficient shown. If this benefit was not maintained in responding patients' future HRQL assessments the associated 'final' coefficient (i.e. that used in the regression model for 'response') will be lower accordingly. In a scenario analysis, the BORRs are assumed equal between POM+LoDEX and the comparators after treatment discontinuation.	Section 5.3

Assumption	Justification	Reference in submission
We assume that AE rates are proportional to the relative proportion of patients discontinuing from treatment due to an AE	Due to inconsistencies in reporting AEs across all datasets, this was considered to make the most use of available data in determining comparable AE rate estimates. In a scenario analysis AE rates associated with comparators are obtained from the relative tolerability profile discussed by the clinicians in the advisory board.	Section 5.4
We assume that the quality of life impact associated with AEs is captured within the original utility regression estimated using MM-003 data.	This method was chosen rather than including utility decrements associated with each event reported in MM-003 to make use of the quality of life information reported in the MM-003 dataset and due to the lack of published utility decrements for each AE specific to multiple myeloma patients. It was considered that inclusion of the AE coefficient in the utility regression equation would capture a more realistic and representative impact of AE events on HRQL. A scenario analysis considers the impact on results of modelling HRQL associated with AE events using decrements available in the literature.	Section 5.4
We assume that only whole packs can be recovered and that only whole packs can be used.	This is in line with the response to the previous NICE submission (TA338) whereby it was commented that recovering individual tablets was not likely to hold in clinical practice.	Section 5.5
We assume there is no vial sharing for BOR	In line with clinical practice	Section 5.5
We assume the hospitalisation rates of the comparators are equal to the HiDEX arm of the MM-003 trial	Hospitalisation rates for the comparator arm were obtained from the MM-003 study control arm as a conservative assumption. Data from the Gooding et al. dataset were assessed; however, these showed notably higher hospitalisation rates than the MM-003 study (0.088 per week); use of this data is considered in a scenario analysis.[37] Use of the trial data therefore provides a conservative estimate and makes use of the larger dataset.	Section 5.5
We assume that the resource use associated with conventional chemotherapies is the same as that for BTD	This is a reasonable assumption given the similarity of the components included within the regimens.	Section 5.5
We assume that the only difference in concomitant medication use is in G-CSF use	This is validated by the resource use questionnaire completed by 6 clinicians attending the advisory board.	Section 5.5
We assume no subsequent therapies following discontinuation of treatment	This assumption is explored in a scenario analysis	Section 5.5

5.7 Base-case results

5.7.1 Base-case incremental cost-effectiveness analysis results

Three sets of base case model results are presented, comparing POM+LoDEX with BTD, PANO+BOR+DEX and conventional chemotherapies in turn. Full incremental analysis is not presented as the clinical trial dataset used for comparison for POM+LoDEX is different for each comparison it is therefore not possible to provide comparison versus a consistent estimate for POM+LoDEX.

Comparison with BTD

The base case results for POM+LoDEX versus BTD are shown in Table 58. Results were subject to discounting at a rate of 3.5% per annum. POM+LoDEX is associated with a gain of 0.67 incremental life years and [redacted] incremental QALYs per patient, and an increase in overall costs of [redacted] per patient. The ICER is £39,273 per additional QALY gained meaning that POM+LoDEX represents a highly cost-effective treatment option when considered against the £50,000 WTP threshold for treatments meeting end of life criteria.

Comparison with PANO+BOR+DEX

The base case results for POM+LoDEX versus PANO+BOR+DEX are shown in

Table 59. Results were subject to discounting at a rate of 3.5% per annum. POM+LoDEX is associated with a reduction of 0.53 incremental life years and [redacted] incremental QALYs per patient, and a reduction in overall costs of [redacted] per patient. The resulting ICER (£176,406) lies in the south west quadrant of the cost-effectiveness scatter plot, therefore it is sensible to interpret results based on the net monetary benefit (NMB) rather than the ICER. The NMB is estimated to be £42,475 when a willingness to pay threshold of £30,000 per QALY is considered.

Comparison with conventional chemotherapies

The base case results for POM+LoDEX versus conventional chemotherapies are shown in

Table **60**. Results were subject to discounting at a rate of 3.5% per annum. POM+LoDEX is associated with a gain of 0.68 incremental life years and [redacted]

incremental QALYs per patient, and an increase in overall costs of [redacted] per patient. The resulting ICER is £45,164.

Table 58: Base case results – vs BTD

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
BTD	[redacted]	1.14	[redacted]	-	-	-	-
POM+ LoDEX	[redacted]	1.81	[redacted]	[redacted]	0.67	[redacted]	£39,273

Key: BTD, bendamustine, thalidomide and dexamethasone; ICER, incremental cost-effectiveness ratio; LoDEX, low-dose dexamethasone; POM, pomalidomide; QALYs, quality-adjusted life years.

Table 59: Base case results – vs PANO+BOR+DEX

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	NMB (£) versus baseline (QALYs)
PANO+BOR+DEX	[redacted]	2.25	[redacted]	-	-	-	-
POM+ LoDEX	[redacted]	1.71	[redacted]	[redacted]	-0.53	[redacted]	£42,475

Key: BOR, bortezomib; DEX, dexamethasone; PANO, panobinostat; ICER, incremental cost-effectiveness ratio; LoDEX, low-dose dexamethasone; POM, pomalidomide; QALYs, quality-adjusted life years; NMB, net monetary benefit.

Table 60: Base case results – vs conventional chemotherapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Conventional chemotherapy	[redacted]	0.78	[redacted]	-	-	-	-
POM+ LoDEX	[redacted]	1.45	[redacted]	[redacted]	0.68	[redacted]	£45,164

Key: ICER, incremental cost-effectiveness ratio; LoDEX, low-dose dexamethasone; POM, pomalidomide; QALYs, quality-adjusted life years.

5.7.2 Clinical outcomes from the model

Table 61 displays the clinical outcomes and the model outcomes for the three main outcome measures; OS, PFS and TTF. Clinical outcomes are presented for all base case comparisons assuming the base case parametric curve fits and adjusting covariates using the CGP method (see Section 5.3).

The median OS, PFS and TTF are comparable and consistent with the respective observed clinical outcomes reported in the trial datasets and in the literature.

Table 61: Comparison of the clinical outcomes with the base case model outcomes

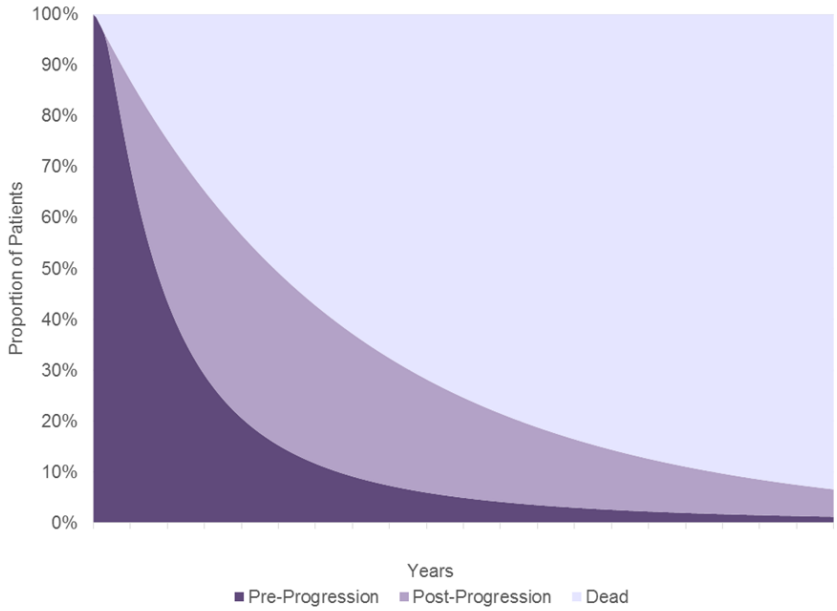
Clinical outcome (values in years)	POM+LoDEX (MM-002)		POM+LoDEX (MM-003, MM-002 and MM-010)		POM+LoDEX (MM-003)		BTD (base case: Gooding et al., Tarant et al. and MUK-One)		PANO+BOR+DEX (base case: PANORAMA-2)		Conventional chemotherapies (assumed same as the HiDEX arm in MM-003)	
	Observed (95% CI)	Modelled medians	Observed (95% CI)	Modelled medians	Observed (95% CI)	Modelled medians	Observed (unadjusted) (95% CI)	Modelled (adjusted)	Observed (95% CI)	Modelled	Observed (95% CI)	Modelled
Median OS (months)	16.5	14.26	13.1 (MM-003) 16.5 (MM-002) 11.9 (MM-010)	13.11	13.1	11.73	8.2 (MUK-One)	8.97	17.5 (10.8-25.2)	16.79	5.7	6.21
Median PFS (months)	4.2	4.83	4.0 (MM-003) 4.2 (MM-002) 4.6 (MM-010)	4.37	4.0	3.68	3.3 (MUK-One)	3.68	5.4 (3.5-6.7)	3.68	1.9	1.84
Median TTF (months)	4.5	3.91	2.9 (MM-003) 4.5 (MM-002)	3.91	2.9	3.91	Not reported	2.99	Not reported	Not modelled	1.8	1.84
Adverse Events	Rates taken from trial and relevant literature.											

Key: BOR bortezomib; BTD, bendamustine, thalidomide and dexamethasone; CI, confidence interval; DEX dexamethasone; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; PANO, panobinostat; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; TTF, time to failure.

Markov traces

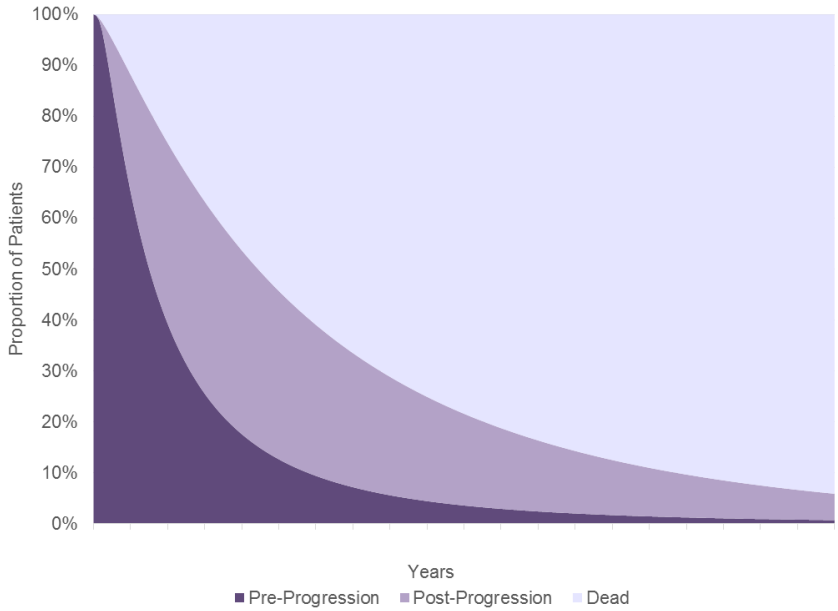
Markov traces are presented for the POM+LoDEX, BTD, PANO+BOR+DEX and conventional chemotherapies in Figure 41 to Figure 46.

Figure 41: Markov trace for POM+LoDEX patients (MM-002 only)



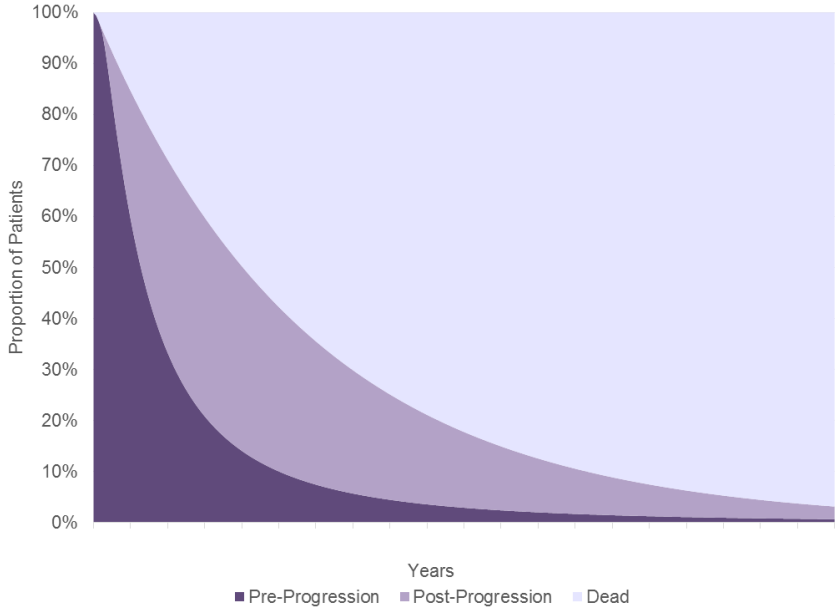
Key: LoDEX, low-dose dexamethasone; POM, pomalidomide

Figure 42: Markov trace for POM+LoDEX patients (MM-003, MM-002 and MM-010)



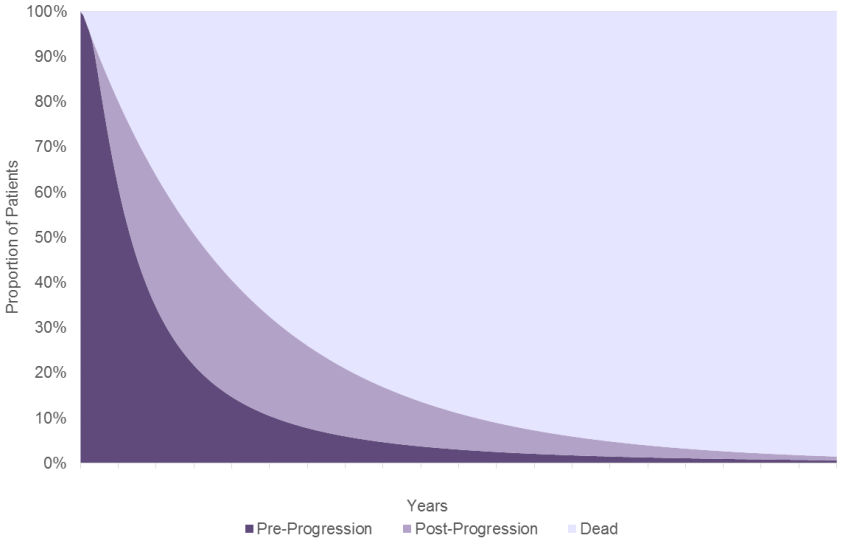
Key: LoDEX, low-dose dexamethasone; POM, pomalidomide

Figure 43: Markov trace for POM+LoDEX patients (MM-003 only)



Key: LoDEX, low-dose dexamethasone; POM, pomalidomide

Figure 44: Markov trace for BTD patients

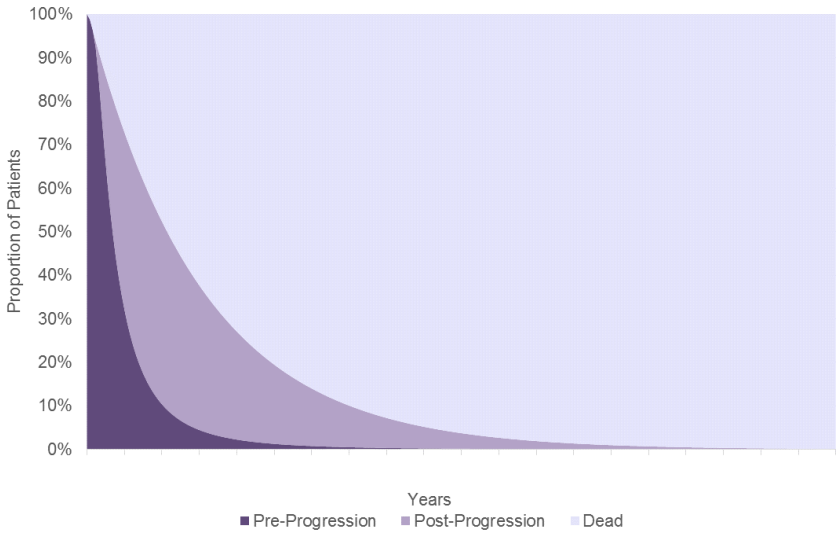


Key: BTD, bendamustine, thalidomide and dexamethasone

Figure 45: Markov trace for PANO+BOR+DEX patients

Key: BOR, bortezomib; DEX, dexamethasone; PANO, panobinostat.

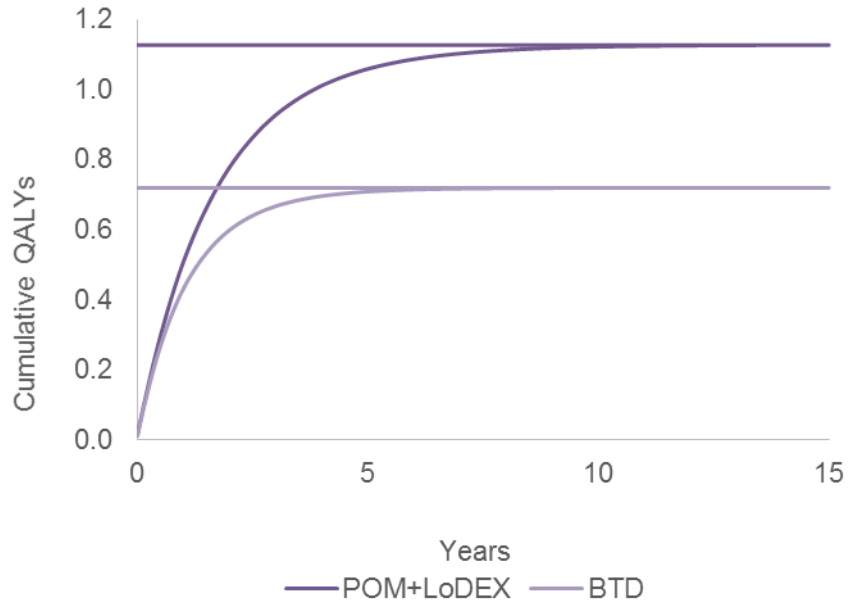
Figure 46: Markov trace for conventional chemotherapy patients



The accumulation of QALYs over time is shown in Figure 47, Figure 48 and Figure 49 for POM+LoDEX compared with BTD, PANO+BOR+DEX and conventional chemotherapies, respectively. QALYs were subject to discounting at a rate of 3.5% per annum. Compared with each of the comparators, the number of QALYs associated with POM+LoDEX at each cycle is consistently higher than the

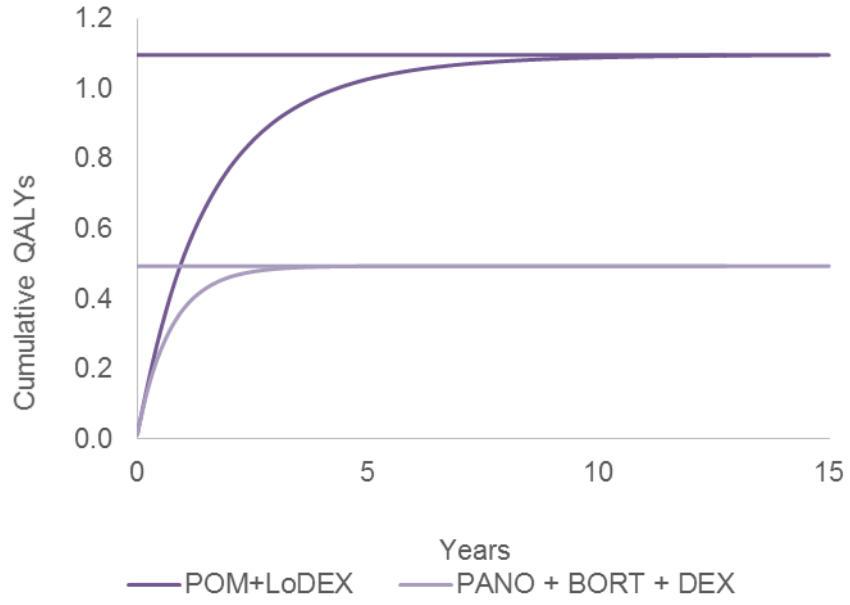
comparator treatment. The majority of QALYs are accrued within the first 5 years of the model.

Figure 47: Accumulation of QALYs; vs BTD



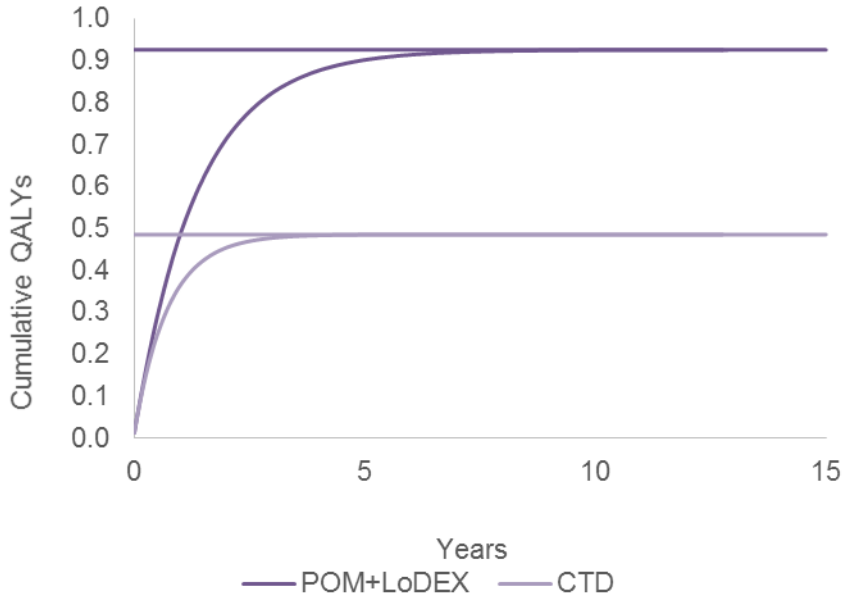
Key: BTD, bendamustine, thalidomide and dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide; QALYs, quality adjusted life years.

Figure 48: Accumulation of QALYs; vs PANO+BOR+DEX



Key: BOR bortezomib; DEX dexamethasone; LoDEX, low-dose dexamethasone; PANO, panobinostat; POM, pomalidomide; QALYs, quality adjusted life years.

Figure 49: Accumulation of QALYs; vs conventional chemotherapies



Key: CTD; Cyclophosphamide, thalidomide and dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide; QALYs, quality adjusted life years.

5.7.3 Disaggregated results of the base case incremental cost effectiveness analysis

Life years

The total life years gained by patients in each health state are shown below. Increases in survival are anticipated both pre and post progression in line with the mechanism of action of POM when compared to BTD and conventional chemotherapy. The modelled decrease in life years versus PANO+BOR+DEX is not considered to be clinically realistic and is rather thought to be a function of inability to adjust for the differences between trials (in particular PANORAMA 2 being conducted at an earlier line and at a time where multiple effective therapies that could be used subsequently were under development). The tables show the results for POM+LoDEX versus each comparator in turn.

Table 62: Life years – vs BTD

Outcome	POM+LoDEX	BTD	Increment
Pre-progression: Life Years	0.76	0.60	0.17
Post-progression: Life Years	1.05	0.55	0.51
Life Years: On treatment	0.62	0.48	0.13
Key: BTD, bendamustine, bortezomib and dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide; QALY, quality-adjusted life year.			

Table 63: Life years – vs PANO+BOR+DEX

Outcome	POM+LoDEX	PANO+BOR+DEX	Increment
Pre-progression: Life Years	0.66	0.54	0.12
Post-progression: Life Years	1.05	1.71	-0.65
Life Years: On treatment	0.62	0.40	0.22
Key: BOR, bortezomib; LoDEX, low-dose dexamethasone; DEX, dexamethasone; PANO, panobinostat; POM, pomalidomide; QALY, quality-adjusted life year.			

Table 64: Life years – vs conventional chemotherapies

Outcome	POM+LoDEX	Conventional chemotherapies	Increment
Pre-progression: Life Years	0.58	0.26	0.32
Post-progression: Life Years	0.87	0.51	0.36
Life Years: On treatment	0.44	0.23	0.21
Key: LoDEX, low-dose dexamethasone; POM, pomalidomide; QALY, quality-adjusted life year.			

QALYs

The following tables show incremental QALYs gained by health state. These values are from the base case where QALYs are calculated using utilities obtained from a regression equation using the MM-003 patient level data. QALYs are discounted using a 3.5% annual rate.

Table 65: Incremental QALYs by health state – vs BTD

Health state	QALYs intervention (POM+LoDEX)	QALYs comparator (BTD)	Increment	% Increment
Pre-progression	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	0.41	100.00%

Key: BTD, bendamustine, thalidomide and dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide; QALY, quality-adjusted life year.

Table 66: Incremental QALYs by health state – vs PANO+BOR+DEX

Health state	QALYs intervention (POM+LoDEX)	QALYs comparator (PANO+BOR+DEX)	Increment	% Increment
Pre-progression	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	-0.29	100.00%

Key: BOR, bortezomib; DEX, dexamethasone; LoDEX, low-dose dexamethasone; PANO, panobinostat; PANO, panobinostat; POM, pomalidomide; QALY, quality-adjusted life year.

Table 67: Incremental QALYs by health state – vs conventional chemotherapies

Health state	QALYs intervention (POM+LoDEX)	QALYs comparator (conventional chemotherapies)	Increment	% Increment
Pre-progression	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	0.44	100%

Key: LoDEX, low-dose dexamethasone; POM, pomalidomide; QALY, quality-adjusted life year.

Costs

Discounted total costs by health state between treatment arms are shown in Table 68. The majority of costs incurred by POM+LoDEX patients occur pre-progression, as patients will be off treatment following disease progression. This is evident in Table 69, showing the summary of predicted resource use by category of cost in the base case analysis, where the costs incurred by POM+LoDEX patients are primarily driven by drug costs.

Table 68: Incremental costs – vs BTD

Health state	Cost intervention (POM+LoDEX)	Cost comparator (BTD)	Increment	% Increment
Pre-progression	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	£16,022	100.00%

Key: BTD, bendamustine, thalidomide and dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide.

Table 69: Summary of predicted resource use by category of cost – vs BTD

Cost item	POM+LoDEX	BTD	Increment	Absolute increment	% Absolute increment
Therapy cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use, on treatment: pre progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use, off treatment: pre progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use, off treatment: post progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
total	[redacted]	[redacted]	£16,022	£16,022	100.00%

Key: BTD, bendamustine, thalidomide and dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide.

Table 70: Incremental costs – vs PANO+BOR+DEX

Health State	Cost intervention (POM+LoDEX)	Cost comparator (PANO+BOR+DEX)	Increment	% Increment
Pre-progression	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	-£51,075	100.00%

Key: BOR, bortezomib; DEX, dexamethasone; LoDEX, low-dose dexamethasone; PANO, panobinostat; POM, pomalidomide.

Table 71: Summary of predicted resource use by category of cost – vs PANO+BOR+DEX

Cost item	POM+LoDEX	PANO+BOR+DEX	Increment	Absolute increment	% Absolute increment
Therapy cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use, on treatment: pre progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use, off treatment: pre progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use, off treatment: post progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	£51,178	100.00%

Key: BOR, bortezomib; DEX, dexamethasone; LoDEX, low-dose dexamethasone; PANO, panobinostat; POM, pomalidomide.

Table 72: Incremental costs – vs conventional chemotherapies

Health state	Cost intervention (POM+LoDEX)	Cost comparator (conventional chemotherapies)	Increment	% increment
Pre-progression	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	£19,878	100.00%

Key: LoDEX, low-dose dexamethasone; POM, pomalidomide.

Table 73: Summary of predicted resource use by category of cost – vs conventional chemotherapies

Cost Item	POM+LoDEX	Conventional chemotherapies	Increment	Absolute increment	% Absolute increment
Therapy cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use, on treatment: pre progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use, off treatment: pre progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use, off treatment: post progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant Medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	£19,878	£19,878	100.00%
Key: LoDEX, low-dose dexamethasone; POM, pomalidomide.					

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

To characterise uncertainty in model inputs a PSA was performed for each comparator. PSA varies all inputs simultaneously, based upon their distributional information (see Section 5.3) and records a resulting ICER which may conceivably be the 'true' underlying ICER. The results of 1,000 PSA iterations are presented in the figures below. Cost-effectiveness planes show the incremental QALYs and costs of POM+LoDEX relative to the comparator in each case, and cost-effectiveness acceptability curves (CEACs) show the likelihood of POM+LoDEX cost-effectiveness at different willingness-to-pay thresholds.

The PSA included the uncertainty around the choice of parametric OS, PFS and TTF curves by selecting the choice of curve by sampling from the probability that each

parametric model is the best of the fitted parametric models using the AIC estimates (see Section 5.3). Different PSA runs therefore have different curve selections, dependent on the likelihood of each being the best fit to the data. This takes into account the fact that there is a chance that the base case curve choices are in fact suboptimal fits to the data. Uncertainty around the parameters of the selected curves was also included, as per standard PSA.

POM+LoDEX vs BTD

Results from the PSA including uncertainty around model selection are presented below. Mean incremental QALYs gained from POM+LoDEX was [redacted] (SD: 0.08; 95% CI: [redacted]). Mean incremental costs were [redacted] (SD: £1,796; 95% CI: [redacted]. The resulting probabilistic ICER from 1,000 iterations was £35,447 (comparable to the deterministic, base case ICER of £39,273).

Figure 50: Cost-effectiveness plane from 1,000 PSA iterations – vs BTD

Key: PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; BTD, bendamustine, thalidomide and dexamethasone

Based on these 1,000 PSA iterations, the CEAC (Figure 51) suggests that there is a 92.8% likelihood of POM+LoDEX cost-effectiveness at a willingness-to-pay threshold of £50,000/QALY (the end-of life threshold recommended by NICE).

Figure 51: Cost-effectiveness acceptability curve – vs BTD

Key: BTD, bendamustine, thalidomide and dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide

POM+LoDEX vs PANO+BOR+DEX

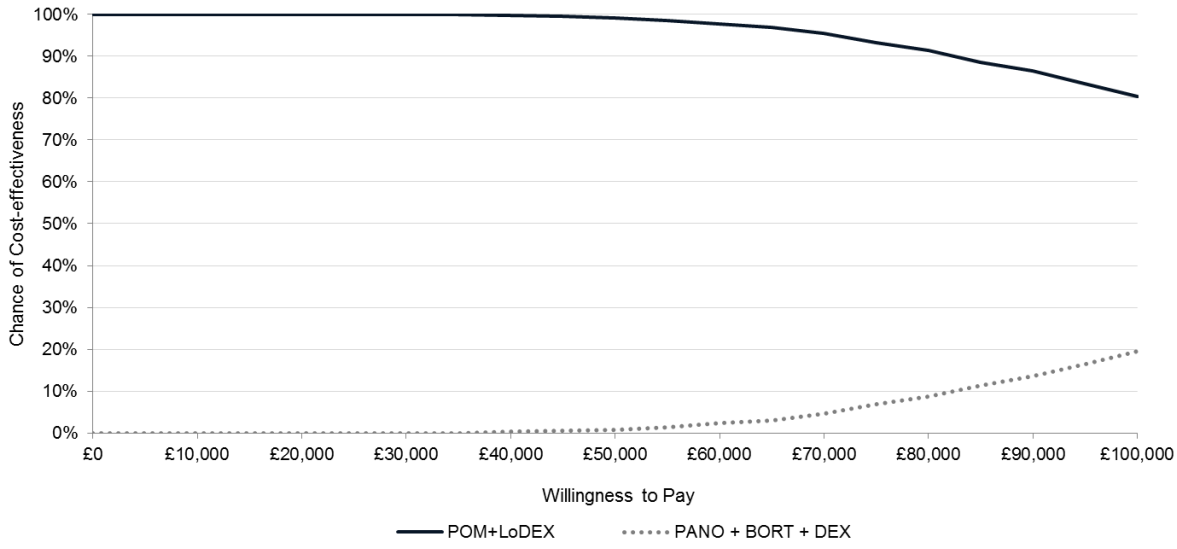
Results from the PSA including uncertainty around model selection, comparing POM+LoDEX with PANO+BOR+DEX, are presented below. Mean incremental QALYs gained from POM+LoDEX were [redacted] (SD: 0.27; 95% CI: [redacted]). Mean incremental costs were [redacted] (SD: £6,348; 95% CI: [redacted]. The resulting probabilistic ICER from 1,000 iterations was £164,842 (deterministic ICER of £176,406); NMB of £41,688 (deterministic NMB of £42,475).

Figure 52: Cost-effectiveness plane from 1,000 PSA iterations – vs PANO+BOR+DEX

Key: BOR, bortezomib; DEX, dexamethasone; PANO, panobinostat; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year

Based on these 1,000 PSA iterations, the CEAC (Figure 53) indicates that there is a 100% likelihood of POM+LoDEX cost-effectiveness at a willingness-to-pay threshold of £30,000/QALY (the threshold recommended by NICE).

Figure 53: Cost-effectiveness acceptability curve – vs PANO+BOR+DEX



Key: BOR, bortezomib; DEX, dexamethasone; PANO, panobinostat; LoDEX, low-dose dexamethasone; POM, pomalidomide

POM+LoDEX vs conventional chemotherapies

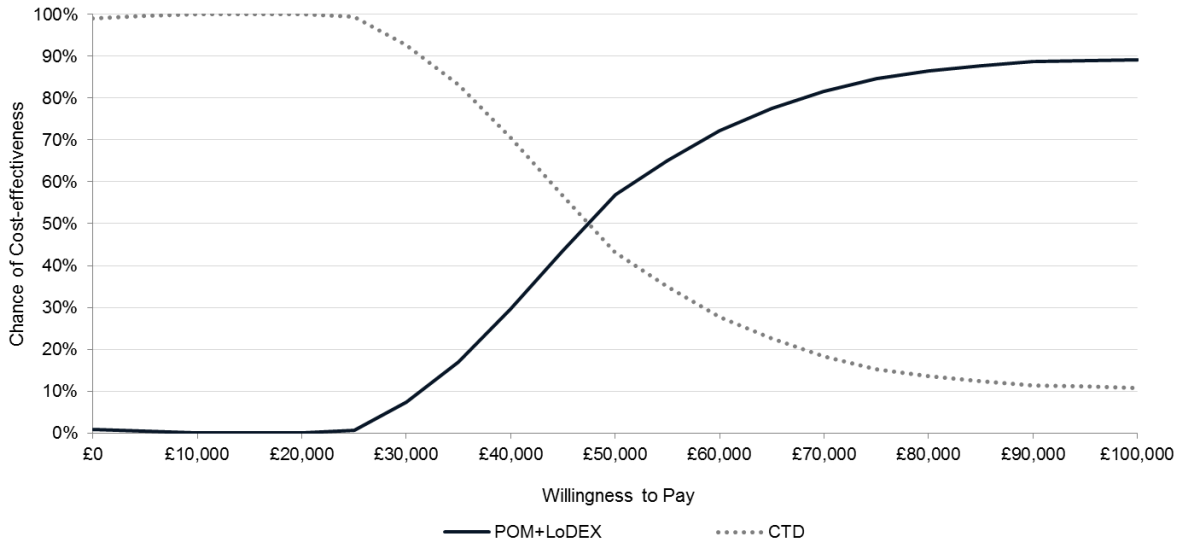
Results from the PSA including uncertainty around model selection, comparing POM+LoDEX with conventional chemotherapies, are presented below. Mean incremental QALYs gained from POM+LoDEX were [redacted] (standard deviation [SD]: 0.34; 95% CI:[redacted]). Mean incremental costs were [redacted] (SD: £5,483; 95% CI: [redacted]. The resulting probabilistic ICER from 1,000 iterations was £48,537 (similar to the deterministic ICER of £45,164).

Figure 54: Cost-effectiveness plane from 1,000 PSA iterations with uncertainty in curve selection accounted for – conventional chemotherapies

Key: PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years

Based on these 1,000 PSA iterations, the CEAC (Figure 51) suggests that there is a 56.9% likelihood of POM+LoDEX cost-effectiveness at a willingness-to-pay threshold of £50,000/QALY (the end-of life threshold recommended by NICE).

Figure 55: Cost-effectiveness acceptability curve with uncertainty in curve selection accounted for – conventional chemotherapies



Key: CTD, cyclophosphamide, thalidomide and dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide

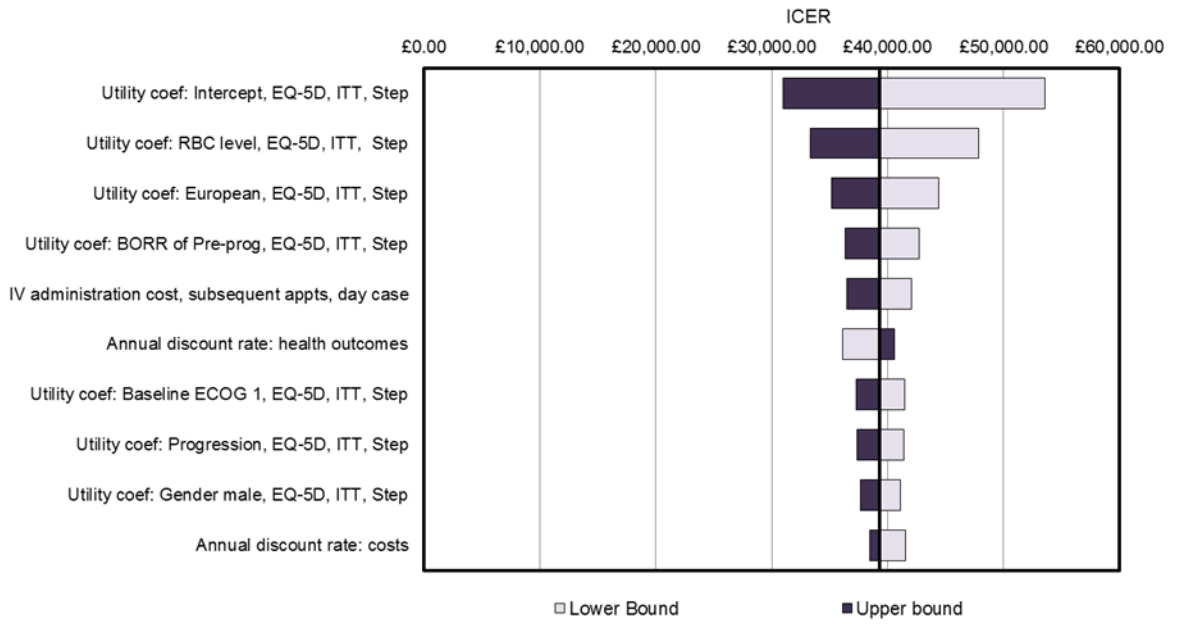
5.8.2 Deterministic sensitivity analysis

POM+LoDEX vs BTD

A series of one-way sensitivity analyses were performed to evaluate the sensitivity of the model ICER to individual inputs, holding all else constant. Distribution information used in the model is provided in Appendix 29. Model results were recorded after changing each input to its upper and lower bound value in turn.

Figure 56 presents a tornado diagram with parameters shown in descending order of ICER sensitivity. The parameters with the greatest impact on model outcomes included in the OWSA were the coefficients used within the regression analysis for utilities. The model is relatively insensitive to the majority of parameters.

Figure 56: Results of one-way sensitivity analysis – BTD

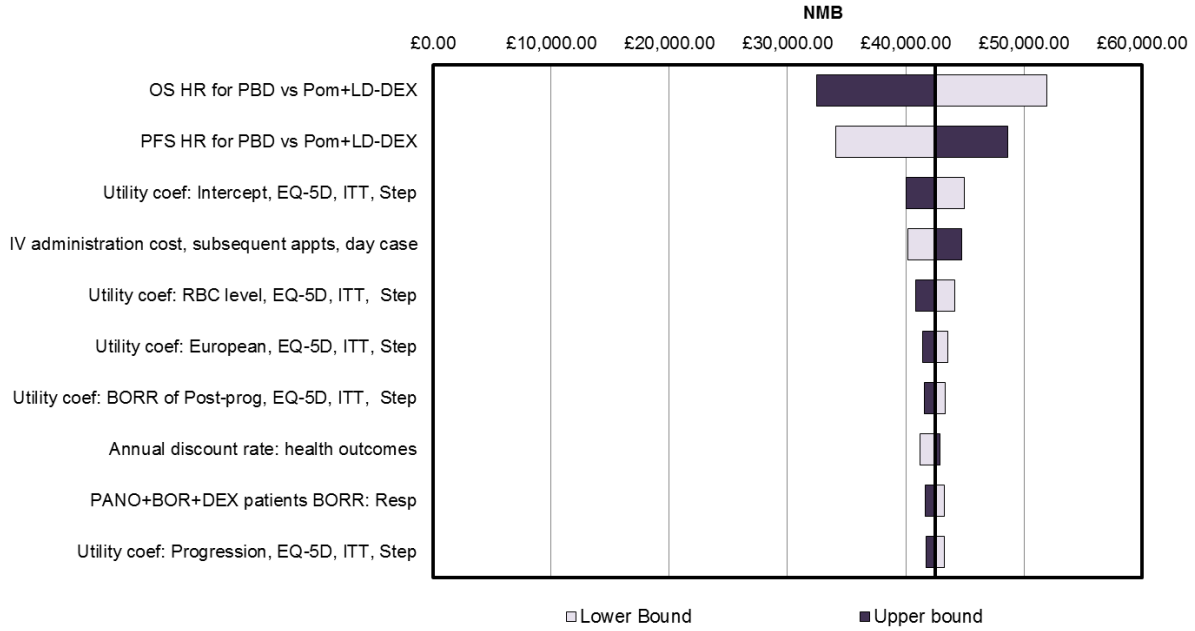


Key: BORR; best overall response rate; BTD, bendamustine, thalidomide and dexamethasone; coef, coefficient; ECOG, Eastern Cooperative Oncology Group; EQ-5D, EuroQol five dimensions; ICER, incremental cost effectiveness ratio; ITT, intention to treat.
Note: as the corrected group prognosis method was used to estimate survival it was not feasible to include covariates used within the survival analysis in the OWSA

POM+LoDEX vs PANO+BOR+DEX

Figure 57 presents a tornado diagram of one-way sensitivity analysis results compared to PANO+BOR+DEX. The parameters with the greatest impact on model outcomes included in the OWSA were the HRs used to model comparative effectiveness. In all cases the NMB remained positive at a WTP threshold of £30,000 per QALY.

Figure 57: Results of one-way sensitivity analysis - PANO+BOR+DEX

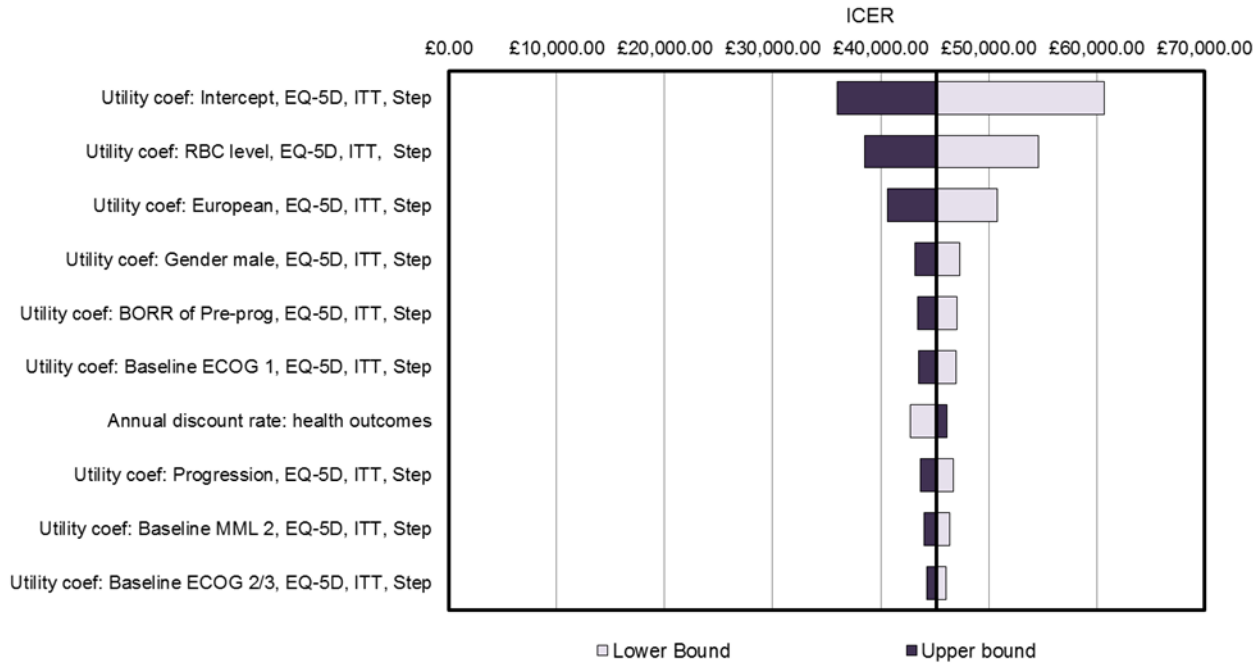


Key: BOR, bortezomib; BORR; best overall response rate; DEX, dexamethasone; coef, coefficient; ECOG, Eastern Cooperative Oncology Group; EQ-5D, EuroQol five dimensions; HR, hazard ratio; ICER, incremental cost effectiveness ratio; ITT, intention to treat; LD-DEX, low-dose dexamethasone; PANO, panobinostat; PBD, panobinostat, bortezomib and dexamethasone; PFS, progression-free survival; OS, overall survival
Note: survival curve fit parameters not included within OWSA

POM+LoDEX vs conventional chemotherapies

Figure 58 presents a tornado diagram of one-way sensitivity analysis results compared to conventional chemotherapies. The parameters with the greatest impact on model outcomes included in the OWSA were the coefficients used within the regression analysis for utilities. The model is relatively insensitive to the majority of parameters.

Figure 58: Results of one-way sensitivity analysis – conventional chemotherapies



Key: BORR; best overall response rate; coef, coefficient; ECOG, Eastern Cooperative Oncology Group; EQ-5D, EuroQol five dimensions; ICER, incremental cost effectiveness ratio; ITT, intention to treat; RBC, red blood count
Note: survival curve fit parameters not included within OWSA

5.8.3 Scenario analysis

The uncertainty around the following structural assumptions has been included within the model, see Table 74.

Table 74: Scenario analyses

Structural assumption in the base case	Scenario analysis
MAIC used for comparison versus PANO+BOR+DEX using OS and PFS information	Hazard ratio for PFS used to model OS (removes potentially bias from differential subsequent therapy use)
Only MM-002 trial data used in the comparison of POM+LoDEX with BTD	All trial data used in the comparison of POM+LoDEX with BTD
OS, PFS and TTF are modelled by generalised gamma curves.	Results displayed for each of the available parametric survival curves for OS, PFS and TTF
IV/SC administration costs uplifted from NICE TA311	IV/SC administration cost from NHS reference costs
Utility benefit is maintained for the duration	Equal BORRs after discontinuation

Structural assumption in the base case	Scenario analysis
of the model	
The data is adjusted for covariates using the CGP method.	The data is adjusted using the mean of covariates method.
Utility values are obtained from a regression analysis using the MM-003 patient level data using the EQ-5D, this includes the AE coefficient	Utility values from the regression analysis using the EORTC-8D.
Utility values are obtained from a regression analysis using the MM-003 patient level data	Utility values are obtained from Quinn et al.
The HRQL impact of AEs is modelled using the coefficient in the regression equation	The HRQL impact of AEs is modelled using the literature
The utility decrement associated with parenteral therapies is 0.025	The utility decrement associated with parenteral therapies is 0.076 to account for the likely underestimation of this for RRMM patients
No cost of subsequent therapies following discontinuation	The cost of a subsequent therapy mix is included based upon data from HMRN
Results in the base case use a 15 year time horizon	Results are shown for 5-, 10-, and 20-year time horizons
Hospitalisation rates are taken from MM-003. The hospitalisation rate associated with comparators is assumed equal to the HiDEX arm.	Hospitalisation rate for POM+LoDEX is taken from the MM-003 trial. Hospitalisation rate for BTD is taken from Gooding et al.
AE rates are calculated using the relative proportion of patients discontinuing due to an AE and applying this to the MM-003 data	AE rates are calculated using the relative safety estimate provided by the clinicians and applied to the MM-003 data.
The utilities associated with response rates are applied in cycle 12, in line with the time of measurement in the clinical trials.	The utilities associated with response rates are applied from cycle 0.

Key: AE, adverse event; BOR, bortezomib; BORR, best overall response rate; BTD, bendamustine + thalidomide + dexamethasone; CGP, corrected group prognosis; DEX, dexamethasone; EQ-5D, EuroQoL five dimensions; EORTC, European Organisation for Research and Treatment of Cancer; HiDEX, high-dose dexamethasone; HMRN, Haematological Malignancy Research Network; HRQL, health-related quality of life; IV, intravenous; LoDEX, low-dose dexamethasone; MAIC, matched adjusted indirect comparison; MM, multiple myeloma; NHS, National Health Service; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; POM, pomalidomide; RRMM, relapsed and refractory multiple myeloma; SC, subcutaneous; TTF, time to failure.

The results from each of these scenarios are given in the tables below for each comparator in turn.

Table 75: Scenario analyses – BTD

Scenario	Incremental Costs	Incremental QALYs	ICER	Diff from base case ICER
POM+LoDEX data for the BTD comparison using all trial data	[redacted]	[redacted]	£46,206	118%
OS curve choices				
Exponential	[redacted]	[redacted]	£39,273	100%
Log-normal	[redacted]	[redacted]	£35,059	89%
Log-logistic	[redacted]	[redacted]	£32,368	82%
Weibull	[redacted]	[redacted]	£38,524	98%
Gompertz	[redacted]	[redacted]	£39,709	101%
Generalised gamma	[redacted]	[redacted]	£37,131	95%
PFS and TTF curve choices				
Exponential	[redacted]	[redacted]	£41,306	105%
Log-normal	[redacted]	[redacted]	£34,560	88%
Log-logistic	[redacted]	[redacted]	£40,499	103%
Weibull	[redacted]	[redacted]	£14,568	37%
Gompertz	[redacted]	[redacted]	£42,177	107%
Generalised gamma	[redacted]	[redacted]	£39,273	100%
Administration costs of IV/SC treatments from NHS reference costs	[redacted]	[redacted]	£44,200	111%
Equal BORRs after discontinuation	[redacted]	[redacted]	£35,706	91%
Mean covariate method used	[redacted]	[redacted]	£37,229	95%
EORTC-8D values used in regression (instead of EQ-5D)	[redacted]	[redacted]	£34,609	88%
Utility values sourced from Quinn et al. (2015)	[redacted]	[redacted]	£35,676	91%
Utility associated with AEs from the literature (base case from the regression)	[redacted]	[redacted]	£38,941	99%

Scenario	Incremental Costs	Incremental QALYs	ICER	Diff from base case ICER
The utility decrement associated with IV/SC administration = 0.076	[redacted]	[redacted]	£38,087	97%
Cost of subsequent therapy included using HMRN data	[redacted]	[redacted]	£39,342	100%
Cost of subsequent therapy included using resource use questionnaires	[redacted]	[redacted]	£44,451	113%
5 year time horizon	[redacted]	[redacted]	£41,605	106%
10 year time horizon	[redacted]	[redacted]	£39,332	100%
20 year time horizon	[redacted]	[redacted]	£39,309	100%
Hospitalisation rate reported in Gooding et al. 2013	[redacted]	[redacted]	£39,285	100%
Adverse events based on relative tolerability profiles	[redacted]	[redacted]	£43,585	111%
BORRs applied from cycle 0	[redacted]	[redacted]	£39,260	100%
Terminal care costs: National Audit Office	[redacted]	[redacted]	£39,502	101%

Key: BTD, bendamustine, thalidomide and dexamethasone; BL, baseline; BORR, best overall response rate; EORTC-8D, European Organisation for Research and Treatment of Cancer eight dimensions; EQ-5D, EuroQoL five dimensions; HiDEX, high-dose dexamethasone; HMRN, Haematological malignancy research network; ICER, incremental cost-effectiveness ratio; IV, intravenous; LoDEX, low-dose dexamethasone; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; SC, subcutaneous; TTF, time to treatment failure; QALY, quality-adjusted life year.

Table 76: Scenario analysis – PANO+BOR+DEX

Scenario	Incremental Costs	Incremental QALYs	ICER	NMB	Difference from baseline ICER
OS curve choices					
Exponential	[redacted]	[redacted]	£204,332	£43,135	116%
Log-normal	[redacted]	[redacted]	£125,351	£40,351	71%
Log-logistic	[redacted]	[redacted]	£123,590	£40,229	70%
Weibull	[redacted]	[redacted]	£230,622	£43,630	130%
Gompertz	[redacted]	[redacted]	£227,216	£43,587	129%
Generalised gamma	[redacted]	[redacted]	£176,406	£42,475	100%
PFS curve choices					
Exponential	[redacted]	[redacted]	£185,876	£45,377	10%
Log-normal	[redacted]	[redacted]	£179,288	£43,294	101%
Log-logistic	[redacted]	[redacted]	£166,529	£39,475	94%

Weibull	[redacted]	[redacted]	£192,734	£47,350	109%
Gompertz	[redacted]	[redacted]	£175,341	£42,254	99%
Generalised gamma	[redacted]	[redacted]	£176,406	£42,475	100%
Administration costs of IV/SC treatments from NHS reference costs	[redacted]	[redacted]	£162,869	£38,547	92%
Equal BORRs after discontinuation	[redacted]	[redacted]	£145,522	£40,628	82%
Mean covariate method used	[redacted]	[redacted]	£196,353	£43,137	111%
EORTC-8D values used in regression (instead of EQ-5D)	[redacted]	[redacted]	£153,108	£41,150	87%
Utility values sourced from Quinn et al. (2015)	[redacted]	[redacted]	£157,809	£41,449	89%
Utility associated with AEs from the literature (base case from the regression)	[redacted]	[redacted]	£185,534	£42,903	105%
The utility decrement associated with IV/SC administration = 0.076	[redacted]	[redacted]	£184,751	£42,868	105%
Cost of subsequent therapy included using HMRN data	[redacted]	[redacted]	£176,631	£42,540	100%
Cost of subsequent therapy included using resource use questionnaires	[redacted]	[redacted]	£141,511	£32,351	80%
5 year time horizon	[redacted]	[redacted]	£252,037	£44,105	143%
10 year time horizon	[redacted]	[redacted]	£186,461	£42,748	105%
20 year time horizon	[redacted]	[redacted]	£174,139	£42,408	99%
Hospitalisation rate reported in Gooding et al. 2013	[redacted]	[redacted]	£176,258	£42,467	100%
Adverse events based on relative tolerability profiles	[redacted]	[redacted]	£168,863	£40,540	96%
BORRs applied from cycle 0	[redacted]	[redacted]	£176,809	£42,494	100%
Terminal care costs: National Audit Office	[redacted]	[redacted]	£176,687	£42,556	99%
Hazard ratio for PFS used to model OS for PANO+BOR+DEX comparison	[redacted]	[redacted]	Pom Dominates		

Key: AEs, adverse events; HiDEX, high-dose dexamethasone; ICER, incremental cost-effectiveness ratio; LoDEX, low-dose dexamethasone; OS, overall survival; PANO+BOR+DEX, panobinostat+bortezomib+dexamethasone; POM, pomalidomide; QALY, quality-adjusted life year.

Table 77: Scenario analysis - conventional chemotherapies

Scenario	Incremental Costs	Incremental QALYs	ICER	Diff from base case ICER
OS curve choices				
Exponential - TS weibull	[redacted]	[redacted]	£45,164	100%
Log-normal - TS weibull	[redacted]	[redacted]	£34,911	77%
Log-logistic - TS weibull	[redacted]	[redacted]	£37,417	83%
Weibull - TS weibull	[redacted]	[redacted]	£50,446	112%
Gompertz - TS weibull	[redacted]	[redacted]	£139,199	308%
Generalised gamma - TS weibull	[redacted]	[redacted]	£62,220	138%

Exponential - RPSFTM	[redacted]	[redacted]	£43,047	95%
Log-normal - RPSFTM	[redacted]	[redacted]	£37,052	82%
Log-logistic - RPSFTM	[redacted]	[redacted]	£39,462	87%
Weibull - RPSFTM	[redacted]	[redacted]	£49,852	110%
Gompertz - RPSFTM	[redacted]	[redacted]	£91,453	202%
Generalised gamma - RPSFTM	[redacted]	[redacted]	£82,712	183%
PFS curve choices				
Extreme values	[redacted]	[redacted]	£46,871	104%
Exponential	[redacted]	[redacted]	£46,544	103%
Log-normal	[redacted]	[redacted]	£45,462	101%
Log-logistic	[redacted]	[redacted]	£45,063	100%
Weibull	[redacted]	[redacted]	£46,718	103%
Gompertz	[redacted]	[redacted]	£46,411	103%
Generalised gamma	[redacted]	[redacted]	£45,164	100%
TTF curve choices				
Extreme values	[redacted]	[redacted]	£45,164	100%
Exponential	[redacted]	[redacted]	£46,664	103%
Log-normal	[redacted]	[redacted]	£52,593	116%
Log-logistic	[redacted]	[redacted]	£54,076	120%
Weibull	[redacted]	[redacted]	£46,127	102%
Gompertz	[redacted]	[redacted]	£49,573	110%
Generalised gamma	[redacted]	[redacted]	£52,512	116%
Administration costs of IV/SC treatments from NHS reference costs	[redacted]	[redacted]	£45,164	100%
Equal BORRs after discontinuation	[redacted]	[redacted]	£42,876	95%
Mean covariate method used	[redacted]	[redacted]	£45,164	100%
EORTC-8D values used in regression (instead of EQ-5D)	[redacted]	[redacted]	£41,327	92%
Utility values sourced from Quinn et al. (2015)	[redacted]	[redacted]	£42,977	95%
Utility associated with AEs from the literature (base case from the regression)	[redacted]	[redacted]	£45,170	100%
The utility decrement associated with IV/SC administration = 0.076	[redacted]	[redacted]	£45,164	100%
Cost of subsequent therapy included using HMRN data	[redacted]	[redacted]	£45,149	100%
Cost of subsequent therapy included using resource use questionnaires	[redacted]	[redacted]	£46,006	102%
5 year time horizon	[redacted]	[redacted]	£46,675	103%
10 year time horizon	[redacted]	[redacted]	£45,208	100%
20 year time horizon	[redacted]	[redacted]	£45,163	100%
Hospitalisation rate reported in Gooding et al. 2013	[redacted]	[redacted]	£45,173	100%
AEs based on relative tolerability profiles	[redacted]	[redacted]	£45,958	102%

BORRs applied from cycle 0	[redacted]	[redacted]	£44,668	99%
Terminal care costs: National Audit Office	[redacted]	[redacted]	£45,373	100%
Key: AE, adverse event; BORR, best overall response rate;EQ-5D, EuroQoL five dimensions; EORTC, European Organisation for Research and Treatment of Cancer; HMRN, Haematological Malignancy Research Network; ICER, incremental cost-effectiveness ratio; IV, intravenous; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; RPSFTM, rank preserving structure failure time model; SC, subcutaneous; TS, two stage method; TTF, time to failure.				

The main finding from the scenario analysis is that the base case ICER is relatively structurally certain in all comparisons (vs BTD, PANO+BOR+DEX and conventional chemotherapies).

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.

Reducing the time horizon increased the ICER; a time horizon of 5 years is associated with an ICER for POM+LoDEX vs BTD, PANO+BOR+DEX and conventional chemotherapies, of £41,605, £261,730 (south west quadrant) and £46,675, respectively. This is unlikely to capture all of the relevant outcomes associated with POM however, which provides important longer term survival benefits.

The use of the EORTC-8D regression model to calculate utility reduces the ICER to £34,609, £158,925 and £41,327, respectively. This disease-specific measure was not used in the base case analysis, as the EQ-5D was preferred to meet the NICE reference case. Nevertheless, this scenario shows that, when a measure is used more closely tailored to multiple myeloma, EORTC-8D results indicate that POM+LoDEX may induce a larger impact on HRQL than is captured by the generic measure.

The final area of potentially important structural uncertainty, the choice of parametric curve form to characterise OS, PFS and TTF, can lead to an upward or downward change in the ICER. Selecting the log-normal or log-logistic models for OS when comparing to BTD, lead to a decreased ICER, with increased incremental QALYs associated with POM+LoDEX. Neither of these curves provide optimal fits to the data; both are associated with comparably high AIC and BIC values as well as poor fit to the KM curves when assessed visually. This is also true of the Weibull model for the PFS

curve. The exponential and generalised gamma models fit well and so are chosen for the base case, respectively.

Selecting Weibull or Gompertz models for OS when comparing to PANO+BOR+DEX will result in an over and underestimation of QALYs respectively; these are associated with high AIC and BIC values. The generalised gamma model proved optimal for the OS and PFS curves and so is used in the base case. The Gompertz Two Stage Weibull and RPSFTM models when comparing to conventional chemotherapies for the OS curve were an extremely poor fit, with very high AIC and BIC values as well as poor visual fit to the KM curves. These greatly underestimate QALY gain and result in much higher ICER values. The log logistic and generalised gamma models suffered similarly for the TTF curve. The exponential and extreme value models fit to the data more appropriately and so used in the base case, respectively.

5.8.4 Summary of sensitivity analyses results

Model results were reasonably robust to sensitivity analysis with the key areas of uncertainty surrounding:

- 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.
- The measure used for and 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
- 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

Probabilistic analysis which included the uncertainty around curve fit choice indicated the following probabilities of cost-effectiveness for each comparison: 92.8% versus BTD, 100% versus PANO+BOR+DEX (at list price for PANO), 53.5% versus CTD.

5.9 Subgroup analysis

No subgroup analyses were specified within the NICE decision problem and therefore no subgroup analysis has been provided.

5.10 Validation

5.10.1 Validation of de novo cost-effectiveness analysis

Internal validation

The model was quality-assured by the internal processes of the external economists who adapted the economic model. In these processes, an economist not involved in model adaptation 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 questioning of the assumptions based upon the Phillips checklist.[190]

External validation of efficacy inputs

External validation of the cost-effectiveness model included:

- An advisory board in the UK
- Comparison of efficacy estimates with previous NICE submissions considering patients with relapsed and refractory multiple myeloma who have received at least 2 lines of prior therapy
- Comparison of cost estimates for current care in the UK with published data

An advisory board was conducted in the UK to validate the clinical inputs informing the cost-effectiveness model. Clinicians were asked to provide their opinion on the relative efficacy of each treatment based on their experience in UK clinical practice. On average, POM+LoDEX was considered the most efficacious, followed by BTD, PANO+BOR+DEX then conventional chemotherapies. This is similar to the published advice from the NCCN.[104]

This finding was supported by the Phase III, MM-003, trial which demonstrated significantly higher OS and PFS for POM+LoDEX compared to HiDEX. Furthermore, POM was also shown to have promising activity and manageable toxicity in patients

who had received multiple previous rounds of therapy, including both BOR and LEN in MM-002 and MM-010 results.

In 2013, Forsberg and Mark reviewed literature for POM with and without DEX. They found that this treatment shows increased efficacy compared to alternatives in heavily pre-treated patients.[191] The model results show that POM+LoDEX, on average, gives a patient more life years and QALYs than BTD and conventional chemotherapies. However, PANO+BOR+DEX is estimated to be considerably more efficacious than POM+LoDEX in this submission. This is driven by post-progression survival benefits; pre-progression POM+LoDEX is associated with greater life years and QALYs. This highlights that there are likely major confounding from subsequent therapy use; lack of subsequent therapy data for patients receiving PANO+BOR+DEX means that we cannot compare what treatments were received by patients between the trials. It is notable that patients in PANORAMA 2 are at an earlier line of therapy compared to the POM+LoDEX trials.

Estimated life years and QALYs were validated against the two previous NICE submissions considering patients who have received at least two previous treatments in relapsed and refractory multiple myeloma (

Table 78). The efficacy estimates for POM+LoDEX reported in this submission are notably lower in all comparisons than those reported in the previous NICE submission (TA338); this submission makes use of longer follow-up and a larger dataset (n=1,097 across all POM+LoDEX trials compared with n=302 in the previous NICE submission (TA338)). More conservative survival curve fits are now selected for comparison.

The efficacy estimates for PANO+BOR+DEX in this submission are extremely similar to the NICE submission (TA380) – this indicates that the results of the MAIC used to predict OS associated with PANO+BOR+DEX are likely over-predicting survival given that TA380 referred to an earlier line of therapy (third line) and survival would not be expected to be the same in patients at this later line of therapy.

Table 78: Comparison of life years and QALYs across NICE submissions for patients who have received at least two prior lines of therapy in RRMM

	Life years	QALYs
POM+LoDEX (MM-002 only)	1.81	1.13
POM+LoDEX (all trials)	1.71	1.10
POM+LoDEX (MM-003)	1.45	0.93
BTD	1.14	0.72
PANO+BOR+DEX using PANORAMA-2	2.25	1.39
Conventional chemotherapy using HiDEX (MM-003)	0.78	0.49
POM+LoDEX – previous NICE submission (TA338)	2.23	1.29
Comparator – previous NICE submission (TA338)	1.17	0.68
PANO+BOR+DEX – NICE submission (TA380)	2.29	1.52
BOR+DEX – NICE submission (TA380)	2.25	1.48

Key: BOR, bortezomib; BTD, bendamustine, thalidomide and dexamethasone; DEX, dexamethasone; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; NICE, National Institute for Health and Care Excellence; PANO, panobinostat; POM, pomalidomide; QALYs, quality-adjusted life years.

External validation of utility inputs

Forsberg and Mark (2013) comment that generalising results across individuals is difficult due to the heterogeneity of the disease; this supports our method of calculating HRQL using a regression equation, which assigns a utility value according to multiple clinically important disease characteristics.

External validation of cost and resource inputs

Gooding et al. (2013) estimate that patients incurred £8,448 in medical resource use costs based on a mean time on treatment of 15.5 weeks during fourth-line anti-multiple myeloma therapy. The model estimates that over 15.5 weeks patients incur £9,480 and £9,147 in medical resource use costs when treated with BTD and conventional chemotherapies respectively (which make up a large proportion of treatments using in the Gooding paper); these costs include the cost of treatment, medical resource use and concomitant medications. The cost of BTD and conventional therapies over 15.5 weeks are very similar to the Gooding estimate, and so validates our method of estimating costs.

5.11 Interpretation and conclusions of economic evidence

Conclusion

POM+LoDex has been demonstrated to be a cost-effective treatment option against all the relevant comparators in UK clinical practise. The results from this submission provide up to date and more robust estimates making use of larger datasets than the previous NICE submission (TA338).

[redacted]

Updates to previous submission

This submission differs from the previous NICE submission (TA338) in that:

- The evidence gathering process conducted to enable this resubmission has provided substantially more data than the previous submission (MM-003, MM-002, Gooding et al. and Tarant et al.) and incorporates the more recent datasets from MM-003, MM-002, MM-010, MUK-One and PANORAMA-2 as sources of clinical data
- As much as possible the comparability of datasets has been increased by adjusting for covariates (including: age, number of prior therapies, refractory to lenalidomide and prior THAL), but covariate adjustment cannot account for all differences between trials. However, the direction of bias is most likely against POM+LoDEX due to the high level of refractoriness and late line of therapy of patients included in the POM+LoDEX trials
- Resource use and AEs have been collected through the medium of resource use questionnaires for POM+LoDEX, BTD, PANO+BOR+DEX individually. This measures resource use across all comparators using the same method, whereas published evidence was either absent or inconsistently reported.

Validity of key findings

The results can be considered validas the estimated life years and QALYs associated with PANO+BOR+DEX are similar to the NICE submission (TA380); 2.3 and 1.4 compared with 2.5 and 1.7 from this submission and TA380, respectively. The estimated costs accruing to fourth-line treatment with PANO+BOR+DEX are

£101,653 in this submission, which is comparable to the £137,447 estimated in the NICE submission (TA380). It should be noted that the comparability of life years is a clear sign that the benefit of PANO+BOR+DEX is overestimated in this submission given that TA380 looked at use at third line in comparison to LEN.

The efficacy of POM+LoDEX was validated by an advisory board where clinicians were asked to provide relative efficacy estimates of all comparators based on their experience across UK centres. The average clinician response validated the model estimates for POM+LoDEX, BTD and conventional chemotherapies. However, the model estimated PANO+BOR+DEX to be the most efficacious of the comparators – this is likely biased because of subsequent therapies confounding the data.

The key strength of the economic evaluation lies within the maturity and size of the datasets available for POM+LoDEX (MM-002, MM-003, MM-010) including EQ-5D data demonstrating a significant treatment effect (p=0.0050). This limits uncertainty around the benefit that can be achieved with POM+LoDEX.

The primary limitation is the inconsistent reporting of all potential covariates across trial datasets. Therefore, covariate adjustment is unlikely to have adjusted for all differences between trials caused by differences in inclusion and exclusion criteria. Another limitation is the paucity and quality of evidence associated with subsequent therapies, which has not allowed for this to be adjusted for. Therefore, there may be significant bias in the OS estimates based on subsequent therapies – this is particularly apparent in the RWE and the comparison of POM+LoDEX with PANO+BOR+DEX. However, the PANO+BOR+DEX comparison demonstrates that POM+LoDEX is associated with higher efficacy in pre-progression which suggests that long term results are biased against POM+LoDEX.

6 Assessment of factors relevant to the NHS and other parties

A budget impact model was included within the cost-effectiveness model to analyze any factors relevant to the NHS and other parties that may fall outside the remit of clinical and cost effectiveness.

6.1.1 Prevalence, incidence and market share.

There were 4,652 new cases of myeloma recorded in England in 2014.[192] 4,703 cases were recorded in 2013, and 4,190 in 2012.[193, 194] Information for earlier years cannot easily be compared as the number of sites included in national statistical analysis varies. It has therefore been assumed that the number of patients diagnosed with multiple myeloma will not vary substantially year on year.

The number of patients eligible for treatment with POM+LoDEX at both third and fourth line was calculated based upon the current treatment pathway and rates of progression for earlier treatment lines.

Through the CDF, 1,394 patients received POM+LoDEX between October 2013 and August 2015.[195-198] This is in line with the above estimates (85 eligible patients per month predicted versus 61 patients per month treated whilst POM was available on the CDF). This implies a market share of 72%.

Table 79: Patients in England eligible for treatment with POM

Item	Number or percentage	Source
Number of incident patients	4652	ONS 2014[192]
First-line SCT (includes BOR as part of induction)	1214	British Society of Blood and Marrow Transplantation website[199]
LEN maintenance post SCT as part of clinical trials	288	Myeloma XI average recruitment per annum between Dec 2010 and Sept 2015 (1367 over 57 months)
Proportion who progress to further treatment (no LEN)	81.7%	Calculated using patient level data from CALG-B (main trial reported in McCarthy et al. 2012[200])
Proportion who progress to further treatment (with LEN)	92.0%	Calculated using patient level data from CALG-B (main trial reported in McCarthy et al. 2012[200])
First-line SCT ineligible	3438	Calculation (4652 - 1214)
Proportion receiving THAL	2922	Assumed 85% receive THAL based on TA228 costing template[201]
Proportion receiving BOR	516	Assumed 15% receive BOR based on TA228 costing template[201]
Proportion progressing on THAL	87.40%[a]	TA228 technology assessment (digitised from survival curves)[90, 202]
Proportion progressing on BOR	86.50%[b]	TA228 technology assessment (digitised from survival curves)[90, 202]
Second line		
Prior BOR (no prior LEN)	1203	Calculation
Prior BOR and LEN	265	Calculation
No prior BOR or LEN	2554	Calculation
Proportion who received LEN at 2nd line post BOR (assumed % of eligible population who had received LEN at 2nd line via the CDF)	50%	LEN came off the CDF in November 2015 therefore by the time of first committee meeting it is expected approx. 50% of patients will already have progressed and received alternative treatment at third-line (Stadtmauer et al. 2009[154])
Proportion progressing on second-line treatment (BOR received if no prior BOR)	86.50%[b]	TA228 technology assessment (digitised from survival curves)[90, 202]
Proportion progressing on second-line treatment (for all patients receiving LEN)	28.60%	TA171 technology assessment[92, 203]

Item	Number or percentage	Source
Proportion progressing on second-line treatment (for all patients not receiving BOR assumed the same as for THAL)	87.40%[a]	TA228 technology assessment (digitised from survival curves)[90, 202]
Third line		
Prior BOR (no prior LEN)	2168	Calculation
Eligible for POM at 3rd line: Prior BOR and LEN	404	Calculation
Patients not eligible for POM progressing on third-line treatment	28.60%[c]	TA171 technology assessment[92, 203]
Fourth line		
Eligible for POM at 4th line: Prior BOR and LEN	620	Calculation
Eligible per month	**85**	
Implied market share based on CDF uptake	**72%**	

Key: BOR, bortezomib; CDF, Cancer Drugs Fund; LoDEX, low-dose dexamethasone; LEN, lenalidomide; ONS, Office of National Statistics; POM, pomalidomide; SCT, stem cell transplantation; THAL, thalidomide.

Notes: [a]Calculated by estimating the proportion of patients still alive at the mean survival time from NICE TA228 (1.04 years) using the survival curves provided; [b]Calculated by estimating the proportion of patients still alive at the mean survival time from NICE TA228 (0.92 years) using the survival curves provided. Assumed the same for first- and second-line treatment as only first-line information available; [c]Calculated as the difference between OS and PFS in Year 1 based upon MM-010 patient level data for patients with one prior therapy.

The estimated eligible patient population is 620 patients per year. It was assumed that POM+LoDEX will achieve 72% market share of incident cases upon its introduction based on CDF uptake (see Section 3.4). No increase in the incident population was assumed overtime as no stable trend in multiple myeloma incidence overtime could be found.

6.1.2 Costs and resource use

Resource savings are expected in individual cost areas, for example through a reduction in administration requirements through the displacement of BOR and BEN which are delivered intravenously by a specialist physician or nurse.

Costs used within the budget impact model were identical to the cost-effectiveness model described in Section 5 of this submission. The model used eMIT, MIMs, national reference costs and published sources where no reference cost was available.

Cost-effectiveness model per-patient outcomes over 1 to 5 years were extracted to inform the likely budget impact per patient. This accounted for the differential costs incurred and differential mortality prospects in patients who receive POM+LoDEX instead of each comparator.

As all evidence used for the budget impact calculation is derived from the cost-effectiveness model the same limitations apply in terms of comparator evidence. There is, however, a good degree of certainty around likely population size and uptake for POM+LoDEX from UK experience.

6.1.3 Budget impact

Budget impact results are presented for POM+LoDEX compared to BTD, PANO+BOR+DEX, and CTD based upon the market shares for each treatment elicited via clinical expert opinion (see Section 3.3). It is assumed that the market share for POM+LoDEX is derived from all three treatments equally.

Table 80: Estimated market share

Treatment	Proportion
PANO+BOR+DEX	40.8%
BEN	22.5%
Other: includes clinical trials and conventional chemotherapy (assigned to CTD for the purposes of budget impact analysis)	36.7%
Total	100%
Key: BEN, bendamustine; BOR, bortezomib; CTD, cyclophosphamide + thalidomide + dexamethasone; DEX, dexamethasone; PANO, panobinostat.	

The gross budget impact was calculated as the total resources demanded of the NHS for the treatment of patients with POM+LoDEX or current care. The net budget impact is the difference between the gross budget impact of POM+LoDEX and current care.

It is estimated that the use of POM+LoDEX would reduce the budget impact to the NHS (due to reduced drug cost versus PANO+BOR+DEX).

Table 81: Gross budget impact

Year	BTD	PANO+BOR+DEX	CTD	Current Care	POM+LoDEX
1	£3,811,217	£25,381,663	£4,221,479	£43,600,383	[redacted]
2	£4,771,987	£27,388,848	£4,900,376	£47,393,369	[redacted]
3	£5,148,024	£28,559,386	£5,082,433	£49,391,481	[redacted]
4	£5,313,400	£29,296,030	£5,131,020	£50,582,950	[redacted]
5	£5,391,783	£29,779,700	£5,143,917	£51,346,246	[redacted]

Key: BOR bortezomib; BTD, bendamustine, thalidomide and dexamethasone; DEX dexamethasone; LoDEX, low-dose dexamethasone; PANO, panobinostat; POM, pomalidomide.

Table 82: Net budget impact

Year	Annual net impact	Total net impact
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]

Key: BOR bortezomib; BTD, bendamustine, thalidomide and dexamethasone; DEX dexamethasone; LoDEX, low-dose dexamethasone; PANO, panobinostat; POM, pomalidomide.

6.1.4 Other opportunities for resource savings or redirection of resources

From anecdotal evidence it is noted that some specialist clinics for myeloma patients are running to full capacity, for example in Oxford where a 7-day clinic is now required compared to the previous 5-day clinic. As an oral therapy which can self administered at home, POM+LoDEX may aid in relieving some of this pressure on capacity, and also reduce any potential patient transport costs which may be incurred. Neither of these factors are included within the model.

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8 List of appendices

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Single technology appraisal

Pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib (review of TA338) [ID985]

Dear Celgene,

The Evidence Review Group, Kleijnen Reviews Ltd and the technical team at NICE have looked at the submission received on 11 July 2016 from Celgene. 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 **5pm** on **Tuesday 23 August 2016.** Your response and any supporting documents should be uploaded to NICE Docs/Appraisals [embed NICE DOCS LINK on '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 Stuart Wood, Technical Lead (Stuart.Wood@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (Stephanie.Yates@nice.org.uk).

Yours sincerely

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Clinical trial information

A1. **Priority request:** Please explain whether the population in MM-003 is comparable to the total population in this appraisal. In Table 19 (page 67) of the company submission, the company reports that in the MM-003 trial the median number of prior anti-myeloma therapies was 5 with a range from 2-17 across both arms. This implies that the population in the trial had received more previous treatment than the population in the scope which specified people with 2 prior therapies or people with 3 or more prior therapies.

- Please provide results for all outcomes specified in the scope for patients in MM-003 who have had exactly 2 prior therapies.
- Please provide the interquartile range (IQR) around the median number of prior anti-myeloma therapies reported in table 19 for the MM-003 trial.
- Please provide a histogram of the number of prior anti-myeloma therapies in the MM-003 trial.

Statistical analysis

A2. **Priority request:** Please clarify the following points in relation to the statistical analyses:

- Section 4.10.2 (page 92): Please provide full details of the statistical methods used to evaluate multicollinearity and any cut-offs used (e.g. variance inflation factor > 10), as well as the statistical commands and software used.
- Appendix 12 (page 89): Please provide details of how correlation was assessed, e.g. size and statistical significance of the Pearson correlation coefficient. Please report the correlation coefficients in Table 29 of the main submission.
- Section 4.10.2 (Table 29, page 93): Please explain why the multicollinearity column is blank for some covariates. Please clarify the significance levels used in the overall survival (OS) and progression-free survival (PFS), as 'significance' may have been defined differently in different studies.
- Section 4.10.2 (page 96): Please provide justification for why the cut-off of 50% missing data was chosen when selecting covariates for the comparison of pomalidomide plus low dose dexamethasone with bendamustine.

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- Page 112: the company submission states 'Patients with missing data for any of the clinically-relevant prognostic factors were not included in the analyses.'
    - How many patients were excluded from each analysis due to missing data?
    - Did the company consider using simple or multiple imputation methods to impute the missing data? If not, please provide an explanation.
- Section 4.10.2 Methods used for covariate adjustment in the comparison of pomalidomide plus low dose dexamethasone with bendamustine plus thalidomide and dexamethasone
    - Please provide full details of the analysis methods, and the relevant R code. Please specify the type of model used (e.g. Cox proportional hazards model, Weibull model etc.), how censoring was defined, whether or not the proportional hazards assumption was checked, and any other derivations or assumptions used.
    - According to the company submission, 'it was not possible to include study as a fixed effect in the statistical models due to linear dependence (...), and therefore it was impossible to determine the study effect when simultaneously estimating the treatment effect'. Although each study contained one treatment, the ERG considers that it may have been possible to include a covariate for study to account for the fact that results were from different studies. Please clarify whether all available methods for adjusting for study in the analysis were explored.
- Please provide covariate adjusted data used to generate the covariate adjusted Kaplan-Meier (KM) curves (e.g. Figure 15 and 17 in the company submission) for overall survival (OS) and progression free survival (PFS) for pomalidomide plus low dose dexamethasone and bortezomib. Please provide the statistical software scripts with corresponding datasets (i.e. all relevant files) which were used to derive all the coefficients for all covariate adjustment analyses that were needed to estimate the HRs and KM curves.
- On page 109 of the company submission, two sensitivity analyses surrounding the inclusion/exclusion of International Staging System (ISS) stage as a prognostic factor are reported. Please explain why the overall goodness of fit or predictive power (e.g. the adjusted R square) was not used in determining the covariate adjustment regression, e.g. to check how including ISS improves the predictive power of the regression function. If goodness-of-fit was checked then please provide the relevant statistics.
- Section 4.10.3 (page 113) states that 'a propensity matched adjusted indirect comparison (MAIC) approach was adopted using SAS'.

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- Please provide full details of this analysis, including analysis methods used, covariates included in the analysis, survival models used, and any derivations and assumptions made.
- Please also provide the relevant SAS code.
- Please provide MAIC un-weighted and MAIC weighted data to generate weighted and un-weighted KM curves for pomalidomide plus low dose dexamethasone and panobinostat plus bortezomib and dexamethasone.
- Please also provide the statistical software scripts with corresponding datasets (i.e. all relevant files) which were used in deriving the propensity weights and the MAIC Cox proportional hazards model results in Table 34.

A3. In section 4.10.1, the company submission states that only studies with > 50 patients were included in the 'indirect comparisons'. Please clarify the justification for the cut-off and report whether any studies excluded based on this criteria could have allowed an indirect comparison or network meta-analysis to be performed.

A4. On page 51 of the company submission the company states: 'This submission included studies where at least 75% of adult RRMM patients had received both bortezomib and lenalidomide to focus the evidence base to a comparable patient population'. Please clarify the justification for the cut-off and report which (if any) studies were excluded based on this criterion.

A5. In Table 17 of the company submission, the company indicates which outcome data were used in the economic analysis.

- Please clarify why the efficacy outcomes were based on a different data cut to the quality of life (QoL) and safety outcomes and discuss how this would influence the results.
- Please provide the full results for all data cuts.

A6. Please provide the 95% confidence interval (CI) for the hazard ratio (HR) in Appendix 12 (Tables 30, 31, 32 etc.) in the results tables for the Cox regression output for the comparisons with bendamustine.

A7. Table 40 of the company submission (End-of-life criteria) states: 'The eligible patient population is expected to be 620.' Based on table 79 this appears to be the total at fourth line. This does not account for those patients eligible at third line (n=404).

- Please explain why numbers are higher for fourth line than for third line.
- Please clarify the total number of patients eligible at third line or above in line with the scope.

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Literature searching

A8. The company states:

> 'This resubmission addresses concerns raised by the evidence review group (ERG) in the original NICE review (TA338) regarding the use of study design filters by adding additional terms to the search strategies around study design in order to make the searches more comprehensive' (company submission; page 52).

- Please confirm what new terms have been added to the strategy to make it more comprehensive. The ERG was able to identify two additional terms in the MEDLINE/Embase strategy (Appendix 2; pages 6-9):
  - #32multi-centre:ti
  - #82'retrospective study'/de

A9. Please confirm whether searches were conducted to identify pre-2013 records on the newly added comparator panobinostat, as the strategies provided in the company submission will only retrieve records added to the databases searched from 2013 onwards. If not, please conduct the relevant searches for this comparator.

A10. Search strategies are not provided for Section 5.5.1: 'Resource identification, measurement and valuation studies'. Please provide details of databases and other resources searched, and search strategies used, as required by the user guide for the company evidence submission template.

A11. Please provide the search terms used for the identification of clinical effectiveness studies from the American Society of Hematology (ASH), American Society of Clinical Oncology (ASCO), European Hematology Association (EHA) and International Myeloma Workshops (IMW) conferences (Appendix 2; page 5).

<u>Section B: Clarification on cost-effectiveness data</u>

Treatment effect in cost effectiveness model

B1. **Priority request:** For the clinical effectiveness parameters (OS, PFS, time to failure (TTF)), different data from different studies and different methods were used for the comparisons of pomalidomide plus low dose dexamethasone compared with bendamustine plus thalidomide and dexamethasone, pomalidomide plus low dose dexamethasone compared with panobinostat plus bortezomib plus dexamethasone and pomalidomide plus low dose dexamethasone compared with conventional chemotherapy. The ERG considers that this approach creates a bias, and results in

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differing outcomes for patients receiving the same treatment (pomalidomide plus low dose dexamethasone) in different comparisons.

- Please provide a full incremental analysis using a single source of data for pomalidomide plus low dose dexamethasone e.g. data from a single trial or pooled data from multiple trials.

- Also, please apply any treatment effects (hazard ratio (HR) or acceleration factors for OS, PFS and TTF) of bendamustine plus thalidomide and dexamethasone, panobinostat plus bortezomib plus dexamethasone and conventional chemotherapy on the OS, PFS and TTF estimates of pomalidomide and low dose dexamethasone based on that single data source.

B2. Please verify the following or explain if otherwise:

- Covariate adjustment (based on either corrected group prognosis (CGP) method or mean covariate adjustment method) was applied based on data obtained from pomalidomide plus low dose dexamethasone or bendamustine plus thalidomide and dexamethasone trials only. Based on the coefficients of covariate adjustment, parametric survival functions were fitted for the bendamustine plus thalidomide and dexamethasone and pomalidomide plus low dose dexamethasone arms. For the panobinostat plus bortezomib and dexamethasone arm, hazard rates obtained from matched adjusted indirect comparison (MAIC) were applied to the parametric survival functions derived for the pomalidomide plus low dose dexamethasone arm based on a proportional hazard assumption.

- In all of the parametric survival functions, the following parameters were used: 67.65, 3.7, 0.84 and 0.78, respectively for the mean age, mean number of prior lines of therapies, proportion of patients that received prior thalidomide and proportion of prior refractoriness to lenalidomide.

B3. Please explain in detail the calculations in the “OS2”, “PFS2”, “TTF2”, “OS2_BEN”, “PFS2_BEN” and “TTF2_BEN” worksheets (especially columns starting from AZ and onwards) and the VBA Macros under the “CGP” module, e.g. macros like “CCGP_OS2”, “CCGP_PFS2”, “CCGP_OS1” etc.. For instance, it was not clear to the ERG how the CGP method was applied and how the numbers in the cell range of BP25: FI4199 in the OS2 (and similar ranges in the other sheets) were obtained. Please provide the details as well as all relevant material (i.e. statistical software scripts, datasets used and their explanations) which were used in these covariate adjusted parametric survival fitting analyses.

B4. Please explain why some of the PFS curves in the “PFS2” sheet start from values greater than 1 (see cell range BG28:BH28).

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B5. Please provide Kaplan-Meier analyses to the following specification:

- Population: The per protocol population, including all patients lost to follow-up or withdrawing from the trial.
- Censoring: Censor lost to follow-up and withdrawn patients at the time recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off, and not when last seen. Please use the format of the table provided below.
- Trial data sets:
  - For bendamustine: Gooding et al, Tarant et al and MUK-One
  - For pomalidomide plus low dose dexamethasone: (a) MM-002,MM-003 and MM-010 (b) MM-002 only (c) MM-003 only
  - For panobinostat plus bortezomib and low dose dexamethasone: pseudo patient level data from PANORAMA-2
  - For conventional chemotherapy: MM-003 only after treatment switching corrections

- Time to death from any cause (overall survival) Kaplan-Meier analyses for bendamustine; for pomalidomide plus low dose dexamethasone based on (a), (b) and (c) above; for panobinostat plus bortezomib and low dose dexamethasone and for conventional chemotherapy (in total 6 analyses)
- Time to progression by investigator assessment (progression free survival) Kaplan-Meier analyses for bendamustine; for pomalidomide plus low dose dexamethasone based on (a), (b) and (c); for panobinostat plus bortezomib and low dose dexamethasone and for conventional chemotherapy (in total 6 analyses)
- Time to treatment discontinuation Kaplan-Meier analyses for bendamustine; for pomalidomide plus low dose dexamethasone based on (a), (b) and (c); panobinostat plus bortezomib and low dose dexamethasone and for conventional chemotherapy (in total 6 analyses)
- Time from progression by investigator assessment to death from any cause (post-progression free survival) Kaplan-Meier analyses for bendamustine; for pomalidomide plus low dose dexamethasone based on (a), (b) and (c); for panobinostat plus bortezomib and low dose dexamethasone and for conventional chemotherapy (in total 6 analyses)

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Product-Limit Survival Estimates						
DAYS		Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP...		.....	.....	.....	...	...
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

Example of output required from specified Kaplan-Meier analyses (e.g. SAS LIFETEST procedure)

B6. In sections 5.3.8, 5.3.9, 5.3.10, 5.3.11 and 5.3.12 of the company submission, it was not clear which data (adjusted or unadjusted) were used in fitting parametric survival curves. Furthermore, all the figures in these sections (i.e. Figures 31 to 36, pages 175 to 184) show unadjusted KM curves compared with the covariate adjusted parametric survival functions. Please state which baseline parameters were used for the covariates (the mean age, mean number of prior lines of therapies, proportion of patients that received prior thalidomide and proportion of prior refractoriness to lenalidomide) for each of these figures.

Furthermore, it was not clear to the ERG which steps were taken to select the fitted parametric survival functions to be used in the base case in the economic analysis. In Appendix 18 and 19, Q-Q and Log cumulative hazard plot (LCHP) plots and parametric curve fits vs KM plots were provided, but the rationale for selection was not clear (use of AIC/BIC or the rationale for accepting/rejecting the appropriateness of proportional hazards or accelerated failure time (AFT) based on Q-Q plots and LCHPs?). Please clarify.

B7. There are some inconsistencies between the company submission and the corresponding results in Appendix 18 and 19. For instance, in the report, for pomalidomide and low dose dexamethasone compared with panobinostat and bortezomib and dexamethasone PFS (section 5.3.12), it was mentioned that Gompertz, exponential, generalized gamma and Weibull curves have the lowest AIC/BIC. However in Appendix 19, in Table 52, it can be seen that log-logistic and log-normal functions have the minimum. Please double check the consistency between the report and the Appendix 19 results for all parametric survival analyses.

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B8. In the current electronic model, because of the common treatment effect assumption, TTF is always smaller than PFS for pomalidomide and low dose dexamethasone, but, in real life practice, there can be situations where TTF is equal to PFS. Therefore, please provide an analysis for TTF, where the same procedure of parametric survival curve fitting exercises have been applied to TTF KM data as PFS and OS. Then, in the electronic model, for TTF, select the minimum of OS, PFS or TTF in order to deal with potential crossing of TTF and PFS curves.

Additionally, please apply a parametric survival curve for TTF of panobinostat and bortezomib and dexamethasone, as well. (In the current version of the electronic model, discontinuation from panobinostat and bortezomib and dexamethasone, due to other reasons than progression was not incorporated.

Utility data

B9. In the company submission, the results of a multivariate analysis (based on EQ-5D data from the MM-003 trial) are used to predict utilities.

- Please justify why the data sources used for the percentage of patients with disease progression, stable disease or progressive disease (i.e. best overall response), hospitalisations and adverse events to predict utilities (i.e. the data which are combined with the coefficients derived from the multivariate analysis) are not the same as for the effectiveness data as shown in Table 45 (for all comparisons)? For example, in the base-case in which pomalidomide plus low dose dexamethasone is compared with bendamustine, data from the MM-003, MM-002 and MM-010 trials are used to estimate the percentage of patients with stable disease or progressive disease (to estimate utilities of patients treated with pomalidomide and low dose dexamethasone). Why are data from the MM-002 trial only not used (as presented in Table 48), given that the MM-002 trial is the main source for the effectiveness of pomalidomide plus low dose dexamethasone within this comparison?

- It is noted that not all covariates in the model are used to find differences in utilities across treatments. Please show the impact on the ICER of limiting the covariates to only those that are used to find differences in utilities across treatments (i.e. disease progression, best overall response, hospitalisations and adverse events as independent variables).

    - Please provide the results of the F-test and the R^2 for this analysis and the analysis including all of the covariates currently presented in Table 47.

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- As no treatment-specific data are available regarding hospitalisation rate for the comparators, please provide results without hospitalisation as a covariate (just including three covariates).

B10. Please document the details on the utility regressions used in the model (such as all related regression coefficients and outputs like test scores of coefficients and goodness of fit).

B11. Please check the data in Table 50 (page 207). There is always the same difference between the results of “MM-002”, “All trials” and “MM-003” using the EQ-5D method. Please comment on how this same difference is observed for EQ-5D and not for EORTC.

B12. In a scenario-analysis, utilities derived from the EORTC QLQ-C30 are used (by applying the algorithm by Rowen et al.), instead of EQ-5D utilities. The results of multivariate analyses to determine the most important predictors of HRQL (based on the EORTC QLQ-C30) are presented in Appendix 23 (Table 61, page 236). In the first model, based on a stepwise and backwards selection, many coefficients equal 0.000. Please explain if this means that these covariates were not statistically significant, and therefore not included in the final model to predict utilities.

B13. In paragraph 5.4.2 (page 200). ‘Description of the identified utility studies’, the numbers in the text do not correspond to the numbers in the PRISMA flow diagram (Figure 40, page 201). Preliminary screening of abstracts and titles was performed on 382 records, and 74 records were included, according to the text. In the Figure slightly different numbers are provided. Please state what the correct numbers are.

Costs

B14. Little data are available regarding dose interruptions for the comparators (and no dose interruptions were taken into account for bendamustine and conventional chemotherapies). Please justify the approach including dose interruptions in the company submission, or, if possible, provide a scenario analysis in which dose interruptions are not taken into account.

B15. The model assumes that only whole packs of thalidomide can be dispensed each cycle. As a consequence, 14 units (i.e. 700 mg) are wasted every cycle (in bendamustine), although these might be used in the following cycle. Similarly, the model assumes that only whole packs of cyclophosphamide can be dispensed each cycle. As a consequence, 3000 mg is wasted every cycle (in cyclophosphamide plus thalidomide and dexamethasone). These might be used in the following cycle. Please confirm whether the company has considered this and, if possible, show the impact of this assumption on the ICER.

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B16. In the economic model, 3 vials of bortezomib are used per patient per week in the first eight cycles and 2 vials in subsequent cycles. Please explain why 2 vials per patient per week in the first eight cycles and 1 vial in subsequent cycles were not used instead (assuming 1 vial per administration)? Additionally, in contrast to the explanation given in Section 5.5.2 of the company submission, in the model a bortezomib dose of 1.3 mg/m^2 twice weekly for 2 weeks in a 21 day cycle is given in the first eight cycles (instead of the first cycle only). Please explain if this is implemented correctly, in spite of the text in section 5.5.2 of the company submission.

B17. In the base-case, the costs associated with IV/SC administration visits were obtained from the recently published bortezomib first-line appraisal (TA311). Please explain why subsequent visits are more expensive than the first visit, i.e. £312.87 compared to £222.13.

B18. Some costs, e.g. administration costs (page 216 of the company submission), were based on historical data (in this case 2011/2012) and uplifted to a more recent price base. Please confirm that no more contemporary unit costs were found after searching in all instances where such price uplifts have been made.

The ERG have found a potentially cheaper price (Actavis UK Ltd) for bendamustine 25 mg powder for concentrate for solution for infusion vials. NHS indicative price = £6.85 for 1 vial. Please provide up-to-date unit costs from BNF medicines to populate Table 52 (page 212) and run the model on these prices.

B19. Please confirm the programming error that outpatient unit costs are applied instead of inpatient unit costs for adverse events (AE) and vice versa (AEs sheet, cells: G79:H119) and correct this error, if applicable.

B20. Although resource use is derived from the answers to the resource use questionnaire, please provide a rationale as to why 'resource use, on treatment: pre progression' is higher for bendamustine and panobinostat plus bortezomib and dexamethasone compared to pomalidomide plus low dose dexamethasone(as these costs exclude administration costs, costs associated with adverse events and costs of concomitant medication). Please confirm that some costs, especially the administration costs were not double counted.

Other

B21. Key data are missing for results of the resource use questionnaire in Appendix 26 cross referenced on page 211 of the company submission. It would be helpful to have access to the full data extraction for all tables (70 to 74 of the Appendices) including all individual responses because variation around the average could be an important source of uncertainty.

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B22. In Section 5.3 of the company submission, it was mentioned that the uncertainty around the choice of parametric curve was incorporated in the probabilistic sensitivity analysis by selecting the type of the parametric survival curve based upon sampling from the probability that each parametric model was the best fitted parametric model, derived from AIC values of each fitted parametric curve.

- Please justify the use of this approach rather than incorporating the structural uncertainty surrounding parametric survival curves in scenario analyses only.
- Please provide any references from published literature where this approach was explained.

Section C: Textual clarifications and additional points

C1. Some references are missing from the main report (e.g. 51, 63, 66 etc.) and from the appendices (e.g. 2, 4, 5, 6 etc.). Please ensure that all references are provided.

C2. Please confirm that the provided references (17, 111 etc.) are the full clinical study reports (CSRs). If not, please provide the full CSRs.

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Dr Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation
10 Spring Gardens
London SW1A 2BU
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Dear Dr Sutcliffe,

RE: **Pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib (review of TA338) [ID985]**

Please see below the responses to the clarification questions requested by NICE and the ERG.

Yours Sincerely,

James Farrell
Senior Health Economist and Outcomes Research Manager

Single technology appraisal

Pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib (review of TA338) [ID985]

Dear Celgene,

The Evidence Review Group, Kleijnen Reviews Ltd and the technical team at NICE have looked at the submission received on 11 July 2016 from Celgene. 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 **5pm** on **Wednesday 24 August 2016.** Your response and any supporting documents should be uploaded to NICE Docs/Appraisals [embed NICE DOCS LINK on '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 Stuart Wood, Technical Lead (Stuart.Wood@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (Stephanie.Yates@nice.org.uk).

Yours sincerely

Dr Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation
Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Clinical trial information

A1. **Priority request:** Please explain whether the population in MM-003 is comparable to the total population in this appraisal. In Table 19 (page 67) of the company submission, the company reports that in the MM-003 trial the median number of prior anti-myeloma therapies was 5 with a range from 2-17 across both arms. This implies that the population in the trial had received more previous treatment than the population in the scope which specified people with 2 prior therapies or people with 3 or more prior therapies.

As stated in sections 4.13.2 and 4.13.3 of the submission, the Phase III MM-003 trial is one of the largest RCT studies to date showing activity in disease refractory to both BOR and LEN. MM-003 has been conducted in an advanced and highly refractory patient population likely to have a poor prognosis, with a reduced ability to benefit from subsequent treatment.

PFS, OS, myeloma response rate, and DOR were similar for patients aged ≤65 years and those aged >65 years, as well as for those aged >75 years. Additionally, there were no obvious differences between the TEAE profile of patients aged >75 years and that of patients aged ≤75 years in the study. The clinical effectiveness and safety of POM is therefore demonstrated across age groups relevant to clinical practice.

Because study MM-003 contains a relapsed and refractory population with a median of 5 prior lines of therapy it is even more impressive that POM+LoDex demonstrates clinical and cost-effectiveness benefits against therapies studied in less advanced populations.

- Please provide results for all outcomes specified in the scope for patients in MM-003 who have had exactly 2 prior therapies.

The results are presented for PFS (Table 1), OS (Table 2), response (Table 3) and safety (Table 4) below. Due to the small numbers of patients (n=10 in the POM+LoDex arm and n=7 in the HiDex arm) these results cannot be credibly interpreted. HRQoL has not been presented as this would have required considerable re-working of the data for only 17 patients.

The HiDex results are further confounded as two of the patients crossed-over to receive POM+LoDex and one of these crossed-over pre-progression. When considering the best response pre-cross-over of the two patients who crossed-over, no patients in the HiDex arm achieve greater than stable disease.

Table 1: PFS for patients who have received exactly 2 prior therapies.

	Statistics	POM+LD-DEX (N=10)	HD-DEX (N=7)	Overall (N=17)
Progression free survival (PFS)	N	10 (100.0)	7 (100.0)	17 (100.0)
Censored	n (%)	2 (20.0)	2 (28.6)	4 (23.5)
Progressed/Died	n (%)	8 (80.0)	5 (71.4)	13 (76.5)
Progression Free Survival Time(weeks)	Median[1]	26.1	28.1	28.1
	Two sided 95% CI[2]	[7.7, 56.1]	[8.1, 45.3]	[8.1, 45.3]
	26 Weeks Event-Free % (SE)	50.00 (15.81)	51.43 (20.39)	50.98 (12.46)
	39 Weeks Event-Free % (SE)	30.00 (14.49)	34.29 (19.51)	31.86 (11.70)
	52 Weeks Event-Free % (SE)	30.00 (14.49)	17.14 (15.56)	25.49 (10.96)

Note: CI=Confidence interval. NE = Not Estimable.
[1] The median is based on Kaplan-Meier estimate.
[2] 95% confidence interval about the median progression free survival time.
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Table 2: OS for patients who have received exactly 2 prior therapies.

	Statistics	POM+LD-DEX (N=10)	HD-DEX (N=7)	Overall (N=17)
Overall Survival (OS)	N	10 (100.0)	7 (100.0)	17 (100.0)
Censored	n (%)	6 (60.0)	4 (57.1)	10 (58.8)
Died	n (%)	4 (40.0)	3 (42.9)	7 (41.2)
Survival Time (weeks)	Median[1]	NA	NA	NA
	Two sided 95% CI[2]	[45.3, NA]	[19.4, NA]	[45.1, NA]

Note: CI=Confidence interval. NE = Not Estimable.
[1] The median is based on Kaplan-Meier estimate.
[2] 95% confidence interval about the median overall survival time.
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Table 3: Response data for patients who have received exactly 2 prior therapies.

Statistics	POM+LD-DEX (N=10)	HD-DEX (N=7)	Overall (N=17)
Response [1]	10 (100.0)	7 (100.0)	17 (100.0)
Stringent Complete Response(SCR)	0 (0.0)	0 (0.0)	0 (0.0)
Complete Response(CR)	0 (0.0)	0 (0.0)	0 (0.0)
Very Good Partial Response(VGPR)	2 (20.0)	0 (0.0)	2 (11.8)
Partial Response(PR)	2 (20.0)	2 (28.6)	4 (23.5)
Stable Disease(SD)	4 (40.0)	4 (57.1)	8 (47.1)
Progressive Disease(PD)	2 (20.0)	1 (14.3)	3 (17.6)
Response Not Evaluable(NE) [2]	0 (0.0)	0 (0.0)	0 (0.0)
With At Least One Post-Baseline Assessment	0 (0.0)	0 (0.0)	0 (0.0)
No Post-Baseline Assessment	0 (0.0)	0 (0.0)	0 (0.0)
Dichotomized response	10 (100.0)	7 (100.0)	17 (100.0)
SCR or CR or VGPR or PR	4 (40.0)	2 (28.6)	6 (35.3)
SD or PD or NE [2]	6 (60.0)	5 (71.4)	11 (64.7)

[1] Response is the best assessment of response.
[2] Including subjects who did not have any response assessment data, or whose only assessment was response not evaluable.
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Table 4: Adverse Event data for patients who have received exactly 2 prior therapies.

System Organ Class/Preferred Term[1]	POM+LD-DEX (N=10)	HD-DEX (N=7)	Overall (N=17)
Number of subjects with at least one adverse event	9 (90.0)	7 (100.0)	16 (94.1)
Blood and lymphatic system disorders	8 (80.0)	7 (100.0)	15 (88.2)
Anaemia	6 (60.0)	5 (71.4)	11 (64.7)
Neutropenia	4 (40.0)	0 (0.0)	4 (23.5)
Leukocytosis	2 (20.0)	0 (0.0)	2 (11.8)
Leukopenia	1 (10.0)	0 (0.0)	1 (5.9)
Lymphopenia	1 (10.0)	2 (28.6)	3 (17.6)
Thrombocytopenia	1 (10.0)	1 (14.3)	2 (11.8)
General disorders and administration site conditions	7 (70.0)	7 (100.0)	14 (82.4)
Asthenia	3 (30.0)	2 (28.6)	5 (29.4)
Pyrexia	3 (30.0)	0 (0.0)	3 (17.6)
Non-cardiac chest pain	2 (20.0)	0 (0.0)	2 (11.8)
Fatigue	1 (10.0)	2 (28.6)	3 (17.6)
Oedema	1 (10.0)	1 (14.3)	2 (11.8)
Pain	1 (10.0)	0 (0.0)	1 (5.9)
Chest pain	0 (0.0)	1 (14.3)	1 (5.9)
General physical health deterioration	0 (0.0)	1 (14.3)	1 (5.9)
Oedema peripheral	0 (0.0)	1 (14.3)	1 (5.9)
Respiratory, thoracic and mediastinal disorders	7 (70.0)	2 (28.6)	9 (52.9)
Dyspnoea	2 (20.0)	2 (28.6)	4 (23.5)
Dyspnoea exertional	2 (20.0)	0 (0.0)	2 (11.8)
Oropharyngeal pain	2 (20.0)	0 (0.0)	2 (11.8)
Acute pulmonary oedema	1 (10.0)	0 (0.0)	1 (5.9)
Cough	1 (10.0)	1 (14.3)	2 (11.8)
Epistaxis	1 (10.0)	1 (14.3)	2 (11.8)
Respiratory depression	1 (10.0)	0 (0.0)	1 (5.9)
Haemoptysis	0 (0.0)	1 (14.3)	1 (5.9)
Musculoskeletal and connective tissue disorders	6 (60.0)	3 (42.9)	9 (52.9)
Back pain	2 (20.0)	1 (14.3)	3 (17.6)
Bone pain	2 (20.0)	0 (0.0)	2 (11.8)

Note: Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first treatment of the study medication and within 30 days after the end of the last cycle of study drug.
[1] System organ classes and preferred terms are coded using the MedDRA dictionary version 14.0. System organ classes and preferred terms are listed in descending order of frequency of POM+LD-DEX Group. A subject with multiple occurrences of an AE is counted only once in the AE category.
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System Organ Class/Preferred Term[1]	POM+LD-DEX (N=10)	HD-DEX (N=7)	Overall (N=17)
Muscle spasms	2 (20.0)	1 (14.3)	3 (17.6)
Groin pain	1 (10.0)	0 (0.0)	1 (5.9)
Musculoskeletal pain	1 (10.0)	0 (0.0)	1 (5.9)
Arthralgia	0 (0.0)	1 (14.3)	1 (5.9)
Muscular weakness	0 (0.0)	1 (14.3)	1 (5.9)
Musculoskeletal chest pain	0 (0.0)	1 (14.3)	1 (5.9)
Pain in extremity	0 (0.0)	1 (14.3)	1 (5.9)
Gastrointestinal disorders	5 (50.0)	5 (71.4)	10 (58.8)
Diarrhoea	2 (20.0)	2 (28.6)	4 (23.5)
Nausea	2 (20.0)	2 (28.6)	4 (23.5)
Abdominal distension	1 (10.0)	1 (14.3)	2 (11.8)
Abdominal pain	1 (10.0)	0 (0.0)	1 (5.9)
Constipation	1 (10.0)	2 (28.6)	3 (17.6)
Vomiting	1 (10.0)	0 (0.0)	1 (5.9)
Dyspepsia	0 (0.0)	1 (14.3)	1 (5.9)
Flatulence	0 (0.0)	1 (14.3)	1 (5.9)
Gastrooesophageal reflux disease	0 (0.0)	1 (14.3)	1 (5.9)
Parotid gland enlargement	0 (0.0)	1 (14.3)	1 (5.9)
Stomatitis	0 (0.0)	1 (14.3)	1 (5.9)
Infections and infestations	5 (50.0)	2 (28.6)	7 (41.2)
Bronchitis	2 (20.0)	0 (0.0)	2 (11.8)
Herpes virus infection	1 (10.0)	0 (0.0)	1 (5.9)
Localised infection	1 (10.0)	0 (0.0)	1 (5.9)
Oral candidiasis	1 (10.0)	0 (0.0)	1 (5.9)
Pharyngitis	1 (10.0)	0 (0.0)	1 (5.9)
Pneumonia	1 (10.0)	0 (0.0)	1 (5.9)
Sinusitis	1 (10.0)	0 (0.0)	1 (5.9)
Upper respiratory tract infection	1 (10.0)	1 (14.3)	2 (11.8)
Cellulitis	0 (0.0)	1 (14.3)	1 (5.9)
Gastroenteritis	0 (0.0)	1 (14.3)	1 (5.9)
Tooth abscess	0 (0.0)	1 (14.3)	1 (5.9)

Note: Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first treatment of the study medication and within 30 days after the end of the last cycle of study drug.
[1] System organ classes and preferred terms are coded using the MedDRA dictionary version 14.0. System organ classes and preferred terms are listed in descending order of frequency of POM+LD-DEX Group. A subject with multiple occurrences of an AE is counted only once in the AE category.
Program Path: \\SUMSASPRODDB\data\dev\Projects\CC-4047\CC-4047-MM-003\programs\Tables\UK_NICE_2016\rae02.sas
Run Date: 17AUG2016 Data Extraction Date: 11SEP13:13:13:56

System Organ Class/Preferred Term[1]	POM+LD-DEX (N=10)	HD-DEX (N=7)	Overall (N=17)
Nervous system disorders	5 (50.0)	3 (42.9)	8 (47.1)
Dysaesthesia	2 (20.0)	0 (0.0)	2 (11.8)
Tremor	2 (20.0)	0 (0.0)	2 (11.8)
Headache	1 (10.0)	2 (28.6)	3 (17.6)
Paraesthesia	1 (10.0)	1 (14.3)	2 (11.8)
Peripheral sensory neuropathy	1 (10.0)	0 (0.0)	1 (5.9)
Amnesia	0 (0.0)	1 (14.3)	1 (5.9)
Polyneuropathy	0 (0.0)	1 (14.3)	1 (5.9)
Metabolism and nutrition disorders	3 (30.0)	5 (71.4)	8 (47.1)
Decreased appetite	1 (10.0)	2 (28.6)	3 (17.6)
Hypercalcaemia	1 (10.0)	0 (0.0)	1 (5.9)
Hyperglycaemia	1 (10.0)	0 (0.0)	1 (5.9)
Hypermagnesaemia	1 (10.0)	0 (0.0)	1 (5.9)
Hyperphosphataemia	1 (10.0)	0 (0.0)	1 (5.9)
Hypocalcaemia	1 (10.0)	0 (0.0)	1 (5.9)
Hypokalaemia	0 (0.0)	1 (14.3)	1 (5.9)
Hypophosphataemia	0 (0.0)	1 (14.3)	1 (5.9)
Increased appetite	0 (0.0)	1 (14.3)	1 (5.9)
Psychiatric disorders	3 (30.0)	4 (57.1)	7 (41.2)
Depression	1 (10.0)	0 (0.0)	1 (5.9)
Insomnia	1 (10.0)	3 (42.9)	4 (23.5)
Nervousness	1 (10.0)	0 (0.0)	1 (5.9)
Anxiety	0 (0.0)	1 (14.3)	1 (5.9)
Confusional state	0 (0.0)	1 (14.3)	1 (5.9)
Hallucination	0 (0.0)	1 (14.3)	1 (5.9)
Sleep terror	0 (0.0)	1 (14.3)	1 (5.9)
Renal and urinary disorders	2 (20.0)	3 (42.9)	5 (29.4)
Renal failure	1 (10.0)	1 (14.3)	2 (11.8)
Renal failure acute	1 (10.0)	1 (14.3)	2 (11.8)
Dysuria	0 (0.0)	2 (28.6)	2 (11.8)
Haematuria	0 (0.0)	2 (28.6)	2 (11.8)

Note: Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first treatment of the study medication and within 30 days after the end of the last cycle of study drug.
[1] System organ classes and preferred terms are coded using the MedDRA dictionary version 14.0. System organ classes and preferred terms are listed in descending order of frequency of POM+LD-DEX Group. A subject with multiple occurrences of an AE is counted only once in the AE category.
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System Organ Class/Preferred Term[1]	POM+LD-DEX (N=10)	HD-DEX (N=7)	Overall (N=17)
Polyuria	0 (0.0)	1 (14.3)	1 (5.9)
Cardiac disorders	1 (10.0)	2 (28.6)	3 (17.6)
Cardiac failure	1 (10.0)	0 (0.0)	1 (5.9)
Ischaemic cardiomyopathy	1 (10.0)	0 (0.0)	1 (5.9)
Palpitations	1 (10.0)	1 (14.3)	2 (11.8)
Atrial fibrillation	0 (0.0)	1 (14.3)	1 (5.9)
Ear and labyrinth disorders	1 (10.0)	0 (0.0)	1 (5.9)
Vertigo	1 (10.0)	0 (0.0)	1 (5.9)
Eye disorders	1 (10.0)	1 (14.3)	2 (11.8)
Conjunctivitis	1 (10.0)	0 (0.0)	1 (5.9)
Cataract	0 (0.0)	1 (14.3)	1 (5.9)
Immune system disorders	1 (10.0)	0 (0.0)	1 (5.9)
Drug hypersensitivity	1 (10.0)	0 (0.0)	1 (5.9)
Injury, poisoning and procedural complications	1 (10.0)	1 (14.3)	2 (11.8)
Rib fracture	1 (10.0)	0 (0.0)	1 (5.9)
Contusion	0 (0.0)	1 (14.3)	1 (5.9)
Excoriation	0 (0.0)	1 (14.3)	1 (5.9)
Investigations	1 (10.0)	3 (42.9)	4 (23.5)
Electrocardiogram QT prolonged	1 (10.0)	0 (0.0)	1 (5.9)
Neutrophil count increased	1 (10.0)	0 (0.0)	1 (5.9)
Blood creatinine increased	0 (0.0)	1 (14.3)	1 (5.9)
Blood lactate dehydrogenase increased	0 (0.0)	1 (14.3)	1 (5.9)
Platelet count decreased	0 (0.0)	1 (14.3)	1 (5.9)
Weight decreased	0 (0.0)	1 (14.3)	1 (5.9)
Weight increased	0 (0.0)	1 (14.3)	1 (5.9)
Skin and subcutaneous tissue disorders	1 (10.0)	3 (42.9)	4 (23.5)
Hyperhidrosis	1 (10.0)	0 (0.0)	1 (5.9)

Note: Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first treatment of the study medication and within 30 days after the end of the last cycle of study drug.
[1] System organ classes and preferred terms are coded using the MedDRA dictionary version 14.0. System organ classes and preferred terms are listed in descending order of frequency of POM+LD-DEX Group. A subject with multiple occurrences of an AE is counted only once in the AE category.
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System Organ Class/Preferred Term[1]	POM+LD-DEX (N=10)	HD-DEX (N=7)	Overall (N=17)
Erythema	0 (0.0)	1 (14.3)	1 (5.9)
Night sweats	0 (0.0)	1 (14.3)	1 (5.9)
Pruritus	0 (0.0)	1 (14.3)	1 (5.9)
Rash erythematous	0 (0.0)	1 (14.3)	1 (5.9)
Skin ulcer	0 (0.0)	1 (14.3)	1 (5.9)
Swelling face	0 (0.0)	1 (14.3)	1 (5.9)
Vascular disorders	1 (10.0)	2 (28.6)	3 (17.6)
Hypertension	1 (10.0)	1 (14.3)	2 (11.8)
Hot flush	0 (0.0)	1 (14.3)	1 (5.9)

Note: Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first treatment of the study medication and within 30 days after the end of the last cycle of study drug.
[1] System organ classes and preferred terms are coded using the MedDRA dictionary version 14.0. System organ classes and preferred terms are listed in descending order of frequency of POM+LD-DEX Group. A subject with multiple occurrences of an AE is counted only once in the AE category.
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- Please provide the interquartile range (IQR) around the median number of prior anti-myeloma therapies reported in table 19 for the MM-003 trial.

Table 5: Quartiles around the median number of prior anti-myeloma therapies

Statistic	POM+LD-DEX (N=302)	HD-DEX (N=153)	Overall (N=455)
N	302	153	455
Mean	5.0	5.2	5.1
Median	5.0	5.0	5.0
SD	1.99	2.22	2.07
Quartiles (Q1,Q3)	(4, 6)	(4, 6)	(4, 6)
Min,Max	(2, 14)	(2, 17)	(2, 17)

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- Please provide a histogram of the number of prior anti-myeloma therapies in the MM-003 trial.

Figure 1: Number of Prior Anti-Myeloma Therapies - ITT Population: POM+LoDex

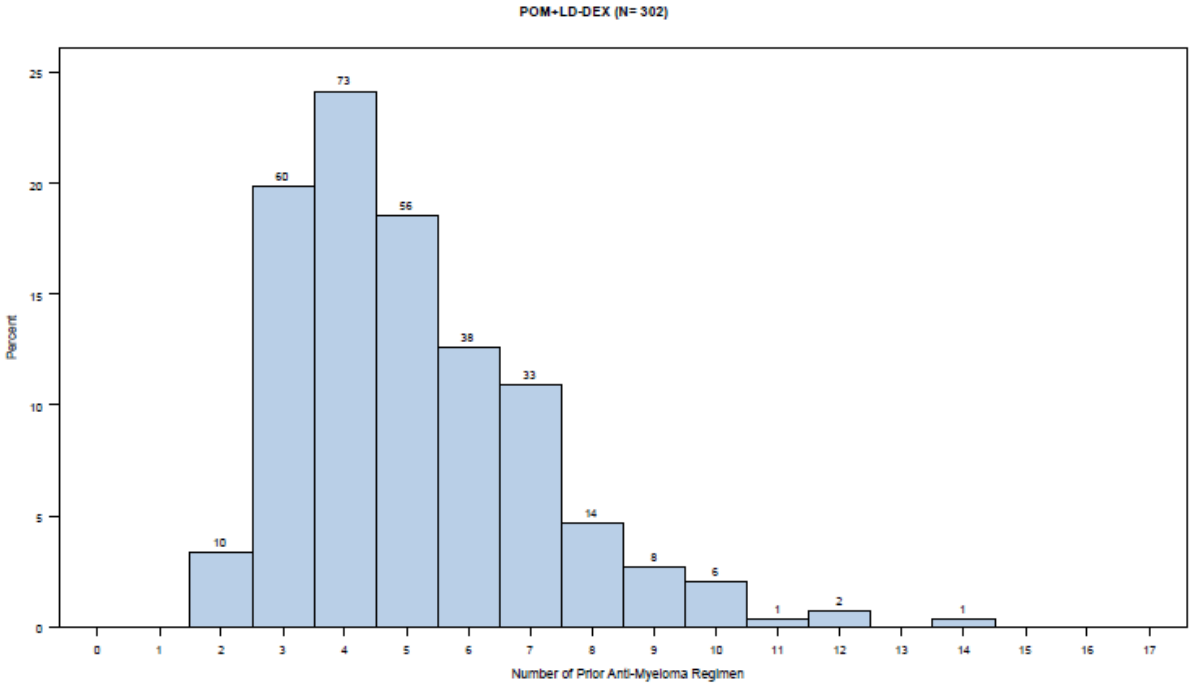


Figure 2: Number of Prior Anti-Myeloma Therapies - ITT Population: HiDex

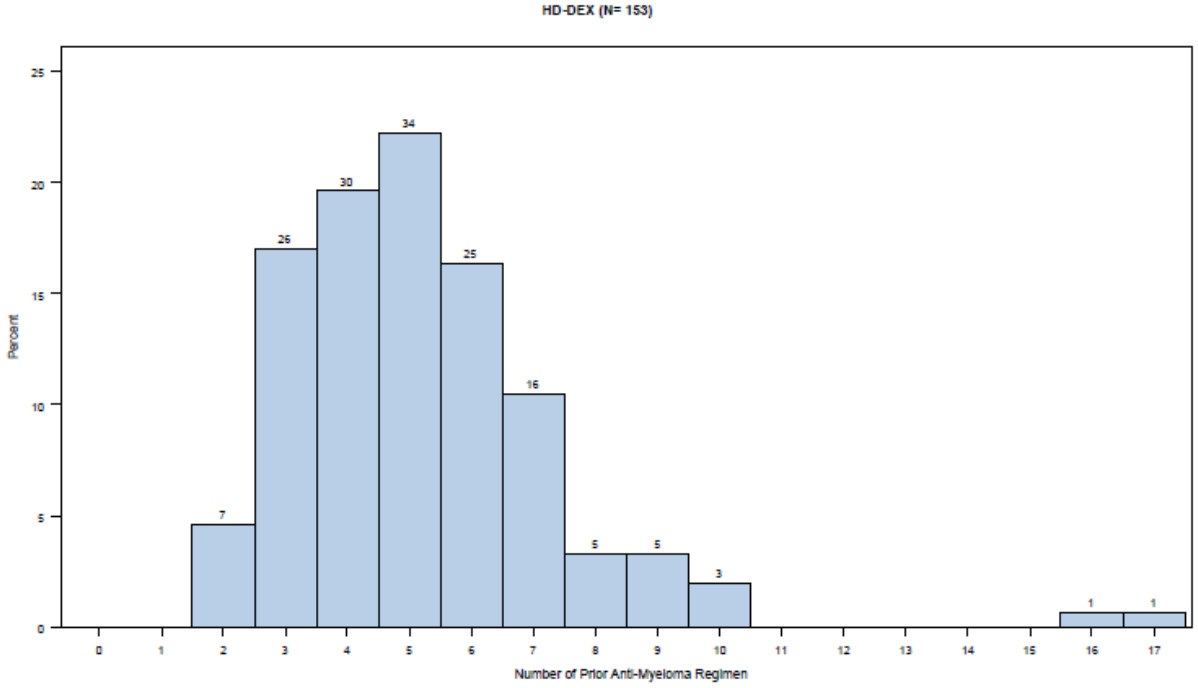
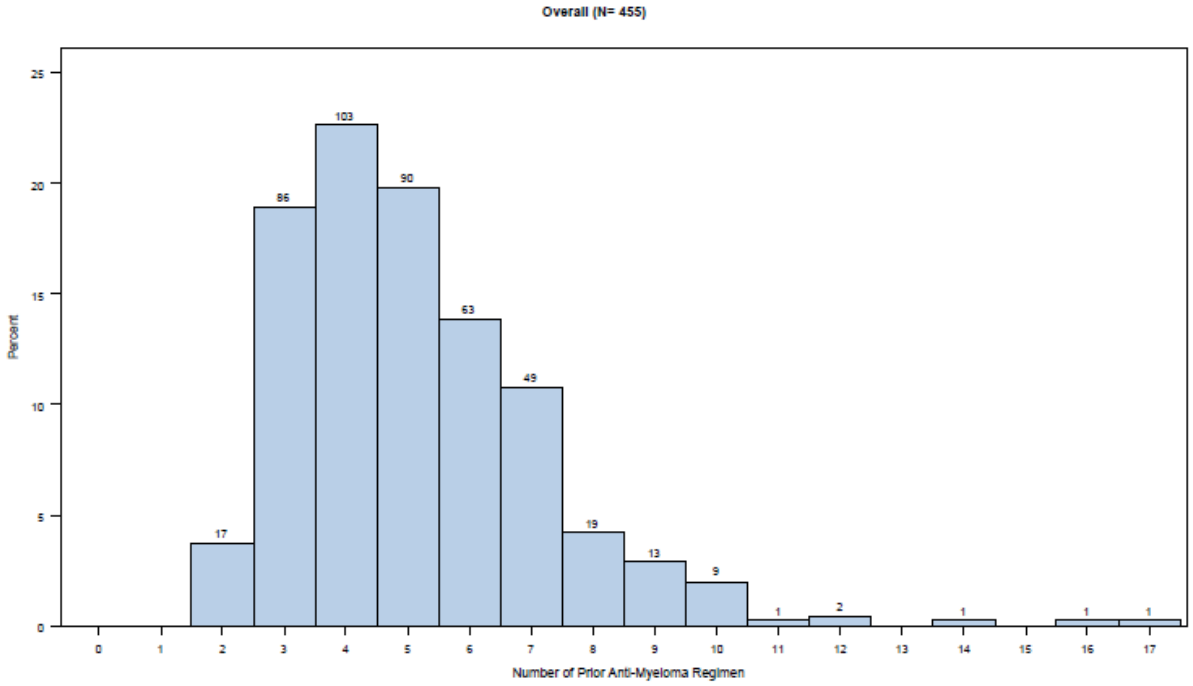


Figure 3: Number of Prior Anti-Myeloma Therapies - ITT Population: Overall



Statistical analysis

A2. **Priority request:** Please clarify the following points in relation to the statistical analyses:

- Section 4.10.2 (page 92): Please provide full details of the statistical methods used to evaluate multicollinearity and any cut-offs used (e.g. variance inflation factor > 10), as well as the statistical commands and software used.

Correlation (multicollinearity) was assessed using Pearson's product moment correlation coefficient. Correlation between variables was assessed using statistical software R, utilising the *rcorr* function within the *Hmisc* package. Figure 5 (Appendix 12) shows the correlation between each of the variables considered for potential inclusion within the statistical model. No strict cut-off values for correlation and/or statistical significance were used to determine which covariates were selected for inclusion in the statistical regression models. Rather, as the ability to indirectly compare POM and BEN relies totally upon being able to adjust for as many differences as possible between study populations, the selection of covariates was based on including an optimal amount of clinically relevant factors known to be prognostic, while taking into consideration the statistical significance of, correlation between, and availability of, covariates.

- Appendix 12 (page 89): Please provide details of how correlation was assessed, e.g. size and statistical significance of the Pearson correlation coefficient. Please report the correlation coefficients in Table 29 of the main submission.

As detailed in the response above and in the manufacturer submission (page 92), correlation between explanatory variables was assessed using Pearson's product moment correlation coefficients, which are presented in Figure 5 (Appendix 12), showing correlation between all variables considered for potential inclusion within the statistical regression model. The statistical significance of the correlation coefficients between variables are presented in

Table 6. Treatment arm is significantly correlated with number of prior lines of therapy, receipt of prior thalidomide and refractory to LEN ($p<0.05$); however, the regression model attempts to adjust for the imbalances between treatment arms as there are multiple sources of (non-randomised) study data. Statistically significant correlation is also observed between prior SCT and age at baseline ($p<0.05$), number of prior lines of therapy and disease duration ($p<0.05$), number of prior lines of therapy and refractory status to LEN ($p=0.004$), receipt of prior THAL and refractory status to LEN ($p=0.015$) and prior SCT and disease duration ($p=0.046$).

Due to statistically significant correlation between prior SCT and age, together with clinical consideration of the two covariates, prior SCT was not included in the statistical model. Similarly, due to the significant correlation between disease duration and number of prior lines of therapy, together with clinical consideration of the two covariates, disease duration was not included in the statistical model. While there was observed correlation between refractory status to LEN and receipt of prior THAL and number of prior lines of therapy, all three covariates were included in the statistical model, as it was believed that these were all clinically important/relevant prognostic factors and the values of Pearson's product moment correlation coefficients were not too high (correlation=-0.18 and correlation=0.21 respectively).

Table 6: Pearson's correlation coefficient p-values

	Arm	Age	Prior lines of therapy	Receipt of prior THAL	Refractory to LEN	Prior SCT	Disease duration
Arm	NA						
Age	0.524	NA					
Prior lines of therapy	**<0.001**	0.323	NA				
Receipt of prior THAL	**<0.001**	0.443	0.244	NA			
Refractory to LEN	**<0.001**	0.384	**0.004**	**0.015**	NA		
Prior SCT	0.422	**<0.001**	0.402	0.961	0.531	NA	
Disease duration	0.702	0.464	**<0.001**	0.056	0.713	**0.046**	NA

Key: LEN, lenalidomide; SCT, stem cell transplantation; THAL, thalidomide
Notes: Bold denotes statistical significance at the 5% level; NA, not applicable.

The correlation coefficients have been added to Table 7 taken from the manufacturer submission represented below as follows:

Table 7: Prognostic factor selection

Covariate	Identified as influential on median survival time in prognostic factor SLR?		Included in TA338?	Identified as relevant by clinicians?	Issues with multicollinearity?	Data availability
	OS (reports/ significance)	PFS (reports/ significance)				
Treatment arm	N/A	N/A	Current care inc. as 1	Y	N	All
Age at start of treatment	11 / 5	11 / 2	Y	Y	Correlated with prior SCT (Pearson's PMCC=-0.47)	All
Disease duration (time since diagnosis)	4 / 2	2 / 2	Y	N	Correlated with no of prior lines (Pearson's PMCC=0.43)	All
Prior lines of therapy	7 / 3	8 / 5	N	Y	Correlated with disease duration (Pearson's PMCC=0.43)	All
ISS stage	10 / 3	9 / 0	Y	Y	N	MM003, MM010, Tarant, MUK-one
Prior THAL	7 / 2	4 / 1	Y	Y	N	All
Prior SCT	9 / 2	10 / 0	Y	N	Correlated with age (Pearson's PMCC=-0.47)	All
Refractory to LEN	9 / 6 [a]	3 / 2 [a]	Y	Y	N	All
Refractory to BOR			Y	Y	N	MM003, MM010, MM002, Tarant, Gooding
ECOG status at start of treatment	4 / 3	2 / 0	N	Y	-	MM003, MM010, MM002
Creatinine clearance at start of treatment	NR, 5 /2 for renal function	8 / 1	N	Y	-	MM003, MM010, MM002
Cytogenetics (note difference categorisations used	19 / 9	18 / 13	N	N[b]	-	MM003, MM010, MM002

Covariate	Identified as influential on median survival time in prognostic factor SLR?		Included in TA338?	Identified as relevant by clinicians?	Issues with multicollinearity?	Data availability
	OS (reports/ significance)	PFS (reports/ significance)				
across papers)						
Disease history (extramedullary manifestations and osteolytic lesions)	2 / 0	NR	N	N		NR
Sex	7 / 2	8 / 1	N	N		All
Durie-Salmon Stage	3 / 1	2 / 1	N	N		MM003, MM010, MM002
Haemoglobin	6 / 4	3 / 1	N	N		MM003, MM010, MM002
LDH	8 / 6	3 / 1	N	N		MM003, MM010, MM002
Paraprotein class	8 / 0	7 / 0	N	N		MM003, MM010, MM002
Platelets	4 / 3	1 / 0	N	N		MM003, MM010, MM002
Beta 2 microglobulin	6 / 5	2 / 2	N	N		MM003, MM010, MM002
Albumin	NR	2 / 1	N	N		MM003, MM010, MM002
Light chain type	3 / 1	2 / 1	N	N		MM003, MM010, MM002

Key: BOR, bortezomib; Pearson's PMCC, Pearson's Product Moment Correlation Coefficient; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; LDH, lactate dehydrogenase; LEN, lenalidomide; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival; SCT, stem cell transplantation; SLR, systematic literature review; TA, technical appraisal; THAL, thalidomide.

Notes: a refractoriness / type relapse or progression, b Clinicians stated non informative and not used at this stage of disease.

Colour coding used for prognostic SLR: Green: 5 or more reports and >50% were significant, Yellow: Either 5 or more reports or >50% of reports were significant, Orange: Neither of the above.

- Section 4.10.2 (Table 29, page 93): Please explain why the multicollinearity column is blank for some covariates. Please clarify the significance levels used in the overall survival (OS) and progression-free survival (PFS), as 'significance' may have been defined differently in different studies.

Some cells in Table 29 are blank due data not being reported for the comparator BEN arm; these variables were not captured in comparator data at a study level so could not be included in the analysis. Therefore, we did not test correlation between these factors as it was not possible to include them in the statistical regression models.

- Section 4.10.2 (page 96): Please provide justification for why the cut-off of 50% missing data was chosen when selecting covariates for the comparison of pomalidomide plus low dose dexamethasone with bendamustine.

Covariates of interest were determined using the following process: availability of the data was assessed first, correlation was assessed in the second instance, and then clinical rationale was used in order to select the final set of covariates.

It was considered that if <50% of patients had information for a prognostically relevant covariate then it would not be feasible for analysis to be conducted robustly as not enough information would be present.

Within the final analysis, however, this cut-off was not used in order to select covariates for inclusion within the statistical regression models as all covariates of interest were either well reported within each dataset with low levels of missing information or were entirely missing (i.e. not collected).

- Page 112: the company submission states 'Patients with missing data for any of the clinically-relevant prognostic factors were not included in the analyses.'
    - How many patients were excluded from each analysis due to missing data?

The flow chart in Figure 13 in the manufacturer submission details the amount of missing covariate data for each of the studies included in the statistical regression model and is summarised as follows:

* Base case analysis – no missing covariate data.

* Sensitivity analysis 1 – no missing covariate data.

* Sensitivity analysis 2 – Tarant (n=1), MUK-One (n=1), Gooding (n=17), MM003 (n=12), MM002 (n=113), MM010 (n=32) – all missing data are due to lack of recorded ISS stage. Since this prognostic factor is missing at the study level for Gooding and MM002, these studies were not included in this sensitivity analysis.

* Sensitivity analysis 3 – no missing covariate data as the data set matches that used in sensitivity analysis 2 but ISS stage is not included in the analysis.

- Did the company consider using simple or multiple imputation methods to impute the missing data? If not, please provide an explanation.

Due to missing ISS stage data at the study level for both Gooding and MM002, imputation methods could not reliably be applied for these studies in an unbiased manner, especially as the use of covariates was used as the key to forming the indirect comparison. Also, there was minimal missing data across the other studies for ISS stage, so imputation was not explored, as it was considered that the issues and biases of imputation at the study (and therefore treatment) level outweighed the minimal additional patient data in the analyses.

- Section 4.10.2 Methods used for covariate adjustment in the comparison of pomalidomide plus low dose dexamethasone with bendamustine plus thalidomide and dexamethasone

  - Please provide full details of the analysis methods, and the relevant R code. Please specify the type of model used (e.g. Cox proportional hazards model, Weibull model etc.), how censoring was defined, whether or not the proportional hazards assumption was checked, and any other derivations or assumptions used.

Definition of censoring (consistent with the primary trial analysis)

The primary analysis for PFS (which was used within the covariate adjusted models) followed the censoring rules based on the EMEA guideline on the evaluation of anti-cancer medicinal products; alternative censoring rules based on the FDA guideline were presented within the main clinical trial analysis in the clinical study report and showed consistent outcomes with the primary analysis. Table 7 provides a summary of the censoring rules for the two sets of guidelines.

Table 8: Censoring rules applied to PFS

Situation	Primary Analysis (EMEA Guideline)	Sensitivity Analysis (FDA Guideline)
No baseline assessments and alive after 2 scheduled assessments	IRAC assessment: censored at date of randomization Investigator assessment: not applicable	Same
Death within the first 2 scheduled assessments without any adequate response assessment	Event at date of death	Same
Progression documented between scheduled assessments	Event at date of documented progression.	Event at date of last scheduled adequate assessment prior to the unscheduled assessment when progression was detected; if no adequate assessment at scheduled visits existed at prior to the unscheduled visit, event date was 1 day after randomization
Death between adequate assessments	Event at date of death	Same
No progression	Censored at date of last adequate assessment with evidence of no progression; if no adequate assessment existed, then censored at randomization date	Same
Death or progression from the long-term follow-up within 2 months after the latest of: treatment phase discontinuation date, end date of study drug in last cycle, and last adequate assessment date during the treatment phase	Event at date of death or documented progression	Same
Death or progression from the long-term follow-up more than 2 months after the latest of: treatment phase discontinuation, end date of study drug in last cycle, and last adequate assessment date during the treatment phase	Censored at date of last adequate assessment with evidence of no progression; if no adequate assessment existed, then censored at randomization date	Same
New anti-myeloma/non-protocol treatment started prior to progression	Event at date of documented progression	Censored at date of last adequate assessment with evidence of no progression before other treatment; if no adequate assessment existed before other treatment, then censored at randomization date
Death or progression during treatment phase after an extended lost-to-follow-up time (2 or more missed scheduled assessments)	Event at date of death or documented progression	Censored at date of last adequate assessment with evidence of no progression before other treatment; if no adequate assessment existed before other treatment, then censored at randomization date

Overall survival was censored at the last date that the subject was known to be alive for subjects who were alive at the time of analysis and for subjects who were lost to follow-up before death was documented.

Time to treatment failure was defined as a composite endpoint measuring time from randomization to treatment failure events including any PD, treatment phase discontinuation due to any reasons, death, or start of another anti-myeloma therapy, whichever occurred earlier.

Methods used to conduct the analysis

In the first instance, a Cox proportional hazards model was fitted to explore the relationship between the selected prognostic factors and survival prognosis. The function used was *coxph* within the *survival* package in R. A series of parametric models were fitted to the data, including exponential, Weibull, log-normal, log-logistic, Gompertz and generalised gamma as described further in Section 5.3.7 of the manufacturer's submission using *flexsurvreg* within the *flexsurv* package in R.

The proportional hazards assumption was explored by way of inspection of Kaplan-Meier curves and log cumulative hazard plots (as described in more detail in the Section 5.3.7 of the manufacturer's submission). In addition, Q-Q plots were examined to assess the suitability of particular accelerated failure time models.

The r code has been uploaded to NICE DOCS labelled as 'A2.6 R code.R'.

- According to the company submission, 'it was not possible to include study as a fixed effect in the statistical models due to linear dependence (...), and therefore it was impossible to determine the study effect when simultaneously estimating the treatment effect'. Although each study contained one treatment, the ERG considers that it may have been possible to include a covariate for study to account for the fact that results were from different studies. Please clarify whether all available methods for adjusting for study in the analysis were explored.

We are unaware of any methods that may be applied to the data in order to adjust for both treatment and study variables, when both predictors are linearly dependent – i.e. each study only contains one treatment arm. Following the ERG suggestion an attempt was made to conduct this analysis in R and as expected a warning message was produced when attempting to adjust for the trial effect:

"Warning message: X matrix deemed to be singular"

This error is produced due to the predictors being linearly dependent. We could not find information on any methods to adjust for study in when linear dependence exists.

- Please provide covariate adjusted data used to generate the covariate adjusted Kaplan-Meier (KM) curves (e.g. Figure 15 and 17 in the company submission) for overall survival (OS) and progression free survival (PFS) for pomalidomide plus low dose dexamethasone and bortezomib. Please provide the statistical software scripts with corresponding datasets (i.e. all relevant files) which were used to derive all the coefficients for all covariate adjustment analyses that were needed to estimate the HRs and KM curves.

The raw data for the base case analysis are supplied via NICE DOCS as separate files for both OS and PFS (labelled as 'base case analysis dataset_OS.csv' and base case analysis dataset_PFS.csv'). The programming functions used in R were *coxph* and *survfit* within the *survival* package.

This is also provided via NICE DOCS labelled as 'A2.7 R code.R'.

- On page 109 of the company submission, two sensitivity analyses surrounding the inclusion/exclusion of International Staging System (ISS) stage as a prognostic factor are reported. Please explain why the overall goodness of fit or predictive power (e.g. the adjusted R square) was not used in determining the covariate adjustment regression, e.g. to check how including ISS improves the predictive power of the regression function. If goodness-of-fit was checked then please provide the relevant statistics.

While the sensitivity analyses were performed in order to see the impact of ISS stage on survival prognosis, the various models were not formally compared to select the best fitting model for the base case. ISS stage is believed to be an important prognostic factor that has a substantial impact on survival outcomes; however, this variable was not captured at the study level for MM002 and Gooding, and therefore, two sensitivity analyses were performed (on the maximum available data) in order to test the sensitivity of including this variable and to investigate the differences in survival prognosis when adjusting for ISS stage. These two sensitivity analyses enabled this impact to be explored using a consistent data set.

The base case was subsequently selected as it was believed that the MM002 POM data were more similar to the comparator BEN data where low levels of refractoriness were observed within the patients included (rather than being selected based on statistical reasoning (e.g. model fit) due to lower levels of refractoriness exhibited within this trial compared to the remainder of the POM+LoDEX data.

Additionally, both MM-003 and MM-010 required patients to have failed prior LEN and BOR according to defined criteria for study inclusion. MM-002 was less strict and did not require this. This is more in line with the inclusion / exclusion criteria for MUK-1 which forms the bulk of the BEN data. More details for selection of the base case data set are provided in Section 4.10.2 of the manufacturer's submission.

- Section 4.10.3 (page 113) states that 'a propensity matched adjusted indirect comparison (MAIC) approach was adopted using SAS'.
    - Please provide full details of this analysis, including analysis methods used, covariates included in the analysis, survival models used, and any derivations and assumptions made.
    - Please also provide the relevant SAS code.
    - Please provide MAIC un-weighted and MAIC weighted data to generate weighted and un-weighted KM curves for pomalidomide plus low dose dexamethasone and panobinostat plus bortezomib and dexamethasone.
    - Please also provide the statistical software scripts with corresponding datasets (i.e. all relevant files) which were used in deriving the propensity weights and the MAIC Cox proportional hazards model results in Table 34.

In the absence of a common comparator to form indirect treatment comparisons (ITCs) between pomalidomide and panobinostat, and in the absence of patient level data (PLD) for panobinostat, the following steps were taken to form the ITC between pomalidomide and panobinostat:

1. Pseudo PLD were recreated from published Kaplan-Meier (KM) curves of panobinostat (from the PANORAMA 2 trial, as detailed in Section 4.10.3 of the submission). The pseudo PLD were created by first digitizing the KM plot to obtain summary KM data, then secondly using the Guyot 2012 algorithm together with known patient numbers for the panobinostat group.
2. To attempt to control for differences between studies, and therefore, form the ITC, the pomalidomide PLD were assigned propensity weights reflecting their 'probability' of coming from a population defined by the average panobinostat baseline characteristics.
    a. The pomalidomide PLD used for this comparison were from the MM-002, MM-003 and MM-010 datasets. As the full panobinostat population consisted of patients that were refractory to bortezomib and not primary refractory. As propensity weighting cannot incorporate covariates that have 100% allocation to a given category, the pomalidomide PLD was subset to only include patients that were refractory to bortezomib and not primary refractory. This subset amounted to approximately 81% of the full pomalidomide PLD.

b. The covariates used to derive the propensity weights were age (continuous), number of prior lines of therapy (continuous), ECOG (0 [reference category], 1, and 2+), and prior thalidomide therapy (yes, no [reference category]).

c. The weights were calculated using a logistic regression where the outcome is treatment (pomalidomide=1, panobinostat=0), and the covariates were age (continuous), number of prior lines of therapy (continuous), ECOG (0 [reference category], 1, and 2+), and prior thalidomide therapy (yes, no [reference category]).

d. The input data for the logistic regression to calculate weights for the OS dataset are given in the file "MAIC_pre_match_data_os.csv" (and "MAIC_pre_match_data_pfs.csv" for the PFS).

e. The SAS code used for the logistic regression is given below:

```
/* Perform logistic regression to calculate propensity weights that patients are assigned to POM
*/
proc logistic data= MAIC_pre_match_data_os;
  model pomtrt=age priorlines ecog1 ecog2p priorthal ;
  output out=predprob(keep=trial patient_id pomtrt ip_0 age priorlines       ecog1 ecog2p
priorthal time event where=(pomtrt=1)) predprobs=i;
run;
```

f. The probability (weight) derived in the logistic regression, were then calibrated to ensure that the average weight across all patients was 1. The resulting dataset for OS was appended to the pseudo panobinostat PLD and is provided in the file "MAIC_post_match_data_os.csv" (and "MAIC_post_match_data_pfs.csv" for the PFS). Note, for the purpose of comparison of adjusted and unadjusted pomalidomide data, 2 versions of pomalidomide PLD are provided in this dataset; "weighted POM" where the weights provided are as derived above, and "unweighted POM" where the weights are all assigned to 1.

3. The KM plots were produced using the following SAS code:

```
proc lifetest data= MAIC_post_match_data_os notable
        plots=survival(atrisk=0 to 1600 by 100);
  time time*event(0);
  strata treatment;
  weight propwt;
run;
```

The hazard ratios and confidence intervals were produced using a Cox proportional hazards model (weighted and unweighted), via the following code:

```
/* HR of PANO vs reweighted POM */
proc phreg data= MAIC_post_match_data_os(where=(treatment ne "unweighted POM"));
  class treatment;
  model time*event(0)=treatment / risklimits ;
  weight propwt;
run;

/* HR of PANO vs unweighted POM – naïve comparison */
proc phreg data= MAIC_post_match_data_os(where=(treatment ne "weighted POM"));
  class treatment;
  model time*event(0)=treatment / risklimits ;
run;
```

A3. In section 4.10.1, the company submission states that only studies with > 50 patients were included in the 'indirect comparisons'. Please clarify the justification for the cut-off and report whether any studies excluded based on this criteria could have allowed an indirect comparison or network meta-analysis to be performed.

The cut-off of 50 patients was selected in order to identify only larger higher quality trials. The data available from the two highest quality data sources for comparators represented larger bodies of information:

- 78 patients across datasets for BEN (after subsetting datasets to those who had received prior BOR and LEN)
- 55 patients for PANO+BOR+DEX

All trials available for POM+LoDEX used within the statistical analysis had >100 patients. During the previous appraisal process the NICE committee indicated their unwillingness to base decisions on small datasets (n=30 patients from the Gooding study; n=56 from Gooding and Tarant) even when patient characteristics were available to allow adjustment for differences in patient characteristics, we therefore excluded small studies from consideration in line with this advice. The cut-off was chosen such that some information was available for PANO+BOR+DEX.

Appendix 4 provides the reasons for exclusion of each dataset from consideration for statistical analysis. No comparator studies were excluded on the basis of small population alone, exclusion based upon population size only occurred for small investigator lead studies for POM+LoDEX. All comparator studies excluded were on the basis of a combination of factors e.g. small population size and no ability to subset to patients who had received both prior LEN and BOR. All studies excluded were single arm studies. As such, including additional studies would not have allowed a network meta-analysis to be performed.

A4. On page 51 of the company submission the company states: 'This submission included studies where at least 75% of adult RRMM patients had received both bortezomib and lenalidomide to focus the evidence base to a comparable patient population'. Please clarify the justification for the cut-off and report which (if any) studies were excluded based on this criterion.

The population of interest for this submission was patients with relapsed or refractory multiple myeloma after receiving at least two prior therapies that included bortezomib and lenalidomide. Therefore, for the presented evidence to be consistent with the population of interest, only studies where the majority of patients met this criterion were included in the submission.

As reported in Figure 5, in Section 4.1 of the submission, 24 references relating to 5 studies were excluded for this reason. For your convenience this is presented in

Figure **4**, below. The references for the studies excluded from the submission are presented in Table 6, in Appendix 2.6 of the main submission.

The specific references that were excluded for this reason are presented here in

Table 9. In all cases very few patients had received prior BOR and LEN making these papers non-relevant for submission.

Figure 4: PRISMA flow diagram for evidence included in the submission

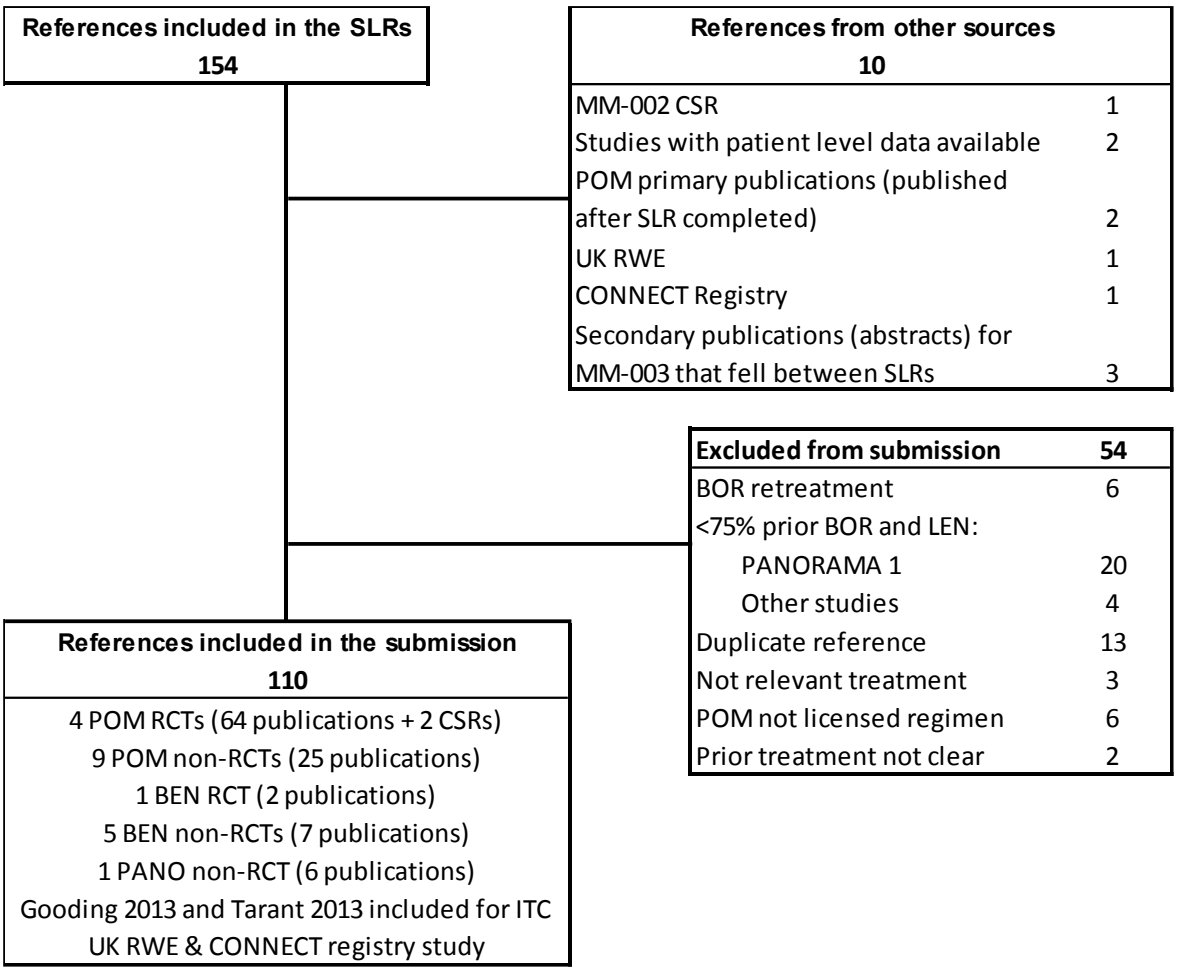


Table 9: References excluded from the submission

No.	Reference	
Reason for exclusion: <75% prior BOR and LEN		**Relevance**
1	San-Miguel JF, Hungria VTM, 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. The Lancet Oncology. 2014; 15:1195-206	PAN+BOR+DEX arm (N = 387): BOR 44%; LEN 19% Placebo+BOR+DEX arm (N = 381): BOR 42%; LEN 22%
2	San-Miguel JF, Hungria VTM, Yoon SS, et al. Update on a phase III study of panobinostat with bortezomib and dexamethasone in patients with relapsed multiple myeloma: PANORAMA 1. Blood. 2011; 118.	Linked references to San-Miguel, 2014, above.
3	Richardson P, Hungria V, Moreau P, et al. Panorama 1: A phase III study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma. Haematologica. 2012; 97:117-8.	
4	San-Miguel JF, Moreau P, Yoon S-S, et al. Phase III study of panobinostat with bortezomib and dexamethasone in patients with relapsed multiple myeloma (PANORAMA 1). Journal of Clinical Oncology 2012; 30(15 SUPPL.1).	
5	Richardson PG, Hungria VTM, Yoon SS, et al. Characterization of the incidence and management of gastrointestinal toxicity in the phase 3 panorama 1 study of panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma. Blood. 2014; 124.	
6	Richardson PG, Hungria VTM, Yoon SS, et al. Panorama 1: A randomized, double-blind, phase 3 study of panobinostat or placebo plus bortezomib and dexamethasone in relapsed or relapsed and refractory multiple myeloma. Journal of Clinical Oncology. 2014; 32	
7	San-Miguel J, Hungria VT, Yoon SS, et al. Randomized, double-blind, placebo-controlled phase 3 study of panobinostat or placebo plus bortezomib and dexamethasone in relapsed or relapsed and refractory multiple myeloma (panorama 1). Haematologica. 2014; 99:219-20.	
8	San Miguel J, Hungria VTM, Yoon SS, et al. Efficacy and safety based on duration of treatment of panobinostat plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma in the phase 3 panorama 1 study. Blood. 2014; 124.	
9	Einsele H, Richardson P, Hungria V, et al. Subgroup analysis by prior treatment among patients with relapsed or relapsed and refractory multiple myeloma in the panorama 1 study of panobinostat or placebo plus bortezomib and dexamethasone. Haematologica. 2015; 100:1.[7]	
10	Hungria VTM, San Miguel JF, Yoon SS, et al. Analysis of outcomes based on response for patients with relapsed or relapsed and refractory multiple myeloma in the phase 3 PANORAMA 1 study. Journal of Clinical Oncology. 2015; 33.[8]	

11	Majer I, Krishna A, Van De Wetering G, et al. Estimating utilities for panobinostat in combination with bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed and/or refractory multiple myeloma; evidence from the panorama-1 trial. Blood. 2015; 126:4504.[9]	
12	Moreau P, San-Miguel J, Hungria V, et al. Analysis of outcomes by response for patients with relapsed or relapsed and refractory multiple myeloma in the phase 3 panorama 1 study of panobinostat or placebo plus bortezomib and dexamethasone. Haematologica. 2015; 100:80-1.	
13	Richardson PG, Hungria VTM, Yoon SS, et al. Subgroup analysis by prior treatment of the efficacy and safety of panobinostat plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma in the panorama 1 study. Clinical Lymphoma, Myeloma and Leukemia. 2015; 15:e78.	
14	Correction to Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: A multicentre, randomised, doubleblind phase 3 trial [Lancet Oncol, 15, (2014) 1195-1206]. The Lancet Oncology. 2015; 16:e6.	
15	San Miguel JF, Hungria VTM, Yoon SS, et al. Analysis of outcomes based on response in patients with relapsed or relapsed and refractory multiple myeloma treated with panobinostat or placebo in combination with bortezomib and dexamethasone in the panorama 1 trial: Updated analysis based on prior treatment. Blood. 2015; 126:4230.	
16	San Miguel JF, Hungria VTM, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma who received prior bortezomib and IMiDs: A predefined subgroup analysis of PANORAMA 1. Journal of Clinical Oncology. 2015; 33.	
17	San-Miguel JF, Hungria VTM, Yoon SS, et al. Final analysis of overall survival from the phase 3 panorama 1 trial of panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma. Blood. 2015; 126:3026.	
18	San-Miguel JF, Hungria VTM, Yoon SS, et al. Impact of treatment duration and dosing on efficacy and safety in a phase 3 study of panobinostat plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma. Clinical Lymphoma, Myeloma and Leukemia. 2015; 15:e270-e1.	
19	Mu S, Kuroda Y, Shibayama H, et al. Panobinostat PK/PD profile in combination with bortezomib and dexamethasone in patients with relapsed and relapsed/refractory multiple myeloma. European Journal of Clinical Pharmacology. 2016; 72:153-61.[10]	
20	Richardson PG, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone in previously treated multiple myeloma: outcomes by prior treatment. Blood. 2016; 127:713-21.[11]	
21	Ponisch W, Rozanski M, Goldschmidt H, et al. Combined bendamustine, prednisolone and thalidomide for refractory or relapsed multiple myeloma after autologous stem-cell transplantation or conventional chemotherapy: results of a Phase I clinical trial. British journal of haematology. 2008; 143(2):191-200.	Prior LEN: not reported Prior BOR: 7% group A; 21% group B

22	Michael M, Bruns I, Bolke E, et al. Bendamustine in patients with relapsed or refractory multiple myeloma. European journal of medical research. 2010; 15(1):13-9.	No prior LEN or BOR reported
23	Petrucci MT, Avvisati G, Tribalto M, et al. Intermediate-dose (25 mg/m2) intravenous melphalan for patients with multiple myeloma in relapse or refractory to standard treatment. European journal of haematology. 1989; 42(3):233-7.	32.4% first relapse after chemotherapy
24	Celesti L, Clavio M, Poggi A, et al. The association of cyclophosphamide and dexamethasone in advanced refractory multiple myeloma patients. Haematologica. 1997; 82(3):351-3.	40% had only 1 prior therapy

A5. In Table 17 of the company submission, the company indicates which outcome data were used in the economic analysis.

- Please clarify why the efficacy outcomes were based on a different data cut to the quality of life (QoL) and safety outcomes and discuss how this would influence the results.

Table 17 presents the outcomes that were available for the two main data cuts from MM-003; the March 2013 and September 2013 data cut. The March 2013 data cut was a pre-planned analysis and so all efficacy, quality of life and safety outcomes were collected. The September 2013 data cut was a post-hoc analysis and only efficacy data were collected. The model uses the most mature efficacy data cut in the comparison with conventional chemotherapy so as to reduce uncertainty in long term extrapolation. Quality of life and adverse event data are only available from the March 2013 data cut. The difference in data cuts is unlikely to impact results:

- Utility is not dependent on time, it is based on a regression equation considering progression status, response status, hospitalisation, adverse events and patient characteristics as independent variables.
- In the MM-003 study, AEs were more likely to occur shortly after treatment initiation (within the first two cycles) and decreased in frequency thereafter (see Section 4.12.1).

- Please provide the full results for all data cuts.

Adverse event and utility data are not available for the September 2013 data cut.

A6. Please provide the 95% confidence interval (CI) for the hazard ratio (HR) in Appendix 12 (Tables 30, 31, 32 etc.) in the results tables for the Cox regression output for the comparisons with bendamustine.

The 95% CIs have been added to each of the relevant tables in Appendix 12.

Table 10: Cox regression output – base case analysis – OS

Covariate	LHR	HR	SE (LHR)	95% CI	p-value
Treatment arm *(ref*=BEN) POM+LoDEX	-0.548	0.578	0.245	[0.36, 0.93]	**0.026**
Age (start of treatment)	0.022	1.022	0.010	[1.00, 1.04]	**0.033**
Number of prior lines of therapy	-0.018	0.982	0.043	[0.90, 1.07]	0.668
Receipt of prior THAL *(ref=No)* Yes	0.479	1.614	0.232	[1.02, 2.54]	**0.039**
Refractory to LEN *(ref=No)* Yes	0.097	1.102	0.205	[0.74, 1.65]	0.634

Key: BEN, bendamustine; CI, confidence interval; HR, hazard ratio; LEN, lenalidomide; LHR, log (hazard ratio); OS, overall survival; POM+LoDEX, pomalidomide + low-dose dexamethasone; SE, standard error; THAL, thalidomide.

Notes: Bold denotes statistical significance at 5% level.

Table 11: Cox regression output – base case analysis – PFS

Covariate	LHR	HR	SE (LHR)	95% CI	p-value
Treatment arm *(ref*=BEN) POM+LoDEX	-0.232	0.793	0.219	[0.52, 1.22]	0.291
Age (start of treatment)	0.002	1.002	0.009	[0.98, 1.02]	0.859
Number of prior lines of therapy	-0.057	0.945	0.039	[0.88, 1.02]	0.152
Receipt of prior THAL *(ref=No)* Yes	0.765	2.148	0.243	[1.33, 3.46]	**0.002**
Refractory to LEN *(ref=No)* Yes	0.456	1.578	0.190	[1.09, 2.29]	**0.017**

Key: BEN, bendamustine; CI, confidence interval; HR, hazard ratio; LEN, lenalidomide; LHR, log (hazard ratio); PFS, progression-free survival; POM+LoDEX, pomalidomide + low-dose dexamethasone; SE, standard error; THAL, thalidomide.

Notes: Bold denotes statistical significance at 5% level.

Table 12: Cox regression output – sensitivity analysis 1 – OS

Covariate	LHR	HR	SE (LHR)	95% CI	p-value
Treatment arm *(ref*=BEN) POM+LoDEX	-0.453	0.636	0.182	[0.44, 0.91]	0.013
Age (start of treatment)	0.007	1.007	0.004	[0.99, 1.01]	0.103
Number of prior lines of therapy	0.002	1.002	0.018	[0.97, 1.04]	0.926
Receipt of prior THAL *(ref=No)* Yes	0.161	1.174	0.083	[1.00, 1.38]	0.053
Refractory to LEN *(ref=No)* Yes	0.160	1.174	0.139	[0.89, 1.54]	0.249

Key: BEN, bendamustine; CI, confidence interval; HR, hazard ratio; LEN, lenalidomide; LHR, log (hazard ratio); OS, overall survival; POM+LoDEX, pomalidomide + low-dose dexamethasone; SE, standard error; THAL, thalidomide.

Notes: Bold denotes statistical significance at 5% level.

Table 13: Cox regression output – sensitivity analysis 1 – PFS

Covariate	LHR	HR	SE (LHR)	95% CI	p-value
Treatment arm *(ref*=BEN) POM+LoDEX	-0.491	0.612	0.161	[0.45, 0.84]	**0.002**
Age (start of treatment)	-0.003	0.997	0.004	[0.99, 1.00]	0.337
Number of prior lines of therapy	0.013	1.013	0.016	[0.98, 1.05]	0.435
Receipt of prior THAL *(ref=No)* Yes	0.037	1.038	0.072	[0.90, 1.19]	0.606
Refractory to LEN *(ref=No)* Yes	0.367	1.443	0.128	[1.12, 1.85]	**0.004**

Key: BEN, bendamustine; CI, confidence interval; HR, hazard ratio; LEN, lenalidomide; LHR, log (hazard ratio); PFS, progression-free survival; POM+LoDEX, pomalidomide + low-dose dexamethasone; SE, standard error; THAL, thalidomide.

Notes: Bold denotes statistical significance at 5% level.

Table 14: Cox regression output – sensitivity analysis 2 – OS

Covariate	LHR	HR	SE (LHR)	95% CI	p-value
Treatment arm *(ref*=BEN) POM+LoDEX	-0.332	0.718	0.221	[0.47, 1.11]	0.133
Age (start of treatment)	-0.003	0.997	0.005	[0.99, 1.01]	0.555
ISS stage *(ref=stage 1)*					
Stage 2	0.539	1.714	0.122	[1.35, 2.18]	**<0.001**
Stage 3	1.131	3.098	0.120	[2.45, 3.92]	**<0.001**
Number of prior lines of therapy	<0.001	0.999	0.021	[0.96, 1.04]	0.976
Receipt of prior THAL *(ref=No)* Yes	0.162	1.176	0.092	[0.98, 1.41]	0.078
Refractory to LEN *(ref=No)* Yes	0.220	1.246	0.182	[0.87, 1.78]	0.226

Key: BEN, bendamustine; CI, confidence interval; HR, hazard ratio; ISS, International Staging System; LEN, lenalidomide; LHR, log (hazard ratio), OS, overall survival; POM+LoDEX, pomalidomide plus low-dose dexamethasone; SE, standard error; THAL, thalidomide.

Notes: Bold denotes statistical significance at 5% level.

Table 15: Cox regression output – sensitivity analysis 2 – PFS

Covariate	LHR	HR	SE (LHR)	95% CI	p-value
Treatment arm *(ref*=BEN) POM+LoDEX	-0.471	0.624	0.185	[0.43, 0.90]	**0.011**
Age (start of treatment)	-0.009	0.991	0.004	[0.98, 1.00]	**0.018**
ISS stage *(ref=stage 1)*					
Stage 2	0.225	1.252	0.093	[1.04, 1.50]	**0.016**
Stage 3	0.586	1.796	0.095	[1.49, 2.16]	**<0.001**
Number of prior lines of therapy	0.013	1.013	0.019	[0.98, 1.05]	0.482
Receipt of prior THAL *(ref=No)* Yes	-0.012	0.988	0.078	[0.85, 1.15]	0.880
Refractory to LEN *(ref=No)* Yes	0.353	1.423	0.158	[1.04, 1.94]	**0.025**

Key: BEN, bendamustine; CI, confidence interval; HR, hazard ratio; ISS, International Staging System; LEN, lenalidomide; LHR, log (hazard ratio), PFS, progression-free survival; POM+LoDEX, pomalidomide plus low-dose dexamethasone; SE, standard error; THAL, thalidomide.

Notes: Bold denotes statistical significance at 5% level.

A7. Table 40 of the company submission (End-of-life criteria) states: 'The eligible patient population is expected to be 620.' Based on table 79 this appears to be the total at fourth line. This does not account for those patients eligible at third line (n=404).

- Please explain why numbers are higher for fourth line than for third line.

Numbers are higher at fourth line than third line as at first line the majority of patients receive thalidomide (4,136 across SCT eligible and ineligible) not bortezomib (516) or lenalidomide (288) and patients are only eligible for pomalidomide if they have already received bortezomib and lenalidomide.

By fourth line, those patients who received thalidomide upfront have generally received both bortezomib and lenalidomide at second and third line.

- Please clarify the total number of patients eligible at third line or above in line with the scope.

The total number of patients eligible is 620 (fourth line) plus 404 (third line), which is equal to 1,024 patients.

It should be noted that since this submission was made, the criteria for life-extending treatments at the end of life has been updated and the reference to patient population removed. The end-of-life criteria now reads:

In the case of a 'life-extending treatment at the end of life', the Appraisal Committee will satisfy itself that all of the following criteria have been met:

  - the treatment is indicated for patients with a short life expectancy, normally less than 24 months and
  - there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment

- In addition, the Appraisal Committee will need to be satisfied that:
  - the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review) and
  - the assumptions used in the reference case economic modelling are plausible, objective and robust.

Literature searching

A8. The company states:

> 'This resubmission addresses concerns raised by the evidence review group (ERG) in the original NICE review (TA338) regarding the use of study design filters by adding additional terms to the search strategies around study design in order to make the searches more comprehensive' (company submission; page 52).

- Please confirm what new terms have been added to the strategy to make it more comprehensive. The ERG was able to identify two additional terms in the MEDLINE/Embase strategy (Appendix 2; pages 6-9):
  - #32multi-centre:ti
  - #82'retrospective study'/de

These were the two terms that were added to the existing search terms for study design that are recommended by the Scottish Intercollegiate Guidelines Network (SIGN)[1] in order to make the searches more comprehensive.

A9. Please confirm whether searches were conducted to identify pre-2013 records on the newly added comparator panobinostat, as the strategies provided in the company submission will only retrieve records added to the databases searched from 2013 onwards. If not, please conduct the relevant searches for this comparator.

A full systematic literature review (SLR) is available for evidence for panobinostat + bortezomib + dexamethasone (PANO+BOR+DEX) within the NICE submission for TA380.[2] The searches for this SLR were conducted in June 2013, with updates in May and December 2014, and therefore covers the period prior to the conduct of our SLR (i.e. pre-2013). It was therefore not considered necessary to run additional searches for literature published on PANO+BOR+DEX before 2013.

A10. Search strategies are not provided for Section 5.5.1: 'Resource identification, measurement and valuation studies'. Please provide details of databases and other resources searched, and search strategies used, as required by the user guide for the company evidence submission template.

No additional formal literature searches were performed to identify resource use or health care costs for this resubmission. The original literature searches, as is often the case, found no information that could be directly used within the economic model. The types of resource use required to be included within the economic model were agreed within the previous appraisal for POM+LoDEX. Resource use was therefore instead gathered by directly

contacting UK clinicians to determine what their resource requirements are on a treatment-specific basis.

A11. Please provide the search terms used for the identification of clinical effectiveness studies from the American Society of Hematology (ASH), American Society of Clinical Oncology (ASCO), European Hematology Association (EHA) and International Myeloma Workshops (IMW) conferences (Appendix 2; page 5).

The conference websites were searched on 31st March 2016 to identify relevant conference abstracts published in the previous two years (2014-2016). The conference websites that were searched and the final number of hits included for each are presented in Table 16. The search terms that were used for each conference website are presented in Table 17.

Table 16: Conference websites searched

S.No.	Conferences	Year hand searched	Search dates	Included
1	American Society of Hematology (ASH)	2015	31/03/2016	4
		2014	31/03/2016	3
2	American Society of Clinical Oncology (ASCO)	2015	31/03/2016	0
		2014	31/03/2016	2
3	European Hematological Association (EHA)	2015	31/03/2016	3
		2014	31/03/2016	0
4	International Myeloma Workshops (IMW)	2015	31/03/2016	5
		2013	31/03/2016	6

Table 17: Search terms used for searches of conference websites

Sr. No.	Search Terms	ASCO hits		ASH hits	EHA hits	IMW hits
		2015	2014			
1	Multiple myeloma	79	85	E-book was available. Hence, hits cannot be defined.	E-book was available. Hence, hits cannot be defined.	E-book was available. Hence, hits cannot be defined.
2	Refractory	387	368			
3	Relapsed	286	270			
4	Pomalidomide	10	15			
5	Dexamethasone	66	63			
6	Bendamustine	23	25			
7	Levact	0	0			
8	Bortezomib	49	40			
9	Velcade	49	40			
10	Panobinostat	10	5			
11	LBH589	3	1			

Sr. No.	Search Terms	ASCO hits		ASH hits	EHA hits	IMW hits
		2015	2014			
12	Farydak	0	0			
13	Faridak	0	0			
14	Cyclophsophamide	110	151			
15	Cytoxan	110	151			
16	Endoxan	0	0			
17	Neosar	110	151			
18	Procytox	0	0			
19	Revimmune	0	0			
20	Etoposide	69	74			
21	Etopophos	0	0			
22	Vepesid	69	74			
23	Doxorubicin	165	161			
24	Caelyx	0	0			
25	Myocet	2	1			
26	Methylprednisolone	5	5			
27	Medrol	5	5			
28	Thalidomide	20	13			
29	Melphalan	22	14			

Section B: Clarification on cost-effectiveness data

Please note that all scenarios and results presented in this section are based on the revised model. The model has been amended based on the updates requested in B4, B9, B16, B17 and B19. The base case results are presented in Table 18, Table 19 and Table 20 for the comparison of POM+LoDEX with bendamustine plus thalidomide and dexamethasone (BTD), PANO+BOR+DEX and conventional chemotherapy, respectively.

The scenario requested in B8 has not been incorporated as we would disagree with the ERG that in real life there are situations where TTF could be equal to PFS. All of the treatment regimens discussed are discontinued in the event of either progression or unacceptable toxicity; MM patients at this line of therapy are often frail and discontinuation due to toxicity is reasonably common even with less toxic treatment regimens such as POM. At the September 2013 datacut 253 and 138 progression or death events had been experienced on the POM+LoDEX and HiDEX arms of the trial respectively compared to 277 and 152 treatment failure events. At no point did the KMs for TTF and PFS come together.

Fitting separate models to TTF and PFS ignores the inter-dependency of these outcomes (given that progression forms a large part of PFS and PFS is always < TTF) and results in non-sensible results where TTF and PFS curves cross within long-term projection. We note that previously Committee's have considered the implementation of minimisation functions, as suggested by the ERG to correct for such clinically non-sensible results, to be a flawed approach (TA171 part-review) and therefore do not consider these analyses robust.

Table 18: Revised base case – POM+LoDEX vs BTD

	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BTD	[redacted]	[redacted]			
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£39,665

Key: BTD, bendamustine + thalidomide + dexamethasone; ICER, incremental cost-effectiveness ratio; POM+LoDEX, pomalidomide + low-dose dexamethasone; QALY, quality-adjusted life year.

Table 19: Revised base case – POM+LoDEX vs PANO+BOR+DEX

	Costs	QALYs	Incremental costs	Incremental QALYs	NMB
PANO+BOR+DEX	[redacted]	[redacted]			
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£32,433

Key: ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PANO+BOR+DEX, panobinostat + bortezomib + dexamethasone; POM+LoDEX, pomalidomide + low-dose dexamethasone; QALY, quality-adjusted life year.

Table 20: Revised base case – POM+LoDEX vs conventional chemotherapies

	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
Conventional chemotherapy	[redacted]	[redacted]			
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£44,811

Key: ICER, incremental cost-effectiveness ratio; POM+LoDEX, pomalidomide + low-dose dexamethasone; QALY, quality-adjusted life year.

Treatment effect in cost effectiveness model

B1. **Priority request:** For the clinical effectiveness parameters (OS, PFS, time to failure (TTF)), different data from different studies and different methods were used for the comparisons of pomalidomide plus low dose dexamethasone compared with bendamustine plus thalidomide and dexamethasone, pomalidomide plus low dose dexamethasone compared with panobinostat plus bortezomib plus dexamethasone and pomalidomide plus low dose dexamethasone compared with conventional chemotherapy. The ERG considers that this approach creates a bias, and results in differing outcomes for patients receiving the same treatment (pomalidomide plus low dose dexamethasone) in different comparisons.

- Please provide a full incremental analysis using a single source of data for pomalidomide plus low dose dexamethasone e.g. data from a single trial or pooled data from multiple trials.

- Also, please apply any treatment effects (hazard ratio (HR) or acceleration factors for OS, PFS and TTF) of bendamustine plus thalidomide and dexamethasone, panobinostat plus bortezomib plus dexamethasone and conventional chemotherapy on the OS, PFS and TTF estimates of pomalidomide and low dose dexamethasone based on that single data source.

Following this request, the functionality to consider a comparison of each intervention using the pooled POM+LoDEX data were included in the revised model (see Controls sheet).

Within this scenario analysis all treatment effects and acceleration factors for the comparison of POM+LoDEX with BTD and PANO+BOR+DEX were based on the pooled POM+LoDEX data (these data were in the original model).

The hazard ratio between the POM+LoDEX and HiDEX treatment arms, was applied to the pooled POM+LoDEX data for OS, PFS and TTF (Table 22, Table 23 and Table 25 in the submission document for PFS, OS and TTF). These hazard ratios were taken from the September 2013 MM-003 data cut; only MM-003 data were considered so as not to break the randomisation between the arms.

Full incremental analysis using the pooled POM+LoDEX data (MM-003, MM-002 and MM-010) is presented in Table 21.

The interventions were first ordered by efficacy. Treatment with BTD is strongly dominated by conventional chemotherapy as it is both more expensive and less efficacious using this method of comparison. The resulting ICER for PANO+BOR+DEX compared with POM+LoDEX is £141,793, and the ICER for POM+LoDEX compared with conventional chemotherapies is £70,147.

Table 21: Incremental analysis using pooled POM+LoDEX data in all comparisons

	Costs	QALYs	Incremental costs	Incremental QALYs	ICER vs next most effective intervention
PANO+BOR+DEX	[redacted]	[redacted]	[redacted]	[redacted]	£141,793
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£70,147
Conventional chemotherapies	[redacted]	[redacted]			
BTD	[redacted]	[redacted]			Strongly dominated by conventional chemotherapy

Key: BTD, bendamustine + thalidomide + dexamethasone; ICER, incremental cost-effectiveness ratio; PANO+BOR+DEX, panobinostat + bortezomib + dexamethasone; POM+LoDEX, pomalidomide + low-dose dexamethasone; QALY, quality-adjusted life year.

The validity of this comparison is, however, extremely questionable.

In the previous NICE submission (TA338), the ERG concluded that differences in patient characteristics meant that the populations included across the clinical data were not comparable. The incremental analysis presented in Table 21 uses clinical data with large disparities in patient characteristics and so comparisons using these data are not meaningful. Additionally the requirement to place conventional chemotherapy data and BTD data within the same comparison necessitated use of hazard ratios for HiDEX vs POM+LoDEX, this assumption is extremely questionable and was not found to be maintained within the original submission.

The unexpected result of HiDEX effectiveness being greater than that for BTD demonstrates the lack of validity within these results.

The within trial comparison using the MM-003 trial data only for POM+LoDEX compared with conventional chemotherapy (HiDEX proxy) avoids the potential for bias arising from differences in clinical data and lack of proportional hazards, and so we believe that this comparison is the most meaningful for assessing the cost-effectiveness of POM+LoDEX versus conventional chemotherapy.

B2. Please verify the following or explain if otherwise:

- Covariate adjustment (based on either corrected group prognosis (CGP) method or mean covariate adjustment method) was applied based on data obtained from pomalidomide plus low dose dexamethasone or bendamustine plus thalidomide and dexamethasone trials only. Based on the coefficients of covariate adjustment, parametric survival functions were fitted for the bendamustine plus thalidomide and dexamethasone and pomalidomide plus low dose dexamethasone arms. For the panobinostat plus bortezomib and dexamethasone arm, hazard rates obtained from matched adjusted indirect comparison (MAIC) were applied to the parametric survival functions derived for the pomalidomide plus low dose dexamethasone arm based on a proportional hazard assumption.

This is correct.

- In all of the parametric survival functions, the following parameters were used: 67.65, 3.7, 0.84 and 0.78, respectively for the mean age, mean number of prior lines of therapies, proportion of patients that received prior thalidomide and proportion of prior refractoriness to lenalidomide.

In the base case, the CGP method is used to account for differences in covariates across the data. CGP estimates the OS, PFS and TTF for every possible combination of covariates found in the dataset and then calculates a weighted OS, PFS or TTF curve using the proportion of patients with each combination of covariates. The mean age remains constant

(67.65), while the number of prior lines, proportion of patients that received prior thalidomide and proportion of prior refractoriness to lenalidomide make up combinations of covariates. Due to the computational and time constraints (for each analysis the model took several hours to run) the CGP analysis was conducted prior to sending the model to NICE. The analyses were conducted for OS, PFS and TTF for pooled POM+LoDEX and BTD data (sheets OS2, PFS2 and TTF2) and for the MM-002 trial and BTD data (sheets OS2_BEN, PFS2_BEN and TTF2_BEN).

To improve the clarity on the analysis, please see the explanation in B3.

When the mean of covariates method is selected the following parameters are used: 67.65, 3.7, 0.84 and 0.94, respectively, for the mean age, mean number of prior lines of therapies, proportion of patients that received prior thalidomide and proportion of prior refractoriness to lenalidomide in all parametric survival functions as stated.

B3. Please explain in detail the calculations in the “OS2”, “PFS2”, “TTF2”, “OS2_BEN”, “PFS2_BEN” and “TTF2_BEN” worksheets (especially columns starting from AZ and onwards) and the VBA Macros under the “CGP” module, e.g. macros like “CCGP_OS2”, “CCGP_PFS2”, “CCGP_OS1” etc.. For instance, it was not clear to the ERG how the CGP method was applied and how the numbers in the cell range of BP25: FI4199 in the OS2 (and similar ranges in the other sheets) were obtained. Please provide the details as well as all relevant material (i.e. statistical software scripts, datasets used and their explanations) which were used in these covariate adjusted parametric survival fitting analyses.

CGP analysis was conducted for all six parametric curves and for OS, PFS and TTF. This analysis was repeated for the comparison of pooled POM+LoDEX and the MM-002 trial data with BTD. Due to the time to run each CGP analysis, and the requirement of 36 CGP analyses, the code was run outside of the model structure. To improve the clarity of the CGP analyses, please see the explanation for sheet OS2 below.

The OS2 sheet considers the pooled POM+LoDEX and BTD data; from these data there are 42 combinations of covariates (listed in column BB, the number of patients in each group listed in column BC (n=1,175)). The code associated with this CGP is presented in the CGP_OS2 macro and detailed in Figure 5.

Cell X10, X11 and X12 were set equal to each combination of covariates. Then for each combination of covariates, survival estimates were calculated using the coefficients of covariate adjustment (recorded in column CC and DT onwards for POM+LoDEX and BTD, respectively, for each subgroup).

Figure 5: Macro associated with CGP on sheet OS2

```
Sub CGP_OS2()
Application.ScreenUpdating = False

Dim sh As Worksheet
Dim a, b

Set sh = Sheets("OS2")
sh.Range("ccgp.analysis2").ClearContents
sh.Range("ccgp.ben.analysis2").ClearContents

b = 0
'Tells the model to use the CGP covariate values
Sheets("OS2").Range("ccgp.flag").Value = 1

'For each combination of covariates the analysis is conducted (42 subgroups)
For a = 1 To 42

'define the covariates
sh.Range("PrLinesThpy.ccgp.os2").Value = sh.Range("PrLinesThpy.ccgp2.OS22").Offset(a, 0).Value
sh.Range("ReceiptPrThal.CCGP.OS2").Value = sh.Range("ReceiptPrThal.CCGP2.OS2").Offset(a, 0).Value
sh.Range("RefracLEN.CCGP.OS2").Value = sh.Range("RefracLEN.CCGP2.OS2").Offset(a, 0).Value


Application.Calculate
'Copy the estimated survival estimate for POM+LoDEX
sh.Range("ccgp.os2").Offset(0, b).Value = sh.Range("POM.OS2.selected").Value

'Copy the estimated survival estimate for BTD
sh.Range("ccgp.ben.os2").Offset(0, b).Value = sh.Range("BEN.OS2.selected").Value

b = b + 1

'move to next combination of covariates
Next a

'reset the model
Sheets("OS2").Range("ccgp.flag").Value = 0
Application.Calculate

Application.ScreenUpdating = True

End Sub
```

The model then calculated a weighted OS curve using the proportion of patients with each combination of covariates, the weighted curve is calculated in column BH and BI for POM+LoDEX and BTD, respectively. The analysis was run for each parametric curve choice and the weighted curve was copied into the appropriate column (columns BP to BU for POM+LoDEX). A VLOOKUP formula was then used to select the survival estimate based on parametric curve choice.

In sheet PFS2, the covariate combinations are reported in columns BA to BE (42 subgroups). The survival estimates associated with each covariate combination are reported from column CB and column DS onwards. The weighted survival estimates are calculated in columns BG and BK for POM+LoDEX and BTD, respectively. The copied estimates for each parametric curve choice are presented in BO:BT and BU:BZ for POM+LoDEX and BTD, respectively. The code is available in the macro “CGP_PFS2.”

In sheet TTF2, the covariate combinations are reported in columns AG to AK (42 subgroups). The survival estimates associated with each covariate combination are reported

from column BG and column CX onwards. The weighted survival estimates are calculated in columns AM and AN for POM+LoDEX and BTD, respectively. The copied estimates for each parametric curve choice are presented in AT:AY and AZ:BE for POM+LoDEX and BTD, respectively. The code is available in the macro "CGP_TTF2."

In sheet OS2_BEN, the covariate combinations are reported in columns BA to BE (34 subgroups). The survival estimates associated with each covariate combination are reported from column CA and column DR onwards. The weighted survival estimates are calculated in columns BG and BH for POM+LoDEX and BTD, respectively. The copied estimates for each parametric curve choice are presented in BN:BS and BT:BY for POM+LoDEX and BTD, respectively. The code is available in the macro "CGP_OS2_KB."

In sheet PFS2_BEN, the covariate combinations are reported in columns AZ to BD (34 subgroups). The survival estimates associated with each covariate combination are reported from column BZ and column DQ onwards. The weighted survival estimates are calculated in columns BF and BG for POM+LoDEX and BTD, respectively. The copied estimates for each parametric curve choice are presented in BM:BR and BS:BX for POM+LoDEX and BTD, respectively. The code is available in the macro "CGP_PFS2_KB."

In sheet TTF2_BEN, the covariate combinations are reported in columns AG to AK (34 subgroups). The survival estimates associated with each covariate combination are reported from column BG and column CX onwards. The weighted survival estimates are calculated in columns AM and AN for POM+LoDEX and BTD, respectively. The copied estimates for each parametric curve choice are presented in AT:AY and AZ:BE for POM+LoDEX and BTD, respectively. The code is available in the macro "CGP_TTF2_KB."

B4. Please explain why some of the PFS curves in the "PFS2" sheet start from values greater than 1 (see cell range BG28:BH28).

This has been corrected in the new model version supplied. This arose from a frequency of patients in one subgroup being defined as n=32, when this should have been n=30, and so more than 100% of the original population were included. This error impacts both POM+LoDEX and BTD equally and so does not impact the base case results.

B5. Please provide Kaplan-Meier analyses to the following specification:

- Population: The per protocol population, including all patients lost to follow-up or withdrawing from the trial.
- Censoring: Censor lost to follow-up and withdrawn patients at the time recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off, and not when last seen. Please use the format of the table provided below.

- Trial data sets:
    - For bendamustine: Gooding et al, Tarant et al and MUK-One
    - For pomalidomide plus low dose dexamethasone: (a) MM-002,MM-003 and MM-010 (b) MM-002 only (c) MM-003 only
    - For panobinostat plus bortezomib and low dose dexamethasone: pseudo patient level data from PANORAMA-2
    - For conventional chemotherapy: MM-003 only after treatment switching corrections

- Time to death from any cause (overall survival) Kaplan-Meier analyses for bendamustine; for pomalidomide plus low dose dexamethasone based on (a), (b) and (c) above; for panobinostat plus bortezomib and low dose dexamethasone and for conventional chemotherapy (in total 6 analyses)

All six KM analyses have been uploaded to NICE DOCS with the following labels:

- 'OS_Summary KM data_unadjusted_pooledPOM.csv',
- 'OS_Summary KM data_unadjusted_pooledBEN.csv',
- 'OS_Summary KM data_unadjusted_POM_MM003.csv',
- 'OS_Summary KM data_unadjusted_POM_MM002.csv',
- 'OS_Summary KM data_ConventionalChemo_MM003.csv',
- 'OS_MAIC_lifetable_data_PANOBOR.csv'.

Time to progression by investigator assessment (progression free survival) Kaplan-Meier analyses for bendamustine; for pomalidomide plus low dose dexamethasone based on (a), (b) and (c); for panobinostat plus bortezomib and low dose dexamethasone and for conventional chemotherapy (in total 6 analyses)

All six KM analyses have been uploaded to NICE DOCS with the following labels:

- 'PFS_Summary KM data_unadjusted_pooledPOM.csv',
- 'PFS_Summary KM data_unadjusted_pooledBEN.csv',
- 'PFS_Summary KM data_unadjusted_POM_MM003.csv',
- 'PFS_Summary KM data_unadjusted_POM_MM002.csv',
- PFS_Summary KM data_ConventionalChemo_MM003.csv',
- 'PFS_MAIC_lifetable_data_PANOBOR.csv'.

- Time to treatment discontinuation Kaplan-Meier analyses for bendamustine; for pomalidomide plus low dose dexamethasone based on (a), (b) and (c);

panobinostat plus bortezomib and low dose dexamethasone and for conventional chemotherapy (in total 6 analyses)

KM analyses associated with BEN, POM+LoDEX based on (a), (b) and (c) and for conventional chemotherapy have been uploaded to NICE DOCS with the following labels:

- 'TTF_Summary KM data_unadjusted_pooledPOM.csv',
- 'TTF_Summary KM data_unadjusted_pooledBEN.csv',
- 'TTF_Summary KM data_unadjusted_POM_MM003.csv',
- 'TTF_Summary KM data_unadjusted_POM_MM002.csv',
- 'TTF_Summary KM data_ConventionalChemo_MM003.csv'.

No information on time to discontinuation was available within the PANORAMA 2 trial for PANO+BOR+DEX.

- Time from progression by investigator assessment to death from any cause (post-progression free survival) Kaplan-Meier analyses for bendamustine; for pomalidomide plus low dose dexamethasone based on (a), (b) and (c); for panobinostat plus bortezomib and low dose dexamethasone and for conventional chemotherapy (in total 6 analyses)

KM analyses associated with BEN, POM+LoDEX based on (a), (b) and (c) and for conventional chemotherapy have been uploaded to NICE DOCS with the following labels:

- 'PPS_Summary KM data_unadjusted_pooledPOM.csv',
- 'PPS_Summary KM data_unadjusted_pooledBEN.csv',
- 'PPS_Summary KM data_unadjusted_POM_MM003.csv',
- 'PPS_Summary KM data_unadjusted_POM_MM002.csv',
- 'PPS_Summary KM data_ConventionalChemo_MM003.csv'.

These data are not available for PANO+BOR+DEX (as the available data are digitised and not actual patient level data).

B6. In sections 5.3.8, 5.3.9, 5.3.10, 5.3.11 and 5.3.12 of the company submission, it was not clear which data (adjusted or unadjusted) were used in fitting parametric survival curves. Furthermore, all the figures in these sections (i.e. Figures 31 to 36, pages 175 to 184) show unadjusted KM curves compared with the covariate adjusted parametric survival functions. Please state which baseline parameters were used for the covariates (the mean age, mean number of prior lines of therapies, proportion of patients that received prior thalidomide and proportion of prior refractoriness to lenalidomide) for each of these figures.

Patient level data were used to fit the parametric survival curves. The unadjusted KM curves represent the patient level data and these are compared with the covariate adjusted parametric survival functions to allow any differences in the shape of the survivor functions between arms to be assessed.

Parametric survival functions were adjusted for age, number of prior lines of therapy, receipt of prior thalidomide and refractoriness to LEN. The parametric survival functions used in the model were adjusted for covariates using the CGP analysis (see B2 and B3). Age remained a constant in the CGP analysis at 67.65. 42 subgroups considering different combinations of prior lines of therapy, receipt of prior THAL and refractoriness to LEN were identified in the analysis using the pooled POM data. 34 subgroups considering different combinations of prior lines of therapy, receipt of prior THAL and refractoriness to LEN were identified in the analysis using the MM-002 trial data only.

The distribution of patients across the covariate defined 42 subgroups are shown in columns BB:BF, BA:BE and AG:AK in sheets OS2, PFS2 and TTF2, respectively. The distribution of patients across the 34 covariate defined subgroups are shown in BA:BE, AZ:BE and AG:AK in sheets OS2_BEN, PFS2_BEN and TTF2_BEN, respectively.

> Furthermore, it was not clear to the ERG which steps were taken to select the fitted parametric survival functions to be used in the base case in the economic analysis. In Appendix 18 and 19, Q-Q and Log cumulative hazard plot (LCHP) plots and parametric curve fits vs KM plots were provided, but the rationale for selection was not clear (use of AIC/BIC or the rationale for accepting/rejecting the appropriateness of proportional hazards or accelerated failure time (AFT) based on Q-Q plots and LCHPs?). Please clarify.

In line with NICE DSU guidance 4 factors were considered when conducting curve selection:

- Assessment of whether or not AFT / proportional hazards assumptions were valid
- Assessment of statistical goodness of fit using AIC/BIC
- Assessment of visual fit to KM
- Clinical plausibility of the extrapolated portion of the curve

All four factors are considered important in determining which survivor functions provide an appropriate fit to the dataset.

Assessment was conducted in the order presented above. First it was determined whether specific model types were plausible based upon AFT / proportional hazards assumptions holding or not, second it was determined which models provided a good statistical fit on AIC/BIC, thirdly fit to KM was assessed and final clinical plausibility of long-term extrapolation assessed.

In Section 5.3.8, the POM+LoDEX vs BTD OS is presented. The exponential was considered the most appropriate fit to the data as this curve had the lowest AIC and BIC (Table 48, Appendix 18.1). The log-normal and log-logistic curves provided a poor fit to the data based on the highest AIC and BIC scores. Furthermore, the QQ plots confirmed the inappropriateness of using an AFT model as the plot does not approximate a linear 45-degree line (Figure 18, Appendix 18.1). The generalised gamma, Weibull and Gompertz curves were considered plausible estimates based upon statistical criteria. All four of the curves presenting statistically plausible estimates provided clinically plausible estimates of long-term survival. Visual fit was poor, however, for the Gompertz curve.

In the short term the LCHPs (Figure 17, Appendix 18.1) are shown to cross; however, in the long term the LCHPs are parallel, and proportional hazards can reasonably be assumed. Therefore, a treatment effect was estimated for BTD compared with POM+LoDEX and applied to the POM+LoDEX fitted exponential OS curve in the base case. As noted plausible alternative curve fits are the generalised gamma and Weibull curves.

In Section 5.3.9, the POM+LoDEX vs BTD PFS is presented. The Q-Q plot (Figure 19, Appendix 19.1) indicated the inappropriateness of using an AFT model as the plot does not approximate a linear 45-degree line. The generalised gamma curve was considered the most appropriate fit to the data as this curve had the lowest AIC and BIC scores (Table 51, Appendix 19.1) after the log-normal and log-logistic curves were proven to be inappropriate by the QQ plot. Plausible alternative curve fits are the Weibull and Gompertz curves. All three of these curves produce clinically plausible long-term outcomes.

Visually assessing the LCHP for PFS indicates that, although in the short term the LCHPs are shown to cross, in the long term the LCHPs are parallel, and proportional hazards can reasonably be assumed (Figure 28, Appendix 19.1). Therefore, a treatment effect was estimated for BTD compared with POM+LoDEX and applied to the POM+LoDEX fitted generalised gamma PFS curve.

In Section 5.3.10, the POM+LoDEX vs BTD TTF is presented. The method used to estimate TTF in the economic model resulted in applying a treatment effect for TTF relative to PFS; therefore, this was applied directly to the selected PFS curve (in this case the generalised gamma curve).

In section 5.3.11, the POM+LoDEX vs PANO+BOR+DEX OS is presented. The LCHPs using the pooled POM+LoDEX data and the pseudo patient level data for PANO+BOR+DEX depict approximately parallel curves and so confirm the appropriateness of fitting the Cox proportional hazards model (Figure 24, Appendix 18.3). Therefore, a treatment effect was estimated for PANO+BOR+DEX relative to the pooled POM+LoDEX data and applied to the

parametric curve fitted to the pooled POM+LoDEX data. The generalised gamma curve was considered the most appropriate fit to the pooled data as this curve had the lowest AIC and BIC score (Table 49, Appendix 18.2). The exponential and Weibull curves also provided a good statistical and visual fit. All three of these curves produce clinically plausible long-term outcomes.

In Section 5.3.12, the POM+LoDEX vs PANO+BOR+DEX PFS is presented. The LCHPs using the pooled POM+LoDEX data and the pseudo patient level data for PANO+BOR+DEX do not look parallel indicating a lack of proportionality of hazards (Figure 35, Appendix 19.3). This is not unexpected given the crossing of KM curves between the treatments, and the fact that full PFS follow-up is reached for PANO+BOR+DEX. The Q-Q plot for OS approximates to a straight line (Figure 36, Appendix 19.3). Therefore, an assumption of a constant relative acceleration factor (for accelerated failure time models) is supported. However, a constant relative acceleration factor for PFS is not supported given the lack of linearity. Minimal extrapolation is required for PFS in the economic model, and therefore, these curves provide enough evidence to support the Cox proportional hazards model.

The direction of bias in assuming proportional hazards is potentially against POM+LoDEX as the PFS curves are diverging at the point of last observation for PANO+BOR+DEX (patients still remain progression free on POM+LoDEX compared to complete follow-up with PANO+BOR+DEX). Therefore, a treatment effect was estimated for PANO+BOR+DEX relative to the pooled POM+LoDEX data and applied to the parametric curve fitted to the pooled POM+LoDEX data.

The generalized gamma curve was considered the most appropriate fit to the pooled POM+LoDEX data as this provided a good fit to the observed dataset, had a low AIC and BIC score (Figure 33, Appendix 19.2) and is consistent with the curve choice for OS. The Gompertz, Weibull and exponential curves also provided a reasonably good statistical and visual fit. All four of these curves produce clinically plausible long-term outcomes.

B7. There are some inconsistencies between the company submission and the corresponding results in Appendix 18 and 19. For instance, in the report, for pomalidomide and low dose dexamethasone compared with panobinostat and bortezomib and dexamethasone PFS (section 5.3.12), it was mentioned that Gompertz, exponential, generalized gamma and Weibull curves have the lowest AIC/BIC. However in Appendix 19, in Table 52, it can be seen that log-logistic and log-normal functions have the minimum. Please double check the consistency between the report and the Appendix 19 results for all parametric survival analyses.

Please see the response to B6 for a detailed explanation of curve selection. In Section 5.3.12 it is stated that the QQ plots confirm the inappropriateness of using an AFT model and so the log-normal and log-logistic curves are not appropriate. Following this, in order, the generalised gamma, Gompertz, Weibull and exponential have the lowest AIC.

B8. In the current electronic model, because of the common treatment effect assumption, TTF is always smaller than PFS for pomalidomide and low dose dexamethasone, but, in real life practice, there can be situations where TTF is equal to PFS. Therefore, please provide an analysis for TTF, where the same procedure of parametric survival curve fitting exercises have been applied to TTF KM data as PFS and OS. Then, in the electronic model, for TTF, select the minimum of OS, PFS or TTF in order to deal with potential crossing of TTF and PFS curves.

Additionally, please apply a parametric survival curve for TTF of panobinostat and bortezomib and dexamethasone, as well. (In the current version of the electronic model, discontinuation from panobinostat and bortezomib and dexamethasone, due to other reasons than progression was not incorporated.

The model currently estimates the TTF curves as a function of PFS using the common treatment effect approach. This method was selected as using standard parametric models, as for OS and PFS, suggested that the TTF was greater than the PFS at a number of time points. While this was true when using the common treatment effect approach in 1-2 cycles only. Therefore, it was considered more appropriate to use the common treatment effect approach in the base case.

The alternative approach requested has been provided in the revised economic model. TTF has been estimated using an identical approach as used for OS and PFS, for the base case analysis (POM – MM002, BEN – Gooding, MUK-One), adjusting for covariates including treatment arm, age, number of prior lines of therapy, receipt of prior thalidomide and refractory to lenalidomide.

The model now includes the analysis for TTF, where parametric survival curves have been applied to the relevant TTF KM data. This analysis can be selected on the Controls sheet and is applied to the revised model. Please note, due to time constraints, these analyses are only valid for the base case scenario – where POM+LoDEX is compared with BTD using MM-002 only data, POM+LoDEX is compared with PANO+BOR+DEX using all pooled trial data and POM+LoDEX is compared with conventional chemotherapy using MM-003 only data.

POM+LoDEX vs BTD

Six parametric curves were fit to the MM-002 TTF data and the pooled Gooding and MUK-One data (TTF data were unavailable from the Tarant dataset): exponential, Weibull,

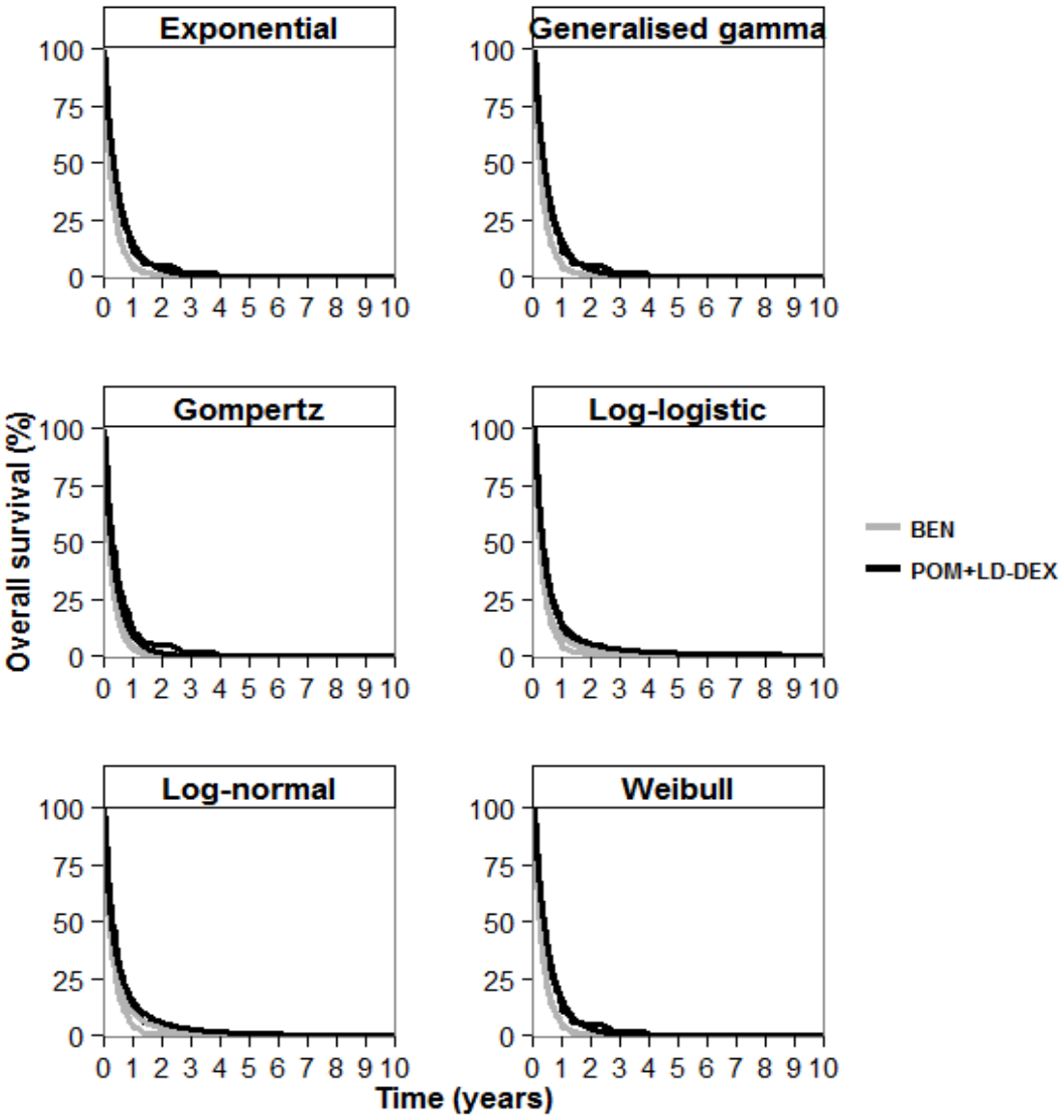
Gompertz, log-normal, log-logistic and generalised gamma. Goodness of fit were assessed based on the AIC and BIC statistics (Table 22), these indicated that the exponential, Gompertz and Weibull distributions provided the best fit to the data. Following visual assessment, the exponential curve was selected in the base case (Figure 6).

Table 22: TTF analysis – POM+LoDEX vs BTD

Model	AIC	BIC
Exponential	2245.494	2264.881
Weibull	2247.099	2269.717
Gompertz	2246.636	2269.254
Log-normal	2280.597	2303.215
Log-logistic	2257.64	2280.258
Generalised gamma	2249.022	2274.871

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; BTD, bendamustine + thalidomide + dexamethasone; POM+LoDEX, pomalidomide + low-dose dexamethasone; TTF, time to failure.

Figure 6: Parametric curve fits compared to KM plots for TTF: POM+LoDEX vs BTD (MM-002 only)



The parametric curves were covariate adjusted using the CGP method (see B2 and B3) in the base case. The calculations can be found in sheet TTF2_BEN_B8 and the code in the macro "CGP_TTF2_BEN_B8()." Full CGP analyses were conducted on this updated analysis based on data from 187 patients across 34 subgroups.

The results of this analysis are presented in Table 23.

Table 23: Results of TTF analysis – POM+LoDEX vs BTD

	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BTD	[redacted]	[redacted]			
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£45,261

Key: BTD, bendamustine + thalidomide + dexamethasone; ICER, incremental cost-effectiveness ratio; POM+LoDEX, pomalidomide + low-dose dexamethasone; QALY, quality-adjusted life year; TTF, time to failure.

POM+LoDEX vs PANO+BOR+DEX

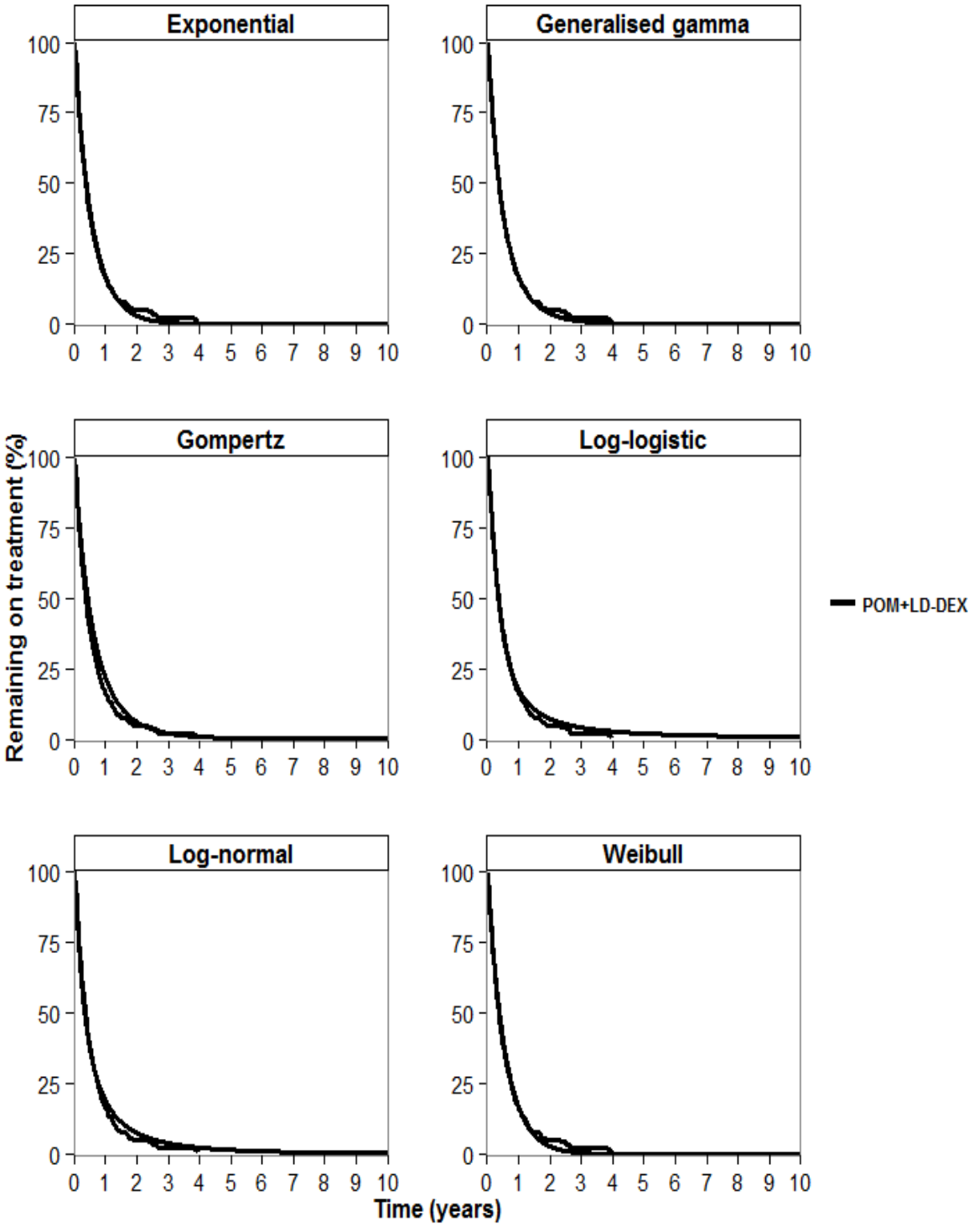
Six parametric curves were fit to the pooled TTF data (MM-003, MM-002 and MM-010): exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma. Goodness of fit were assessed based on the AIC and BIC statistics (Table 24), these indicated that the generalised gamma and the Gompertz provided the best fit to the data. Following visual assessment, the generalised gamma curve was selected in the base case (Figure 7).

Table 24: TTF analysis – POM+LoDEX v. PANO+BOR+DEX

Model	AIC	BIC
Exponential	12163.847	12188.821
Weibull	12165.452	12195.421
Gompertz	12160.523	12190.492
Log-normal	12224.749	12254.718
Log-logistic	12162.23	12192.199
Generalised gamma	12150.143	12185.107

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PANO+BOR+DEX, panobinostat + bortezomib + dexamethasone; POM+LoDEX, pomalidomide + low-dose dexamethasone; TTF, time to failure.

Figure 7: TTF parametric curve fits compared to KM data – POM+LoDEX (all pooled data)



The parametric curves were covariate adjusted using the CGP method (see B2 and B3) in the base case. The calculations can be found in sheet TTF2_B8 and the code in the macro "CGP_TTF2_B8()." Full CGP analyses were conducted on this updated analysis based on data from 1,091 patients across 42 subgroups.

TTF for PANO+BOR+DEX was not modelled as this is not relevant for a fixed dose regimen. The proportion of treatment interruptions is instead taken into account when modelling treatment with PANO+BOR+DEX.

The results of this analysis are presented in Table 25.

Table 25: Results of TTF analysis – POM+LoDEX vs PANO+BOR+DEX

	Costs	QALYs	Incremental costs	Incremental QALYs	NMB
PANO+BOR+DEX	[redacted]	[redacted]			
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£33,612

Key: NMB, net monetary benefit; PANO+BOR+DEX, panobinostat + bortezomib + dexamethasone; POM+LoDEX, pomalidomide + low-dose dexamethasone; QALY, quality-adjusted life year; TTF, time to failure.

POM+LoDEX vs conventional chemotherapy

The curve fits from the original NICE submission were used to model TTF for patients receiving POM+LoDEX using MM-003 data only (sheet TTF_CC). These parametric curves included the extreme value, log-logistic, log-normal and Weibull. The analysis for the HiDEX arm is already in the model as a proxy for TTF for patients receiving conventional chemotherapy (sheet OS_CC). In the base case, the extreme value curve is selected to remain consistent with the curve selection for HiDEX.

The parametric curves are not covariate adjusted as this analysis is a within trial comparison.

The results of this analysis are presented in Table 26.

Table 26: Results of TTF analysis – POM+LoDEX vs conventional chemotherapy

	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
Conventional chemotherapy	[redacted]	[redacted]			
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£44,795

Key: ICER, incremental cost-effectiveness ratio; POM+LoDEX, pomalidomide + low-dose dexamethasone; QALY, quality-adjusted life year; TTF, time to failure.

Additionally, please apply a parametric survival curve for TTF of panobinostat and bortezomib and dexamethasone, as well. In the current version of the electronic model, discontinuation from panobinostat and bortezomib and dexamethasone, due to other reasons than progression was not incorporated.

PANO+BOR+DEX is a fixed dose regimen and so there are no published TTF data available. Dose interruptions are included in the model for the PANO+BOR+DEX arm based on the relative dose intensity specified in the PANORAMA-2 trial. This captures early discontinuation due to the fixed nature of the regimen.

Utility data

B9. In the company submission, the results of a multivariate analysis (based on EQ-5D data from the MM-003 trial) are used to predict utilities.

- Please justify why the data sources used for the percentage of patients with disease progression, stable disease or progressive disease (i.e. best overall response), hospitalisations and adverse events to predict utilities (i.e. the data which are combined with the coefficients derived from the multivariate analysis) are not the same as for the effectiveness data as shown in Table 45 (for all comparisons)? For example, in the base-case in which pomalidomide plus low dose dexamethasone is compared with bendamustine, data from the MM-003, MM-002 and MM-010 trials are used to estimate the percentage of patients with stable disease or progressive disease (to estimate utilities of patients treated with pomalidomide and low dose dexamethasone). Why are data from the MM-002 trial only not used (as presented in Table 48), given that the MM-002 trial is the main source for the effectiveness of pomalidomide plus low dose dexamethasone within this comparison?

The data used should have been the same as the effectiveness data. This has been corrected in the revised model.

- It is noted that not all covariates in the model are used to find differences in utilities across treatments. Please show the impact on the ICER of limiting the covariates to only those that are used to find differences in utilities across treatments (i.e. disease progression, best overall response, hospitalisations and adverse events as independent variables).
    - Please provide the results of the F-test and the R^2 for this analysis and the analysis including all of the covariates currently presented in Table 47.

The full results from the utility regression model presented in the manufacturer's submission (Model 1) and the requested regression model including only disease progression, best overall response, hospitalisations and adverse events (Model 2) are presented in response to question B10. Model diagnostics are also presented in response to B10.

The results of the regression considering only disease progression status, BORR status, hospitalisations and adverse events as independent variables are shown in

Table 27.

Table 27: Regression analysis including disease progression status, BORR status, hospitalisation and adverse events only

Covariate	Estimate	Standard error	Test statistic[a]	p-value
(Intercept)	0.750	0.041	--	--
Disease progression status (ref=Not progressed)				
Progressed	-0.039	0.023	-1.683	0.093
BORR status (ref=Response)				
Stable disease	-0.095	0.033	-2.858	**0.004***
Progressive disease	-0.126	0.055	-2.306	**0.021***
Hospitalisation (ref=No)				
Yes	-0.165	0.041	-4.062	**<0.001***
Adverse event(s) (ref=no)				
Yes	-0.069	0.024	-2.887	**0.004***

Key: BORR, best overall response rate.
Notes: * Significant at 5% level; a, t-value.

The model results when using this regression equation are presented in Table 28,

Table 29 and Table 30 for POM+LoDEX compared with BTD, PANO+BOR+DEX and conventional chemotherapy, respectively. The results show a favourable decrease in the ICER for BTD and increase in the NMB for PANO+BOR+DEX and a moderate increase in the ICER for conventional chemotherapy.

Table 28: Model results when using regression analysis – POM+LoDEX vs BTD

	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BTD	[redacted]	[redacted]			
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£39,618

Key: BTD, bendamustine + thalidomide + dexamethasone; ICER, incremental cost-effectiveness analysis; POM+LoDEX; pomalidomide + low-dose dexamethasone; QALY, quality-adjusted life year.

Table 29: Model results when using regression analysis – POM+LoDEX vs PANO+BOR+DEX

	Costs	QALYs	Incremental costs	Incremental QALYs	NMB
PANO+BOR+DEX	[redacted]	[redacted]			
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£32,660

Key: NMB, net monetary benefit; PANO+BOR+DEX, panobinostat + bortezomib + dexamethasone; POM+LoDEX; pomalidomide + low-dose dexamethasone; QALY, quality-adjusted life year.

Table 30: Model results when using regression analysis – POM+LoDEX vs conventional chemotherapy

	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
Conventional chemotherapy	[redacted]	[redacted]			
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£45,491

Key: ICER, incremental cost-effectiveness analysis; POM+LoDEX; pomalidomide + low-dose dexamethasone; QALY, quality-adjusted life year.

- As no treatment-specific data are available regarding hospitalisation rate for the comparators, please provide results without hospitalisation as a covariate (just including three covariates).

The results of the regression considering only disease progression status, BORR status and adverse events as independent variables are shown in Table 31.

Table 31: Regression analysis model including disease progression status, BORR status and adverse events only

Covariate	Estimate	Standard error	Test statistic[a]	p-value
(Intercept)	0.749	0.041	--	--
Disease progression status (ref=Not progressed)				
Progressed	-0.041	0.023	-1.746	**0.081**
BORR status (ref=Response)				
Stable disease	-0.096	0.034	-2.869	**0.004**
Progressive disease	-0.138	0.055	-2.511	**0.012**
Adverse event(s) (ref=no)				
Yes	-0.077	0.024	-3.218	**0.001**

Key: BORR, best overall response rate.
Note: * Significant at 5% level; a, t-value.

The model results when using this regression equation are presented in Table 32, Table 33 and Table 34 for POM+LoDEX compared with BTD, PANO+BOR+DEX and conventional chemotherapy, respectively. The ICERs and the NMB show a small increase from the base case values.

Table 32: Model results when using regression analysis POM+LoDEX vs BTD

	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BTD	[redacted]	[redacted]			
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£39,798

Key: BTD, bendamustine + thalidomide + dexamethasone; ICER, incremental cost-effectiveness analysis; POM+LoDEX; pomalidomide + low-dose dexamethasone; QALY, quality-adjusted life year.

Table 33: Model results when using regression analysis POM+LoDEX vs PANO+BOR+DEX

	Costs	QALYs	Incremental costs	Incremental QALYs	NMB
PANO+BOR+DEX	[redacted]	[redacted]			
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£32,719

Key: NMB, bet monetary benefit; POM+LoDEX; pomalidomide + low-dose dexamethasone; PANO+BOR+DEX, panobinostat + bortezomib + dexamethasone; QALY, quality-adjusted life year.

Table 34: Model results when using regression analysis POM+LoDEX vs conventional chemotherapy

	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
Conventional chemotherapy	[redacted]	[redacted]			
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£45,550

Key: ICER, incremental cost-effectiveness analysis; POM+LoDEX; pomalidomide + low-dose dexamethasone; QALY, quality-adjusted life year.

B10. Please document the details on the utility regressions used in the model (such as all related regression coefficients and outputs like test scores of coefficients and goodness of fit).

Results from the utility analysis regression models are presented as follows:

Table 35: Model 1 utility analysis results (based on stepwise selection methods)

Covariate	Estimate	Standard error	Test statistic[a]	p-value
(Intercept)	0.727	0.090	--	--
Disease progression status (ref=Not progressed)				
Progressed	-0.037	0.023	-1.607	0.109
BORR status (ref=Response)				
Stable disease	-0.095	0.032	-3.004	**0.003***
Progressive disease	-0.139	0.053	-2.638	**0.009***
Hospitalisation (ref=No)				
Yes	-0.138	0.040	-3.476	**0.001***
Adverse event(s) (ref=no)				
Yes	-0.076	0.023	-3.290	**0.001***
Gender (ref=male)				
Gender	0.074	0.027	2.760	**0.006***
ECOG Status (ref=0)				
1	-0.134	0.030	-4.491	**<0.001***
2 or 3	-0.332	0.040	-8.296	**<0.001***
Red Blood Count level (10^12/L)	0.049	0.020	2.498	**0.013***
Continent (ref=America)				
Australasia	-0.134	0.085	-1.578	0.115
Europe	-0.069	0.039	-1.765	0.079
MML Stage (ref=3)				
2	0.071	0.030	2.355	**0.019***
1	0.030	0.049	0.609	0.543

Key: BORR, best overall response rate.

Notes: * Significant at 5% level; a, t-value. AIC=32.856, BIC=111.931.

Table 36: Model 2 utility analysis results

Covariate	Estimate	Standard error	Test statistic[a]	p-value
(Intercept)	0.750	0.041	--	--
Disease progression status (ref=Not progressed)				
Progressed	-0.039	0.023	-1.683	0.093
BORR status (ref=Response)				
Stable disease	-0.095	0.033	-2.858	**0.004***
Progressive disease	-0.126	0.055	-2.306	**0.021***
Hospitalisation (ref=No)				
Yes	-0.165	0.041	-4.062	**<0.001***
Adverse event(s) (ref=no)				
Yes	-0.069	0.024	-2.887	**0.004***

Key: BORR, best overall response rate.

Notes: * Significant at 5% level; a, t-value. AIC=107.495, BIC=147.032.

Table 37: Model 3 utility analysis results

Covariate	Estimate	Standard error	Test statistic[a]	p-value
(Intercept)	0.749	0.041	--	--
Disease progression status (ref=Not progressed)				
Progressed	-0.041	0.023	-1.746	**0.081**
BORR status (ref=Response)				
Stable disease	-0.096	0.034	-2.869	**0.004**
Progressive disease	-0.138	0.055	-2.511	**0.012**
Adverse event(s) (ref=no)				
Yes	-0.077	0.024	-3.218	**0.001**

Key: BORR, best overall response rate.

Notes: * Significant at 5% level; a, t-value. AIC=121.954 BIC=156.549.

A summary of model fit and model comparison statistics are presented in Table 38. The likelihood ratio tests indicate that Model 1 (i.e. the stepwise model) gives a significantly improved model fit in comparison to both Model 2 and Model 3. While Model 2 gives a statistically improved fit over Model 3. This is also supported by the AIC values, which suggest that the stepwise model is the most parsimonious model, followed by Model 2. Goodness of fit was evaluated, and results are presented in Table 38. Diagnostic plots were evaluated for each model – Q-Q plot, fitted values vs predicted values, histogram of residuals and are presented below.

Figure 8: Model 1: Q-Q plot

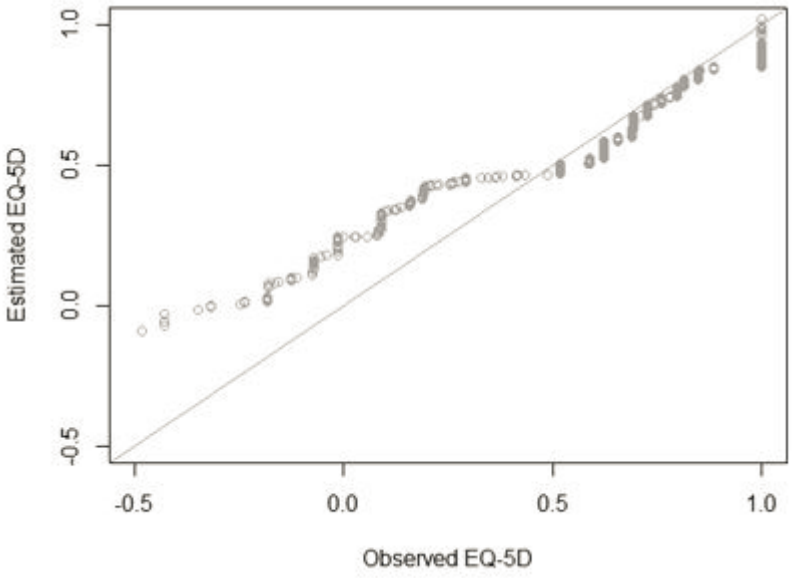


Figure 9: Model 1: histogram of residuals

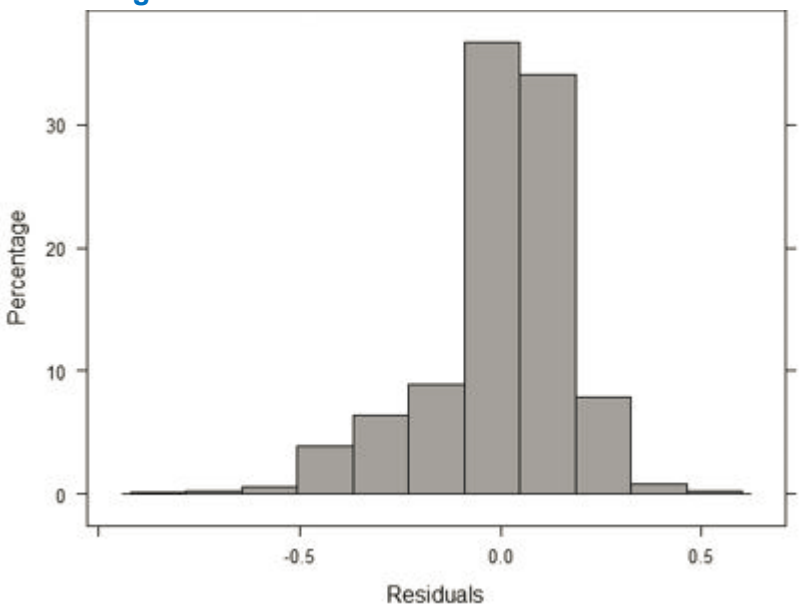


Figure 10: Model 1: fitted values vs predicted values

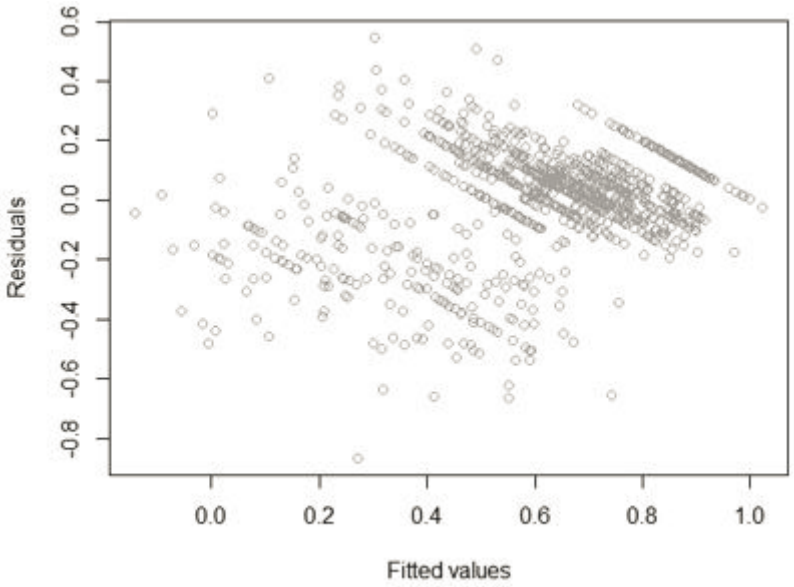


Figure 11: Model 2: Q-Q plot

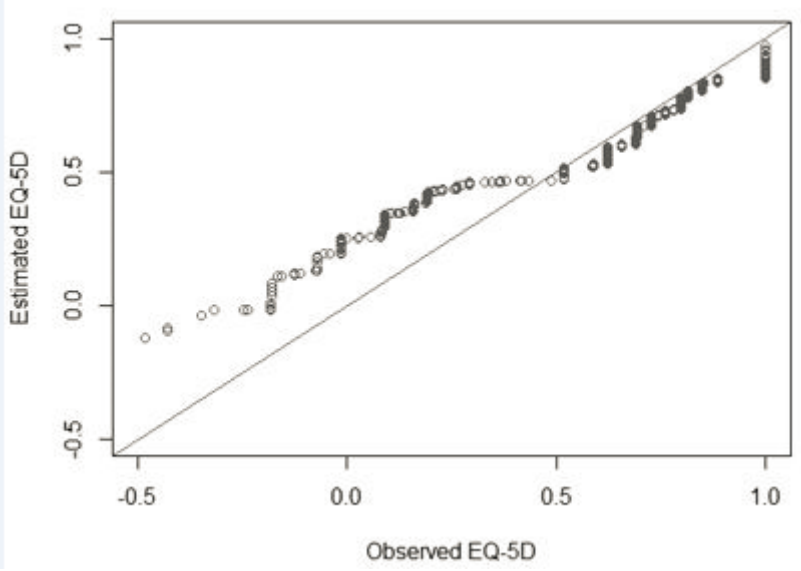


Figure 12: Model 2: histogram of residuals

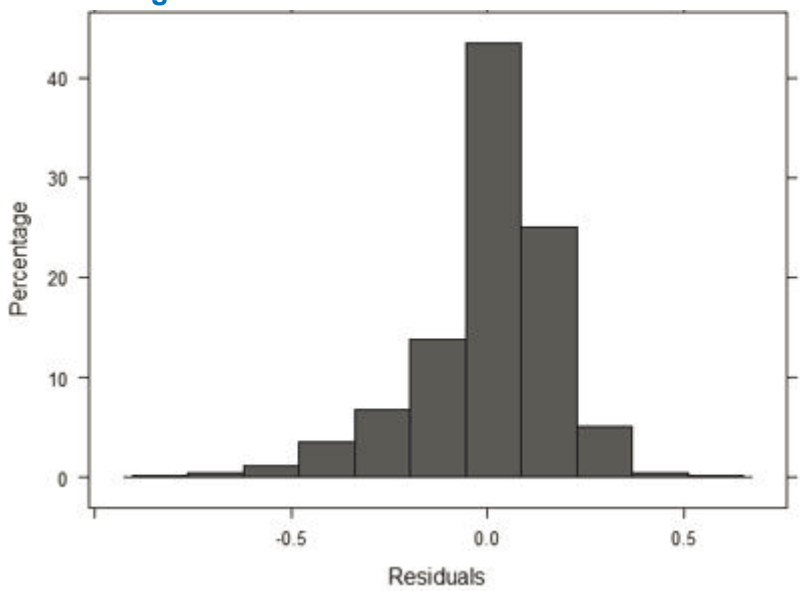


Figure 13: Model 2: fitted values vs predicted values

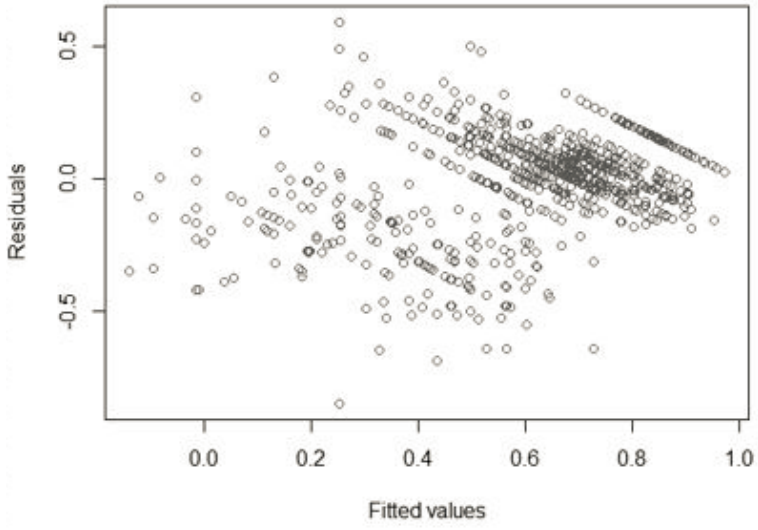


Figure 14: Model 3: Q-Q plot

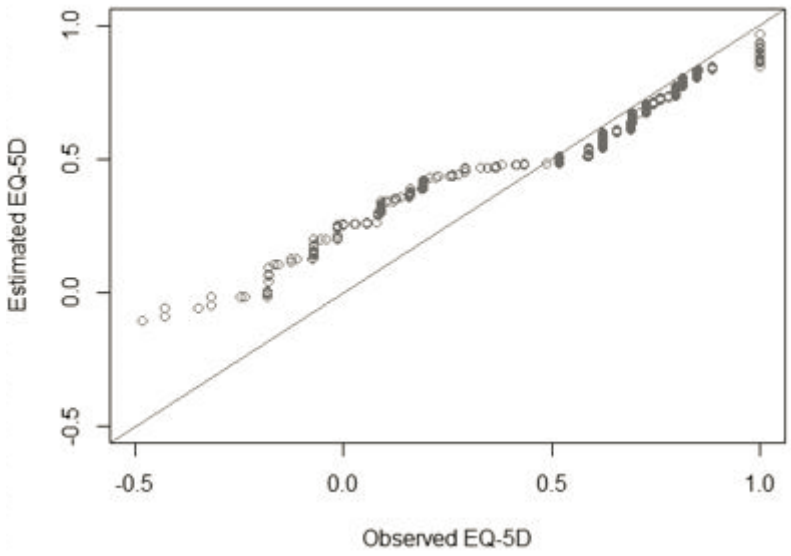


Figure 15: Model 3: histogram of residuals

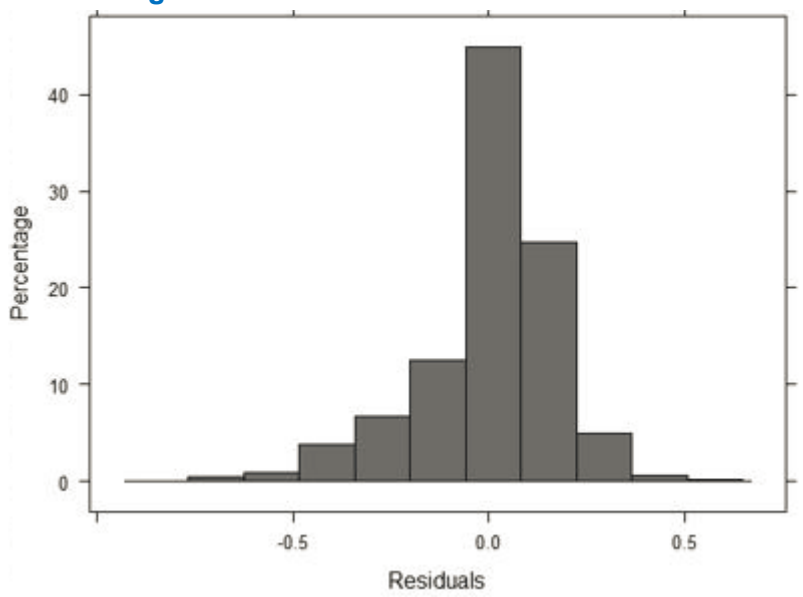


Figure 16: Model 3: fitted values vs predicted values

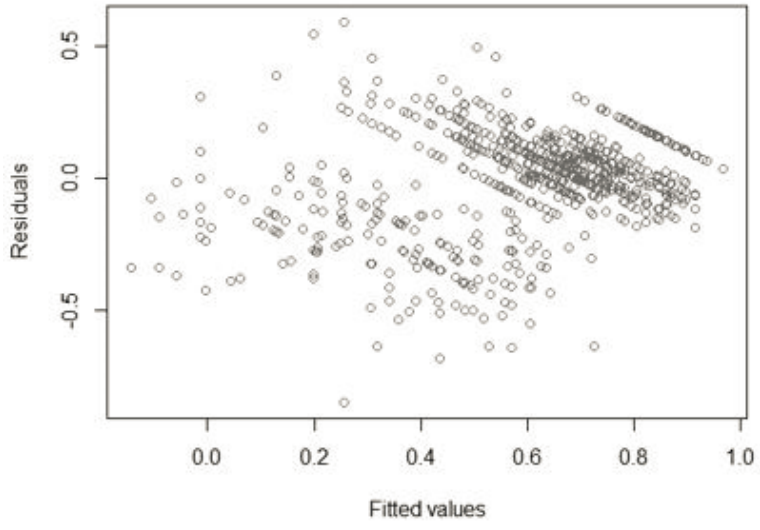


Table 38: Model fit comparison statistics

Model	N	DF	Marginal R^2	Conditional R^2	AIC	BIC	Likelihood ratio vs stepwise model [p-value]	Likelihood ratio vs model 2 [p-value]	Likelihood ratio vs model 3 [p-value]
Model 1	1035	16	0.200	0.600	32.856	111.931	NA	90.64 [<0.001]*	107.10 [<0.001]*
Model 2	1035	8	0.039	0.603	107.495	147.032	90.64 [<0.001]*	NA	16.46 [<0.001]*
Model 3	1035	7	0.029	0.600	121.954	156.549	107.10 [<0.001]*	16.46 [<0.001]*	NA

Key: AIC, Akaike Information Criterion, BIC; Bayesian Information Criterion; DF, Degrees of freedom; N, number of observations.

Notes: *Significant at 1% level; The marginal R^2 value and conditional R^2 values for mixed effects models describe the proportion of variation explained by only the fixed factors and the proportion of variation explained by the fixed and random factors, respectively.

B11. Please check the data in Table 50 (page 207). There is always the same difference between the results of "MM-002", "All trials" and "MM-003" using the EQ-5D method. Please comment on how this same difference is observed for EQ-5D and not for EORTC.

These results have been double checked and are correct. The only differences between the results presented are in the patient characteristics used (which means that the difference between datasets remains constant). Due to rounding to 2 decimal places there appear to be some minor differences of 0.01 between EORTC results; these are not actual differences and if more decimal places are used the difference between the trials remains constant as would be expected.

B12. In a scenario-analysis, utilities derived from the EORTC QLQ-C30 are used (by applying the algorithm by Rowen et al.), instead of EQ-5D utilities. The results of multivariate analyses to determine the most important predictors of HRQL (based on the EORTC QLQ-C30) are presented in Appendix 23 (Table 61, page 236). In the first model, based on a stepwise and backwards selection, many coefficients equal 0.000. Please explain if this means that these covariates were not statistically significant, and therefore not included in the final model to predict utilities.

This is correct.

B13. In paragraph 5.4.2 (page 200). 'Description of the identified utility studies', the numbers in the text do not correspond to the numbers in the PRISMA flow diagram (Figure 40, page 201). Preliminary screening of abstracts and titles was performed on 382 records, and 74 records were included, according to the text. In the Figure slightly different numbers are provided. Please state what the correct numbers are.

Please find the correct text below:

"Systematic database searches identified 384 records. Preliminary screening of abstracts and titles was performed on 380 records after removing four duplicates. After preliminary screening, 71 records were included. The majority of the records (155) were excluded on the basis of study type. Secondary screening was performed by reading the full texts of these records, after which eight publications were included and relevant data were extracted from four unique studies."

Costs

B14. Little data are available regarding dose interruptions for the comparators (and no dose interruptions were taken into account for bendamustine and conventional chemotherapies). Please justify the approach including dose interruptions in the company submission, or, if possible, provide a scenario analysis in which dose interruptions are not taken into account.

Dose interruptions were applied in the model based on the data available from the POM+LoDEX trials and the PANORAMA-2 trial. Due to lack of data dose interruptions were only applied to the POM+LoDEX and PANO+BOR+DEX arms. The following scenario considers using the data available for the POM and PANO treatments (as in the original

model) and then applying the maximum proportion of these skipped packs to the remaining treatments (see Controls and Dosing sheets).

The maximum proportion of skipped packs is 4.43% per cycle as indicated by the PANORAMA-2 data. In this scenario it is assumed that 4.43% of doses are skipped each cycle for BORT, THAL, BEN and CYC. Due to the negligible cost associated with LoDEX, and the fact that this treatment is received in all treatment regimens, the model assumes no dose interruptions for LoDEX.

The results of this scenario are presented in Table 39, Table 40 and Table 41 for POM+LoDEX compared with BTD, PANO+BOR+DEX and conventional chemotherapy, respectively.

Table 39: Results from the dosing interruptions scenario – POM+LoDEX vs BTD

	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BTD	[redacted]	[redacted]			
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£40,599

Key: BTD, bendamustine + thalidomide + dexamethasone; ICER, incremental cost-effectiveness ratio; POM+LoDEX, pomalidomide + low-dose dexamethasone; QALY, quality-adjusted life year.

Table 40: Results from the dosing interruptions scenario – POM+LoDEX vs PANO+BOR+DEX

	Costs	QALYs	Incremental costs	Incremental QALYs	NMB
PANO+BOR+DEX	[redacted]	[redacted]			
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£31,613

Key: NMB, net monetary benefit; PANO+BOR+DEX, panobinostat + bortezomib + dexamethasone; POM+LoDEX, pomalidomide + low-dose dexamethasone; QALY, quality-adjusted life year.

Table 41: Results from the dosing interruptions scenario – POM+LoDEX vs conventional chemotherapy

	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
Conventional chemotherapy	[redacted]	[redacted]			
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£45,261

Key: ICER, incremental cost-effectiveness ratio; POM+LoDEX, pomalidomide + low-dose dexamethasone; QALY, quality-adjusted life year.

B15. The model assumes that only whole packs of thalidomide can be dispensed each cycle. As a consequence, 14 units (i.e. 700 mg) are wasted every cycle (in bendamustine), although these might be used in the following cycle. Similarly, the model assumes that only whole packs of cyclophosphamide can be dispensed each cycle. As a consequence, 3000 mg is wasted every cycle (in cyclophosphamide plus thalidomide and dexamethasone). These might be used in the following cycle. Please

confirm whether the company has considered this and, if possible, show the impact of this assumption on the ICER.

Following the feedback from the original NICE submission where the ERG (Kleijnen Systematic Reviews) commented that the "manufacturer does not justify enough the issue of wastage in drug dosing." When Celgene took this approach, we considered that as a conservative approach, it was assumed that only whole packs of each treatment can be dispensed each cycle. This is applied to POM, BEN, THAL, CYC and PANO in the model. Wastage associated with HiDEX is not accounted for because of the use of an average weekly dose. Furthermore, the costs associated with HiDEX are likely to have a very small impact on results given the negligible acquisition costs for HiDEX.

The model includes the functionality to assess the impact on results of excluding drug wastage from the drug cost (see Controls sheet). The results of this scenario are presented in Table 42, Table 43 and Table 44.

Table 42: Scenario analysis excluding wastage from total costs – POM+LoDEX vs BTD

	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BTD	[redacted]	[redacted]			
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£42,130

Key: BTD, bendamustine + thalidomide + dexamethasone; ICER, incremental cost-effectiveness ratio; POM+LoDEX, pomalidomide + low-dose dexamethasone; QALY, quality-adjusted life year.

Table 43: Scenario analysis excluding wastage from total costs – POM+LoDEX vs PANO+BOR+DEX

	Costs	QALYs	Incremental costs	Incremental QALYs	NMB
PANO+BOR+DEX	[redacted]	[redacted]			
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£32,433

Key: NMB, net monetary benefit; PANO+BOR+DEX, panobinostat + bortezomib + dexamethasone; POM+LoDEX, pomalidomide + low-dose dexamethasone; QALY, quality-adjusted life year.

Table 44: Scenario analysis excluding wastage from total costs – POM+LoDEX vs conventional chemotherapy

	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
Conventional chemotherapy	[redacted]	[redacted]			
POM+LoDEX	[redacted]	[redacted]	[redacted]	[redacted]	£46,948

Key: ICER, incremental cost-effectiveness ratio; POM+LoDEX, pomalidomide + low-dose dexamethasone; QALY, quality-adjusted life year.

B16. In the economic model, 3 vials of bortezomib are used per patient per week in the first eight cycles and 2 vials in subsequent cycles. Please explain why 2 vials per patient per week in the first eight cycles and 1 vial in subsequent cycles were not used instead (assuming 1 vial per administration)? Additionally, in contrast to the

explanation given in Section 5.5.2 of the company submission, in the model a bortezomib dose of 1.3 mg/m^2 twice weekly for 2 weeks in a 21 day cycle is given in the first eight cycles (instead of the first cycle only). Please explain if this is implemented correctly, in spite of the text in section 5.5.2 of the company submission.

There was an error in the model here which has now been corrected. Vial numbers were incorrectly rounded up following production of the estimates of vial numbers required using the method of moments technique.

Within the revised model version, 2 vials of BORT are used per patient per week in the first 8 cycles and then 1 vial in subsequent cycles.

The BORT dose of 1.3mg/m2 is given twice weekly for 2 weeks in a 21-day cycle for the first 8 cycles, then BORT is given once weekly for 2 weeks in a 21-day cycle for subsequent cycles. This is applied in the model.

The dosing of BEN has also been corrected to provide the correct number of vials per cycle.

B17. In the base-case, the costs associated with IV/SC administration visits were obtained from the recently published bortezomib first-line appraisal (TA311). Please explain why subsequent visits are more expensive than the first visit, i.e. £312.87 compared to £222.13.

The costs were taken from the following HRG codes from the 2011-12 National Schedule Reference costs: SB12Z - Deliver simple Parenteral Chemotherapy at first attendance (Day case) and SB15Z - Deliver subsequent elements of a Chemotherapy cycle (Day case).

In responding to this question it was noticed that the latest version of the reference costs had not been used. Updating the costs to the most recent National Schedule of Reference costs (2014-15) amends these to SB12Z - £239.12 and SB15Z - £362. It remains the case that the cost for subsequent elements is greater than the cost for first attendance. The use of these updated costs has minimal impact on the ICER.

The chemotherapy delivery HRGs are assigned for each attendance for treatment to reflect the complexity of treatment and resource usage. We cannot be sure as to why subsequent visits are more expensive. However, these codes have been used in numerous NICE assessments (including the assessment for bortezomib) and are generally regarded as the most accurate data source available.

B18. Some costs, e.g. administration costs (page 216 of the company submission), were based on historical data (in this case 2011/2012) and uplifted to a more recent price base. Please confirm that no more contemporary unit costs were found after searching in all instances where such price uplifts have been made.

We can confirm that with the exception of the administration costs presented in answer to question B17 and the costs in the table below that there are no other costs for which more contemporary unit costs exist. This is mainly due to amendments to the HRG groupings, which have resulted in a loss of granularity, especially around monitoring and tests.

> The ERG have found a potentially cheaper price (Actavis UK Ltd) for bendamustine 25 mg powder for concentrate for solution for infusion vials. NHS indicative price = £6.85 for 1 vial. Please provide up-to-date unit costs from BNF medicines to populate Table 52 (page 212) and run the model on these prices.

There is no price for bendamustine ACTAVIS UK in the current version of BNF or eMIT (both accessed 11/08/16). This leads us to believe that this formulation is not currently available in the UK and therefore cannot be included for comparison in this assessment.

Table 52 references eMIT and MIMs in accordance with NICE methods (MIMs provides the same information as BNF but on a more regular basis). If taking all costs from BNF, the table would read as follows:

Table 45: BNF costs added to table 52 from submission

Therapy	Unit dose (mg)	Pack size	Unit cost including any PAS original submission	BNF Unit cost including any PAS	New Source
POM	1,2,3 or 4	28	[redacted]	[redacted]	Celgene PAS.
DEX	2	100	£50.31	£ 78.00	BNF accessed 11/08/16
	2	50	£27.76	£ 52.50	
BEN	25	1	£69.45	£69.45	BNF accessed 11/08/16;
	100	1	£275.81	£275.81	BNF accessed 11/08/16;
THAL	50	28	£298.48	£298.48	BNF accessed 11/08/16; thalidomide, 50mg cap, 28=£298.48
PANO	20	6	£4,656	Not in BNF	BNF accessed 11/08/16; panobinostat 20mg red cap
BOR	3.5	1	£762.38	£762.38	BNF accessed 11/08/16; 3.5mg powder in vial
CYC	50	100	£139.00	£139.00	BNF accessed 11/08/16; 50mg tab
Subsequent therapies (scenario analysis only)					
Melphalan	2	25	£45.38	£42.88	BNF accessed 11/08/16; melphalan 2mg tab 25=£45.38
Prednisolone	5	28	£0.24	£1.61	BNF accessed 11/08/16
CYC	500	1	£9.00	£9.20	BNF accessed 11/08/16
	1000	1	£16.28	£10.66	
	2000	1	£27.89	£21.32	(1g vial x2)

Key: BEN, bendamustine; BOR, bortezomib; CYC, cyclophosphamide; DEX, dexamethasone; eMIT, drugs and pharmaceutical electronic market information; MIMs, Monthly Index of Medical Specialties; PANO, panobinostat; THAL, thalidomide.

Implementing these costs instead of the costs used within the submission has minimal impact on the results, with the ICER vs BEN improving to £39,526 per QALY, the NMB vs PANO+BOR+DEX improving to £32,482 and the ICER vs CTD improving to £44,697 per QALY.

The impact on the scenario when subsequent therapies are included shows an improvement in the ICERs or NMB favouring POM+LoDEX of similar magnitudes.

B19. Please confirm the programming error that outpatient unit costs are applied instead of inpatient unit costs for adverse events (AE) and vice versa (AEs sheet, cells: G79:H119) and correct this error, if applicable.

This error is confirmed and has been corrected within the revised model.

B20. Although resource use is derived from the answers to the resource use questionnaire, please provide a rationale as to why 'resource use, on treatment: pre progression' is higher for bendamustine and panobinostat plus bortezomib and dexamethasone compared to pomalidomide plus low dose dexamethasone(as these costs exclude administration costs, costs associated with adverse events and costs of concomitant medication). Please confirm that some costs, especially the administration costs were not double counted.

Routine follow up resource use is dependent on the treatment schedule and side effects. At the advisory board conducted to gain clinical input to data analysis for this submission clinicians stated that they would expect lower resource use with POM+LoDEX versus comparator treatments. POM+LoDEX was also stated to have a more favourable toxicity profile (see Section 4.12). When clinicians were asked to rate safety of the comparators out of ten (10=best; 1=worst), they gave a mean score of 4.8 for BEN, 3.9 for PANO+BOR+DEX and 4.3 for conventional chemotherapy, compared with 7.4 for POM. This is likely to have translated into the increased resource use associated with the comparators in the resource use questionnaires. During the recent advisory board meeting, clinical advisors echoed the clinical study findings presented in Section 4.12; the advisors commented that patients require careful monitoring due to the toxicity profile of comparator treatments.

The resource use questionnaire collected data associated with the resource use in routine follow up care for each of the comparators. This was conveyed to the clinicians upon receipt of the questionnaire and within the questionnaire itself: the instructions stated: "Please describe the frequency of routine follow-up care for patients with RRMM based upon the categories presented in the following table." The table was also labelled "Estimation of resource use for routine follow-up care."

Furthermore, comments within the questionnaires indicated that these estimates did not consider day unit attendances or administration. Therefore, we consider it unlikely that costs associated with administration, adverse events and concomitant medication are double counted.

Other

B21. Key data are missing for results of the resource use questionnaire in Appendix 26 cross referenced on page 211 of the company submission. It would be helpful to have access to the full data extraction for all tables (70 to 74 of the Appendices)

including all individual responses because variation around the average could be an important source of uncertainty.

The data extraction for the six completed resource use questionnaires is provided via NICE DOCS and labelled as 'resource use_B21'. Averages were estimated across the completed responses. Where responses were not provided or a vague response that could not be interpreted numerically were provided this observation was omitted.

B22. In Section 5.3 of the company submission, it was mentioned that the uncertainty around the choice of parametric curve was incorporated in the probabilistic sensitivity analysis by selecting the type of the parametric survival curve based upon sampling from the probability that each parametric model was the best fitted parametric model, derived from AIC values of each fitted parametric curve.

- Please justify the use of this approach rather than incorporating the structural uncertainty surrounding parametric survival curves in scenario analyses only.

Burnham and Anderson (2004) discuss methodology based on the likelihood of each curve providing the best statistical fit to the data. The method estimates goodness of fit based on AIC scores, and hence considers the goodness of fit of each curve to the observed Kaplan-Meier data. We recognise that this does not take into account the degree of uncertainty captured by the proportion of the curve beyond the observed Kaplan-Meier data and makes the assumption that the curves fitted are the only curves which could provide a good fit to the data. However, the data used in the model are considered mature enough for the AIC estimates to be largely reflective of overall curve goodness of fit.

Therefore, the model uses this methodology in addition to standard scenario analyses to more fully account for the uncertainty associated with the goodness of fit of each parametric curve in the probabilistic sensitivity analysis. The uncertainty associated with the curve beyond the observed data is also captured in a scenario analysis where the impact of individual parametric curves on the results are presented.

- Please provide any references from published literature where this approach was explained.

The reference explaining the methods is provided in the original submission document and is also presented below:

Burnham KP and Anderson DR. Multimodel inference understanding AIC and BIC in model selection. Sociological methods & research. 2004; 33(2):261-304

Section C: Textual clarifications and additional points

C1. Some references are missing from the main report (e.g. 51, 63, 66 etc.) and from the appendices (e.g. 2, 4, 5, 6 etc.). Please ensure that all references are provided.

We have checked the references provided and have found that there are some missing. The complete reference packs have been re-sent by courier to NICE today. We would like to apologise for the inconvenience caused.

We have also provided on the CDs with the references updated reference lists for the main submission document and the appendices as we noticed a couple of errors. The referencing within the main bodies of the documents is unchanged.

Please also note that Please note that the following references have not been provided:

- Ref 51: (MIMs) Imnovid 2016. This can be accessed via the web link provided with the reference.
- Ref 66: Howlader N et al. SEER cancer statistics review, 1975–2013. 2016. This can be accessed via the web link provided with the reference.
- Ref 106: Ref 159 and 106 are the same documents and present all consultation carried out as part of the previous appraisal – Ref 106 is incorporated in ref 159.
- Ref 151: This is a book & therefore we do not provide a PDF.
- Ref 195, 196, 197, 201: These are large excel files that can be accessed via the web link provided with the reference.

C2. Please confirm that the provided references (17, 111 etc.) are the full clinical study reports (CSRs). If not, please provide the full CSRs.

We can confirm that the full CSRs have been provided.

References

1. Scottish Intercollegiate Guidelines Network (SIGN). Search filters. 2015 (Updated: 27/08/2015). Available at: http://www.sign.ac.uk/methodology/filters.html Accessed: 15/06/2016.
2. National Institute for Health and Care Excellence (NICE). TA380 Final Appraisal Determination: Panobinostat for treating multiple myeloma after at least 2 previous treatments. 2016. Available at: https://www.nice.org.uk/guidance/TA380/documents/final-appraisal-determination-document Accessed: 13 May 2016.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib (review of TA338) [ID985]

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: [redacted]

Name of your organisation: Myeloma UK

Your position in the organisation: [redacted]

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 is a complex cancer originating from abnormal plasma cells in the bone marrow. Treatment can halt its progress for periods of time and improve quality of life. Due to the availability of new novel drugs and drug combinations, survival in myeloma has improved greatly. However, it remains a challenging cancer to treat, with high mortality rates. There is therefore an urgent and continual need for new treatments to continue to improve patient outcomes.

At diagnosis, given the non-specificity of the symptoms of myeloma, patients are more likely to be diagnosed late. Patients often present in secondary care with bone lesions, fractures and in worse cases collapsed vertebrae. This impacts negatively on their pain levels, mobility and their ability to complete everyday tasks. The major complications of myeloma include: bone destruction, bone pain, fatigue, kidney impairment and a severely depleted immune system.

As myeloma is incurable, this can have a substantial effect on patients' emotional wellbeing, particularly as the vast majority experience a number of relapses and/or quickly become refractory to available treatments. As patients experience multiple relapses, they report that the disease takes a toll on their emotional and physical well-being. Treatment side-effects and frequent hospital visits 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
Myeloma can also have a significant impact on myeloma carers and family members. They tell us that:

- Looking after someone with myeloma has significant emotional, social and practical implications. These represent a change in lifestyle, particularly when a myeloma patient is on an intensive treatment or is not responding to treatment
- Anti-myeloma treatment can improve the quality of life of myeloma patients and their ability to complete normal daily activities. This can have a positive effect on the lives of carers and family members
- The impact of myeloma on the well-being of carers is often overlooked. There is a lack of training and support (including financial support) available for myeloma carers
- Carers and family members report carrying a significant emotional burden with them, which they often do not talk about. There is a major worry attached to looking after loved ones, particularly where there is a noticeable deterioration over time

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. 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:

- The treatment outcomes they value most are those to do with length and quality of life, progression free (PFS) and overall survival (OS)

- Any incremental gain in survival for treatment is seen as a “bridge” to further treatments coming down the line. Survival benefits of one treatment cannot be seen in isolation to others

- They want treatments that increase in remission (i.e. disease free periods) for the longest possible time and reduce their paraprotein to stable or non-detectable levels. As well as improving the quality of life for patients, the impact on carers is reduced during disease free periods

Treatments with minimal impact on quality of life are very important, particularly as few side effects as possible and of low severity. Patients tell us that long-term side-effects, which persist after the termination of treatment, have a detrimental impact on their quality of life. Carers also tell us there is less of a burden on them where treatments have a minimal impact on quality of life.

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 the individual and heterogeneous nature of myeloma, 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.

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.

Please note that Imnovid is not likely to replace these treatments. Instead it will be added to the treatment options for relapsed and refractory patients.

Farydak® (panobinostat) in combination with Velcade and dexamethasone

NICE guidance (TA380) recommends Farydak® (panobinostat) in combination with Velcade® (bortezomib) and dexamethasone as an option for treating relapsed and/or refractory myeloma patients who have received at least two prior regimens, including Velcade and an immunomodulatory agent. As it was only approved a few months ago, we are still waiting to see a picture of how this is used in clinical practice.

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. It prolongs PFS in the group of patients covered by the NICE guidance. 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).

It has also opened up the possibility of Velcade retreatment for patients, as it has been restricted by NHS England.

Disadvantages

The main disadvantage of the Farydak combination treatment is gastrointestinal problems, in particular diarrhoea. Other side effects include neuropathy (associated with the Velcade®), fatigue, low blood counts and nausea. However, patients and doctors report that these have been adequately managed through communication

and supportive care. Neuropathy associated with Velcade has also decreased significantly given the subcutaneous formulation of the drug.

Bendamustine

Bendamustine is only routinely approved for myeloma patients living in England and is usually prescribed in combination with thalidomide and dexamethasone. In Wales, patients have to access bendamustine through an individual patient funding request (IPFR).

Advantages

As there are little treatment options available for myeloma patients, bendamustine offers patients a further treatment option with a good anti-myeloma affect particularly when given in combination with thalidomide and dexamethasone. It prolongs PFS in eligible patients and patients who receive it tell us it is well tolerated.

It also offers a different mechanism of action to other alkylating agents, which is particularly beneficial.

Disadvantages

Whilst effective in some patients, it 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

These are usually used in a “salvage setting” and consist of a range of different options, including melphalan, cyclophosphamide and other treatments such as DTPACE and ESHAP. There is no one standard chemotherapy option in this setting. Decisions usually come down to doctor preference and a 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.

Imnovid was previously available to myeloma patients living in England and is currently approved in Wales and Scotland. From the experience of myeloma clinicians, from the real-world data collected by Celgene and from talking to myeloma patients who have received Imnovid, we understand that it has a strong anti-myeloma affect and is well-tolerated in patients. We also know that Celgene has worked extremely hard (both nationally and at a global level) to try and make the best value proposition possible to the NHS, which is something that Myeloma UK commends and hope NICE considers.

Below we list the advantages of Imnovid in clinical practice. To inform this submission, we conducted interviews with patients who had already received Imnovid – either as part of a clinical trial or via the Cancer Drugs Fund. Their feedback has been taken into account in our response.

It prolongs both progression free and overall survival

As myeloma is a relapsing and remitting cancer, and one that is currently incurable, the goal of treatment is to prolong the depth and length of the remissions patients experience and overall survival, whilst at the same time improving their quality of life. Clinical trial data highlights that Imnovid extends both progression free and overall survival in myeloma patients, which is a major benefit of the treatment.

One myeloma patient we interviewed, who had been receiving pomalidomide for three years through the Stratus trial commented, “I firmly believe that I would not be here if I had not received pomalidomide as part of a clinical trial.” Another patient on the same trial commented, “I am aware that pomalidomide, at the stage of myeloma I am at, is not a ’wonder drug’ or a ’cure’ but I know that it is something that it is effective at keeping my myeloma in plateau and I hope that it will prolong my life by a considerable period of time.”

The significant improvement of both PFS and OS when patients receive pomalidomide is important to patients, as in simple terms it allows them to remain alive for longer. This is something that is very important to both patients and their families.

It meets a major area of unmet need

Whilst Farydak and bendamustine are available at third line and beyond, they are not treatments suitable for all patients in this setting and doctors and patients tell us they would value access to Imnovid.

Farydak also needs to be prescribed in combination with Velcade, which may not be the most appropriate treatment in patients who have not had a good response/reacted badly to Velcade previously. Imnovid would represent a treatment of choice for these patients.

Imnovid may also be used before or following Farydak and bendamustine, so it doesn’t directly replace these treatments for patients. It is important, particularly in the relapsed setting, that there are varying treatment options available for patients so they can received personalised treatment rather than a one-size-fits all approach.

It reduces fear of relapse in myeloma patients

Having a treatment option approved for routine use in patients in the multiply relapsed and refractory setting, will reduce the fear that myeloma patients have of reaching the “end” of treatment options for their cancer.

Myeloma patients who have been through a number of relapses tell us that relapsing can have a major impact on their emotional wellbeing. A study on the emotional burden of myeloma on patients with relapse found that whilst in some patients the burden of having relapsing myeloma grew less intensive with increasing relapses as they “knew what to expect”, a high proportion of patients reported that multiple relapses were associated with increasing distress, as they felt that they were exhausting treatment options.

Relapse can also impact on a patient’s emotional state and on the anxiety carers/family member’s face, as when in remission, they have the hope of potentially being treatment free for a long period of time, but being told that their myeloma has returned can put an end to this hope. One patient outlined on the Myeloma UK Discussion Forum that whilst they are currently in remission, “Even the smallest worry about my myeloma results generates huge waves of worry/depression about relapsing.”

Knowing that there is another treatment option at third relapse and beyond will reduce the anxiety associated with relapse for both patients and carers, as they know that there is another treatment available for them when they get there, even if they

are refractory to previous treatments. It will also improve their quality of life as their emotional wellbeing is improved.

Alleviating symptoms

As patients experience multiple relapses, their physical wellbeing will often deteriorate over time given the cumulative toxicities associated with repeated treatments (for example, peripheral neuropathy is a frequently reported side-effect) and the symptoms and complications of their myeloma will add to the impact on their quality of life.

Treating the underlying myeloma with an effective novel agent combination (with chemotherapy and/or steroids) will often contain and in some cases alleviate the symptoms and complications patients' experience (for example, treatment will reduce bone pain associated with myeloma). In some patients, this will improve their ability to carry on with day-to-day tasks and it will also improve their quality of life and physical wellbeing. It also reduces reliance on carers and family members.

Whilst in multiply relapsed patients, they will still experience effects related to the cumulative toxicities of previous treatments, it will improve their overall quality of life as they won't have to experience additional issues relating to their cancer where the treatment has an anti-myeloma effect.

In addition to this, below we outline the reduced side-effect profile associated with the treatment which means it is unlikely to worsen any cumulative toxicities experienced by the patient.

It has a reduced side-effect profile

Imnovid has a less severe side-effect profile that Farydak, Velcade and dexamethasone and bendamustine, so would be a beneficial treatment option for multiply relapsed myeloma patients in England. This is particularly important given the stage of myeloma patients are at, where side-effects may be less easy to tolerate.

It also has a better side-effect profile than other immuno-modulatory drugs approved earlier on in the treatment pathway.

One patient commented, "In terms of the impact on my quality of life, the side-effects I have experienced compared to Revlimid have been virtually nil; in fact they are 10 times better than when I was on Revlimid". The same myeloma patient expressed, "If I hadn't received Revlimid I probably wouldn't even notice any side-effects, as I experienced bad side-effects on Revlimid, I just fear them returning again!"

It is an oral treatment

We know from a Myeloma UK survey of 606 patients (Low et al 2012), that 41.1% of patients would prefer to have a treatment that they could receive at home (preferably in tablet form) due to ease, convenience, the fact it reduces hospital visits and allows patients to avoid invasive procedures such as infusions.

In patients who have multiply relapsed myeloma, using oral treatments such as pomalidomide allows them to spend more time at home with their families and to continue living as normal a life as possible according to their individual circumstances.

This is particularly important for elderly patients or patients living in more rural areas who may not be able to regularly travel down to a cancer centre to receive IV treatment. One patient we spoke to about their experience of pomalidomide expressed, “From speaking to people at the Support Group I belong to, I feel particularly sorry for patients who have to travel from rural Wales to the hospital clinic to receive IV treatment – oral treatments such as pomalidomide are very useful for these patients in particular.”

Oral treatments such as Imnovid can also have a positive impact on carers, as patients may be less reliant on being routinely taken to hospital.

The regimen is relatively easy to follow

As well as pomalidomide being an oral treatment, it also has a relatively straightforward treatment regime. This means that patients and their doctors are confident they will be able to comply with reducing the financial and health costs associated with non-compliance.

In addition, as pomalidomide is similar to other myeloma treatments (IMiDs such as lenalidomide and thalidomide) and as it has been available recently through the Cancer Drugs Fund and large Phase III clinical trials, doctors are confident in how to use it and they have real-world experience of the treatment regime and what to look out for in terms of side-effects.

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

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.

One patient we interviewed who had a negative experience whilst receiving pomalidomide outlined that she experienced muscle pain and shortness of breath and that due to the severity of the side effects she had to come off the treatment. However, she expressed, "Pomalidomide just simply hasn't worked for me or my myeloma, although I am sure it works for other patients."

Poor patient experience on treatments can be negated by appropriate doctor 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 cancer not all patients will respond well to pomalidomide. However, it is important that pomalidomide is made available to allow doctors the flexibility to prescribe pomalidomide to patients they think will benefit clinically.

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.

The clinical trial evidence suggests that as well as being beneficial for the majority of patients in the relapsed and/or refractory setting, it is suitable for patients with kidney impairment (compared to other treatments in the same setting).

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 know from speaking to clinicians who have prescribed Imnovid in their patients that is very well tolerated by patients and has a good anti-myeloma affect. It is now a standard of care in Wales and in Scotland and is a treatment of choice by doctors in these areas.

The patient experience of using the treatment does reflect, or even better, that of patients within the clinical trials. Any side-effects are better managed in the real-world setting due to a less restrictive setting and the ability to moderate dosing.
There is not any robust real-world data available from the Cancer Drugs Fund to support the comments above, however, data collected by Celgene to support this second appraisal, does point to it being a very important drug for the treatment of myeloma.

As with all drugs and in all clinical trials, not all patients respond similarly to Imnovid, but it is important for doctors to be allowed to make a well-informed clinical judgement on the basis of their patient's individual circumstances and previous response to treatments. The MUK Seven Imnovid trial, run by Myeloma UK, is also likely to help in the future with the identification of patients that will respond to treatment given the addition of the biomarker.

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 agree that the clinical trials have captured the outcomes that are important to patients and we are not aware of any limitations in the trial. Whilst in the first appraisal there was a discussion about the appropriateness of the comparator in the appraisal, Myeloma UK considers that high-dose dexamethasone was appropriate given the previous lack of a standard of care in the fourth line setting.

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?

We are not aware of any additional side-effects with Imnovid.

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)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

Muhlbacher et al. Evaluating patients' preferences for multiple myeloma therapy, a Discrete Choice Experiment (2008)

Raven D et al. Comparison if 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.

Myeloma UK considers Imnovid to be a very innovative drug and patients who have received it through clinical trials, the Cancer Drugs Fund and in Scotland and Wales report that it is well tolerated and impacts significantly on progression free and overall

survival. The clinical trial data from both the NIMBUS and STRATUS studies also demonstrates that it is an extremely effective drug in relapsed and refractory patients.

Are there any other issues that you would like the Appraisal Committee to consider?

Not applicable

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Imnovid has previously been available in NHS England and is currently available in Wales. Patients who have received Imnovid in the real-world setting tell us it improves survival and has little impact on their quality of life
- The oral nature of the treatment allows patients and carers to get on with normal daily activities, particularly as it does not require frequent hospital visits
- Imnovid has a better side-effect profile than other myeloma treatments which may be used in the relapsed setting, which is particularly beneficial for heavily pre-treated patients
- Imnovid will add to the treatment options available to myeloma patients in the relapsed and/or refractory setting, where treatment options are depleting and where there is a major emotional burden on patients and carers. It is important, particularly in the relapsed setting, that there are varying treatment options available for patients so they can received personalised treatment rather than a one-size-fits all approach

Email: [redacted]

09 October, 2016

Dr Andrew Stevens
Chair, Technology Appraisals Committee C
National Institute for Health and Care Excellence

Dear Dr Stevens,

I am writing on behalf of the UKMF to express our strongest support for the current re-appraisal of Pomalidomide (TA338) for the treatment of patients with relapsed refractory myeloma, and to provide you with some soon to be published data that we have collated based on the use of Pomalidomide in the UK during the brief period of access provided by the Cancer Drugs Fund.

Pomalidomide under its license is for use at third line or later in the treatment pathway, where patients have failed both lenalidomide and bortezomib and progressed on their latest therapy. At this stage of their myeloma, such patients have a poor outlook with a survival of around 9 months, prior to the licensing of Pomalidomide. The survival benefit reported in the phase 3 study of Pomalidomide with Dexamethasone versus High Dose Dexamethasone was 4.6 months, with a PFS benefit of 2.1 months. An important finding was that for those patients achieving a partial response (PR) or better the median overall survival was 22 months (Moreau et al, 2016), and even patients achieving only disease stability (SD) benefited, with a median survival of 16.2 months. The uplift in survival benefit of Pomalidomide therapy (4 months) over the control arm of dexamethasone accords with a study analysing 173 studies in over 22,000 patients with multiple myeloma, that found a 2.5 month survival increment for every month gained in disease free survival (Felix et al, 2014).

We have recently analysed the **outcomes of seventy patients treated with Pomalidomide at 5 major UK centres** under the Cancer Drugs Fund. Our patients had received a median of 3 prior lines (range 2-8) of treatment, and were aged 66 years (median, range 40-89), with 17.6% over the age of 75 years. The majority (93%) were refractory to their last treatment, and 92% fulfilled the inclusion criteria for the Phase 3 MM-003 study. The overall response rate was 52.9%, the median progression free survival (PFS) was 5 months (95% CI 3.6 – 6.3), and overall survival (OS) 13 months, (95% CI 10.8 – 15.2). The survival data are remarkably similar to those reported from the MM-003 study, and, given the similarity in our patient cohort to the trial population, these results provide important confirmation of the expected benefit for our patients. Importantly, renal impairment

(glomerular filtration rate <45ml/min) or the presence of adverse genetics was not associated with worse outcomes, suggesting that Pomalidomide may also benefit these particular patient subgroups who have traditionally fared worse with currently available therapies. These data have been accepted for presentation at the Annual meeting of the American Society of Haematology meeting in December this year, and the full manuscript has just received a favourable review by the British Journal of Haematology. We enclose the abstract at the end of this letter. These results are similar to a **recently published report of another UK retrospective study of 39 patients** who received pomalidomide and dexamethasone; in this report, the overall response rate was 41%, and median PFS 5.2 months with median OS 13.1 months (Sriskandarajah et al, 2016).

Our clinical experience is that this technology is well tolerated, and being oral, has the advantage of convenience and less intrusion on patient lifestyle. The main toxicities of reduced blood counts are easily managed with monitoring and dose adjustment. A notable advantage is the benefit seen in patients with renal failure, and in the elderly. Evidence of improvements in wellbeing of patients receiving pomalidomide is provided by health related quality of life data from the phase 3 study, where Pomalidomide treatment was associated with significantly better scores in several domains including fatigue and physical functioning (Song et al, 2014).

It is regrettable that information on response, disease free survival and overall survival for patients treated with Pomalidomide on the Cancer Drugs Fund was not collected, as this would have provided valuable data regarding efficacy and clinical benefit, to inform discussions on access and reimbursement. Nevertheless, we hope that the information provided here goes some way to fill this gap, and we urge that this committee approve pomalidomide within its licensed indication for the treatment of patients with multiple myeloma.

Yours sincerely,

[redacted]

On behalf of the UK Myeloma Forum

References

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TITLE: Real-World Use of Pomalidomide and Dexamethasone in Double Refractory Multiple Myeloma: A Multicentre UK Experience

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Introduction. The outlook for myeloma patients who relapse after or become refractory to bortezomib and IMiDs is poor, with limited therapeutic options and a median survival (OS) of 9 months. In the phase 3 MM-003 study, pomalidomide plus low dose dexamethasone resulted in a significant PFS (median 4 vs 1.9 months) and OS (median 13.1 vs 8.1 months) benefit, compared to high dose dexamethasone. Information on real-world outcomes of pomalidomide therapy is limited. We carried out a retrospective analysis of patients receiving pomalidomide in the UK, to compare outcomes and tolerability with published clinical trial data, and focussing on high risk subgroups.

Methods. All patients treated with pomalidomide at 5 major UK centres between August 2013 and March 2016 were identified from chemotherapy records, and clinical data including toxicity and survival from patient records. Disease response and adverse FISH were defined as per IMWG. Survival was estimated using Kaplan-Meier, and correlations made using log rank methods. Key subgroups: eGFR <45ml/min, adverse genetics, and older age were assessed.

Results. A total of 85 patients were identified. Of these, 70 (82%) had measurable disease (IMWG criteria) and received ≥1 cycle so were included in response analyses. Baseline patient characteristics are reported in Table 1.

Table 1: Patient Characteristics and comparison with MM003 trial

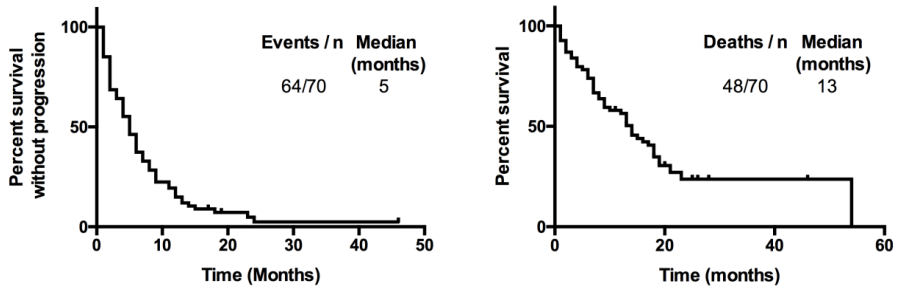
Parameter	n (%) or median [range]			Parameter	n (%) or median [range]		
	UK series (all)	UK series (response evaluable)	MM003 poma/dex arm		UK series (all)	UK series (response evaluable)	MM003 poma/dex arm
Total patient number	85	70	302	eGFR < 60ml/min	32 (37.6)	25 (36)	95 (31)*
Male sex	50 (59)	41 (59)	181 (60)	eGFR < 45ml/min	19 (22.4)	12 (17)	Excluded
Age	66 [40-89]	61 [41-82]	64 [35-84]	Time from diagnosis to pomalidomide (years)	4 [<1-18]	5 [<1-11]	5.3 [0.6-30]
Age > 75	15 (17.6)	9 (13)	24 (8)	No. of previous treatments	3 [1-8]	3 [2-7]	5 [2-14]
Age > 65	48 (56.5)	37 (53)	135 (45)	> 2 previous treatments	73 (85.9)	62 (89)	285 (94)
Isotype							
IgG	46 (54.1)	40 (57)	Not available	FISH performed	45 (52.9)	38 (46)	225 (74.5)**
IgA	20 (23.5)	15 (21)	Not available	Adverse FISH (where performed)	29 (64.4)***	24 (63)	Not available^^
IgD	1 (1.2)	1 (1)	Not available	Adverse FISH (excl 1q gain)	20 (44.4)	16 (42)	99 (44)^^^
Light chain only	17 (20)	14 (20)	Not available	FISH including 17p deletion	14 (31.1)	11 (29)	55 (24.4)
Non secretory	1 (1.2)	0	Not available				
International Staging System (ISS)				Median follow up (months)	9 [<1-54]	8 [<1-28]	10 [N/A]
I	8 (9.4)	7 (10)	Not available				
II	13 (15.3)	12 (17)	Not available	MM003 criteria fulfilled	78 (91.8)	65 (93)	302 (100)
I or II	21 (24.5)	19 (27)	197 (65)				
III	16 (18.8)	10 (14)	93 (31)	* creatinine clearance used in MM003, ** of 302 patients, *** percentage of cases where FISH performed, ^^ 1q gain not reported, ^^^ del(17p), t(4;14) or both			
Missing	48 (56.5)	41 (59)	12 (4)				

96.5% of patients were refractory to one or more IMiDs, and 72.9% were refractory to both IMiDs and bortezomib. 92.9% were refractory to their last treatment. The median dose of pomalidomide was 4mg (2-4). Grade 3–4 non-haematological toxicities occurred in 42.4%: pneumonia (16.5%), neutropenic sepsis (8.2%), and acute kidney injury (7.1%), were most common. Grade 3-4 neutropenia occurred in 38% and thrombocytopenia in 24%. Seven patients died on treatment, 6 during the first cycle (2 PD and sepsis, 2 neutropenic sepsis, 1 PD and AKI, 2 pneumonia).

In the 70 patients assessable for response, ORR was 52.9% (5.7% VGPR, 47.1% PR, 38.6% SD). Median duration of response (DoR) was 4 months. With median follow-up of 13 months, median PFS was 5 months (95%CI 3.6–6.4), and median OS 13 months (95%CI 10.8–15.2).

Figure 1. PFS and OS for the edited group of 70 patients

Figure 1. PFS and OS for the disease evaluable group of 70 patients



Patients with renal failure (eGFR <45ml/min) had PFS and OS that were similar to those with eGFR ≥45ml/min ((HR=0.95, 95%CI 0.49–1.82, and HR=1.22, 0.59–2.53). Patients with adverse FISH (44%) had similar outcomes to those with standard FISH (ORR 45.8 vs 50%, median PFS 6 vs 5 months (HR=0.86, 95%CI 0.44–1.67, and median OS 10 vs 8 months, HR=1.223, 0.55–2.68). Patients aged >65yrs had similar outcomes to younger patients, ORR 54.1 vs 51.5%, median PFS and OS were comparable in both groups. Rates of toxicity were not influenced by renal impairment, adverse genetics, or older age.

The most important predictors of PFS and OS were depth and durability of response. PFS was 6 months for patients achieving PR, 4 months for SD and 1 month for PD, while OS was 18 months in patients achieving PR, 13 months for SD and 3 months for PD. For patients with DoR >4 months, PFS was 11 months and OS 23 months. In contrast, in patients whose DoR was< 4 months or who did not respond, OS was 9 months.

Conclusions. Our real-world data on the characteristics and outcomes of patients receiving pomalidomide for relapsed/refractory myeloma in the UK reflect results of published clinical trials. The ORR of 52.9% in our cohort is higher than in MM-003 and MM-010, but PFS (5 months) and OS (13 months) were remarkably similar. Rates of haematological toxicity and infections are low, confirming the good tolerability of pomalidomide in this patient group.

Depth and sustainability of response were important predictors of survival: achievement of PR was associated with improved PFS and OS, while patients who achieved SD still derived a survival benefit. Patients who maintained a response for at least with 4 months had an estimated survival of nearly 2 years. No difference in response, survival or tolerability was seen in key subgroups, including those with moderate renal impairment, adverse cytogenetics and older age. Our findings confirm the efficacy of pomalidomide in these heavily pre-treated patients and add to the evidence for the benefit in high risk groups.

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Single Technology Appraisal (STA)

Pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib (review of TA338) [ID985]

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. Matthew Streetly
Name of your organisation: UK Myeloma Forum / Guys and St. Thomas' NHS Foundation Trust

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) yes (trustee and Advocacy Lead for 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: None

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Please note that this is the same submission as from Dr. Neil Rabin also representing the UK Myeloma Forum

What is the expected place of the technology in current practice? Pomalidomide if approved by NICE will be offered to myeloma patients who have relapsed following treatment with both bortezomib and lenalidomide. This may be at second relapse (3rd line) but more likely will be given at third relapse (4th line) or beyond. The normal treatment algorithm outside of clinical trials is outlined below.

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?
The treatment landscape for myeloma is changing. The following lists current clinical practice. Myeloma is treatable but incurable and relapse is inevitable. There is little geographical variability in practice in England due to funding constraints that clinicians work with. There are geographical variations in practice in other parts of the United Kingdom where pomalidomide is funded on the NHS.

Currently newly diagnosed myeloma patients will receive bortezomib or thalidomide as initial therapy (TA311 or TA228), consolidated with high dose chemotherapy in suitable patients.

At first relapse (2nd line) bortezomib is NICE approved (TA 129). This is applicable to patients who are bortezomib naïve or those who have previously received bortezomib and had a suitable depth and duration of response without significant related toxicity (such as neurotoxicity). A proportion of patients may have received lenalidomide at first relapse if they were unsuitable for bortezomib (available via the Cancer Drugs Fund until November 2015).

At second relapse (3rd line) most patients will receive lenalidomide and dexamethasone (TA 171). A small proportion will receive bortezomib, panobinostat and dexamethasone (TA 380) at second relapse (3rd line).

Published international and national data for patient outcomes at this stage (i.e. relapsed and refractory following prior bortezomib and lenalidomide treatment) report appalling outcomes in terms of event free survival for "conventional" approaches and median overall survival of 6 – 9 months.

Most patients at third relapse (4th line) or beyond will have had prior treatment with both bortezomib and lenalidomide. Options for treatment at this stage include:

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1. **Bortezomib, panobinostat and dexamethasone (TA 380) assuming they had a suitable depth and duration of response without any associated toxicity issues. The advantage is that panobinostat enhances the activity of bortezomib in those previously exposed to this drug. The disadvantage is the need to attend hospital on a regular basis (4 times during a 3 or 4 week cycle for bortezomib administration) and side effects of both bortezomib and panobinostat (such as neurotoxicity and gastrointestinal side effects).**
2. **Bendamustine (which may be combined with thalidomide and dexamethasone) currently available via the Cancer Drugs Fund. The advantage is that this is an active agent. The disadvantage is the need for hospital attendance for bendamustine administration (3 times in a 4 week cycle) and side effects (such as risk of infection or need for transfusion).**

Cyclophosphamide, melphalan and thalidomide would generally be considered as purely palliative approaches for symptom control rather than an active approach (in comparison to the treatments outlined above). There is no evidence to support these agents at this stage in the modern era of myeloma therapy and toxicity particularly with conventional chemotherapy agents is high (predominantly cytopenia and infections)

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?
Patients with relapsed myeloma acquire additional mutations leading to resistance to conventional chemotherapy, such as 17p deletion (known as high risk cytogenetics). There is evidence that pomalidomide is able to overcome the inferior outcome in those patients with high risk cytogenetics in the published randomised phase 3 clinical trial. There is no data to support this effect in the named comparators listed above.

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)?
Myeloma patients receive treatment in secondary or tertiary care, under the care of consultant haematologists in conjunction with other allied health professionals. There would not be any additional professional input needed if this technology were approved.
Patients would be reviewed by their haematologist on a monthly basis in an outpatient clinic and pomalidomide would be dispensed by the hospital pharmacist (usually the same day).

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?
This technology is not available within the NHS. It is available in the context of clinical trials for a small group of patients. It was previously available in England up until November 2015 via funding from the Cancer Drugs fund. The most recent data published by NHSE report that there were a total of 838

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applications for pomalidomide administration between October 2014 and September 2015 (mean 69.8/month). In the same time period there were 238 applications for bendamustine (mean 19.8/month) demonstrating the importance of pomalidomide for relapsed/refractory myeloma patients.

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.
There are published guidelines on the diagnosis and management of myeloma in the UK (British Committee for Standardisation in Haematology). However, these were published prior to the license for pomalidomide, and deal with the initial management of this condition. There are local guidelines within cancer networks that support the use of pomalidomide therapy, where it is available. National treatment algorithms are being developed by NHS-England but have not been implemented at present.

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?
Alternative treatments for patients with relapsed myeloma previously treated with lenalidomide and bortezomib are:

1.	**Bortezomib panobinostat and dexamethasone.**
	This is in patients who have achieved a durable deep response to previous bortezomib treatment without any significant side effects related to bortezomib (such as neurotoxicity), based on subgroup analysis in a phase 3 randomised study. The advantage of this combination is that panobinostat enhances the activity of bortezomib in those previously exposed to this drug. The disadvantage is the need to attend hospital on a regular basis (4 times during a 3 or 4 week cycle for bortezomib subcutaneous, or rarely intravenous administration) and side effects of both bortezomib and panobinostat (such as neurotoxicity and gastrointestinal side effects respectively).
2.	**Bendamustine**
	The advantage is that this is an active agent in those with relapsed myeloma, although not supported by randomised phase 3 data in an equivalent setting. The disadvantage is the need for hospital attendance for bendamustine intravenous administration (3 times in a 4 week cycle) and the side effects of this treatment (such as risk of infection or need for transfusion).
3.	**Cyclophosphamide, melphalan, high dose dexamethasone and thalidomide would generally be considered as a palliative approach rather than an active approach (in comparison to the treatments outlined above). These are NOT appropriate comparators. There is no**

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evidence to support these agents at this stage of therapy in the modern era of myeloma therapy (other than as palliative treatments).

The advantage of pomalidomide is that it is an oral drug taken at home by the patient. Bortezomib and bendamustine require up to 4 hospital attendances every month to allow parenteral administration, whilst those receiving pomalidomide would attend hospital just once every month. Pomalidomide is therefore easier to administer. This is particularly advantageous in a heavily pre-treated population with myeloma- associated co-morbidities, such as significant fatigue and bone pain.

Additional treatments that are needed when patients receive pomalidomide include thromboprophylaxis. This can be administered at home and does not require additional hospital attendance.

Pomalidomide is very well tolerated with manageable side effects.

Transfusions and infections are as expected in this heavily pre-treated population.

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.
Patients receiving pomalidomide would attend outpatients on a monthly basis. Assessment of response is based upon routine blood and urine tests that are performed as a standard of care for all patients (ie no additional testing). Patients should continue on treatment so long as they are achieving a clinical benefit.

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?
Pomalidomide was widely available in England with funding from the Cancer Drugs Fund until November 2015. Clinical experience demonstrates an at least equivalent efficacy and safety as described in the randomised phase 3 clinical trial. With the flexibility allowed for dose /regimen modifications and support outside of clinical trials efficacy and Quality of life are likely to be superior to that reported in Clinical Trials. A multi-centre retrospective analysis of myeloma patients receiving pomalidomide in England showed an equivalent clinical benefit and safety profile.

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?

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Patients with relapsed myeloma have issues related to bone marrow failure (manifest as infections and need for transfusion), as well those related to bone disease (manifest as bone pain and fractures). The side effects and adverse reactions reported with pomalidomide are manageable and expected in this heavily pre-treated population.

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

No issues.

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.
None identified.

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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)?
We do not anticipate there being any issues in delivering this technology. Haematologists are used to managing patients receiving other immunomodulatory agents (such as lenalidomide or thalidomide). Pomalidomide has similar side effects.

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Patient/carer expert statement (STA)

Pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib (review of TA338) [ID985]

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: Alan Chant
Name of your nominating organisation: Myeloma UK
Do you know if your nominating organisation has submitted a statement?

X☐ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

X☐ 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?

X☐ Yes ☐ No

- a carer of a patient with the condition?

☐ Yes **X**☐ No

- a patient organisation employee or volunteer?

☐ Yes **X**☐ No

Do you have experience of the treatment being appraised?

☐ Yes **X**☐ 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?

I was diagnosed with myeloma in 2011 and am currently in my third line treatment.

My initial symptoms were back pain and a collapsed spine, which required an emergency operation to fit titanium rods. I was a hospital inpatient for 17 weeks. Neural damage resulted in me being initially bed-ridden and then receiving rehabilitation and physiotherapy in order to learn to walk again. At the same time cancer was discovered on my left kidney and it was surgically removed.

My treatment regime has included radiology, CDT, stem cell transplant carfilzomib (MUK5 trial) and recently Revlimid.

I have been taking Revlimid since October 2015 and whilst it has controlled the myeloma through a reduction in the light chain levels, I have suffered severely from side effects, including all those detailed in the information leaflet that accompanies the drug. As a result, the initial dosage of 25mg daily was reduced to 10mg by my consultant, then to 10mg on alternative days and then recently had to be stopped completely. The reason for the complete stoppage of the drug temporarily is that it appears to be causally related to my increasing creatinine levels (doubled from previous levels) and the risk of Acute Kidney Injury (AKI) for my remaining kidney. If causality is attributable to Revlimid I will need an alternative treatment regimen – hence my current interest in Pomalidomide authorisation.

On a broader level, the impact of myeloma on my business life has been to curtail thoughts of full-time employment during the last 5 years. Domestically I have learnt to rely more heavily on my wife (for shopping, paying service suppliers, gardening etc) and to employ contractors for work I would have undertaken myself. Socially I have had to reduce my ability to commit to social engagements in the middle-future in case I become unwell (e.g. holidays, Christmas occasions booked in advance). Physically, I have had to learn to deal with fatigue and the other side effects of the disease and drugs. Psychologically, I have learnt to deal with the relapse/remission cycle and the level of perceived well-being being determined by the results of the latest blood test, biopsy and scan.

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.

- Survival length
- Quality of Life
- Drugs to be tolerated with small number of side effects
- Longer remission times

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

Treatment has been very good – especially at the Churchill Hospital in Oxford.

The availability of numerous drugs from which consultants can choose from is desirable, given that some patients react better than others to some drugs (both with regards efficacy and tolerance). This is important both on medical grounds, but also reassuring on psychological grounds that provide the patient with continuing hope of managing the disease for as long as possible.

Drugs that have less side effects are vital for the quality of life of the patient. Survival benefits of a drug are long term and unknown (verses what might have been if receiving another treatment) to the patient, but adverse side effects are immediate and can substantially impact on daily life. For instance, my recent experience of Revlimid (detailed above) resulted in my quality of life reducing, subjectively, from 8 out of 10 to 4 out of 10, resulting in restricted quality at home and reduced social activity. Conversely, whilst on the Carfilzomib MUK5 trial I experienced few side effects (only some fatigue and light nausea at times).

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.

- Efficacy and safety.
- Increased survival time.
- Improved remission times.
- Well tolerated, with few side effects – thereby ensuring quality of life.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

Revlimid has been proved to be well tolerated by many patients. However, I belong to a subset for whom the drug causes severe side effects, including kidney impairment, of which there seems to be a causal relationship. For patients such as myself for whom an IMiD should be part of the treatment plan, Pomalidomide – with its proven benefit to patients with kidney impairment (Phase II MM-013 trial) and tolerated side effects – provides a lifeline, as at the third line treatment stage patients are running out of options.

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.

Not applicable.

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 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 you have about current NHS treatments in England.

There is a need to ensure the timely authorisation of novel drugs that can be added to the consultants' toolkit of existing drugs. Consultants need the options and flexibility to prescribe drugs that are right for patients (as different patients react differently to drugs, both medically and with regard to adverse side effects) and in the order that will produce the best overall survival, PFS and quality of life for the individual patient.

Please list any concerns you have about the treatment being appraised.

None

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.

Not aware of any differences.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

As stated above, I believe that those patients suffering from kidney impairment will benefit significantly from this drug compared with other IMiDS (especially if the only option available is Revlimid).

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

No

7. Research evidence on patient or carer views of the treatment

Are you 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 your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Not applicable.

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?

Outcomes relevant to patients have been captured.

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?

X☐ Yes ☐ No

If yes, please provide references to the relevant studies.

Those undertaken by Myeloma UK – detailed in Section 3 of their submission.

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.

No

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.

Although Pomalidomide is another IMiD in the line of thalidomide and lenalidomide, it represents an advancement in being well tolerated (in trials) and an alternative to lenalidomide for those suffering from kidney impairment.

Is there anything else 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.

- Pomalidomide is an effective IMiD with tolerated side effects that should be authorised for use by consultants.

- The drug is currently authorised for use in Scotland and Wales and patients in England should not be discriminated against.

- Pomalidomide was initially made available on the National Cancer Drugs Fund until November last year – a recognition by NHS England that the drug fulfilled an important unmet need.

- Pomalidomide is especially necessary for patients in third/fourth line treatment – who are running out of options and for whom this drug is a lifeline. It will both provide an effective treatment for myeloma and psychological comfort to those patients at this critical stage of their treatment pathway - and also for those who are in earlier stages who seek hope for the availability of future treatment options to manage their survival.

- Pomalidomide is a crucially important drug for patients suffering from kidney impairment – who have few alternative treatment options.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

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

Produced by Kleijnen Systematic Reviews Ltd. (KSR) in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout 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.

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Contributions of authors

Debra Fayter acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Nasuh Büyükkaramikli acted as health economics project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Saskia de Groot, Fernando Albuquerque de Almeida and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Richard Birnie and Robert Wolff acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AE	Adverse event
AF	Acceleration factor
AFT	Accelerated failure time
AIC	Akaike information criterion
APC	Antigen-presenting cell
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
ASH	American Society of Hematology
ATE	Arterial thrombotic event
AWMSG	All Wales Medicines Strategy Group
BCSH	British Committee for Standards in Haematology
BEN	Bendamustine
BI	Budget impact
BIC	Bayesian information criterion
BOR	Bortezomib
BORR	Best overall response rate
BSA	Body surface area
BTD	Bendamustine + thalidomide + dexamethasone
CADTH	Canadian Agency for Drugs and Technologies in Health
CC	Conventional chemotherapy
CDF	Cancer Drugs Fund
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curves
CFZ	Carfilzomib
CGP	Corrected group prognosis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
cm	Centimetre
CPG	Corrected group prognosis
CR	Complete response
CrCl	Creatinine clearance
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
CTD	Cyclophosphamide + thalidomide + dexamethasone
CYC	Cyclophosphamide
DALY	Disability-adjusted life year
DARE	Database of Abstracts of Reviews of Effects
Del	Chromosomal deletion
Den	Denominator
DEX	Dexamethasone
Df	Degrees of freedom
DOR	Duration of response
DSU	Decision Support Unit
EBMT	European Society for Blood and Marrow Transplantation

ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EHA	European Hematology Association
EMA	European Medicines Agency
eMIT	Drugs and pharmaceutical electronic market information
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European public assessment report
EQ-5D	EuroQoL five dimensions
ERG	Evidence review group
EU	European Union
EUR	Erasmus University Rotterdam
FAD	Final appraisal determination
FDA	Food and Drug Administration
G-CSF	Granulocyte colony stimulating factor
GEE	Generalised estimating equation
GFR	Glomerular filtration rate
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
IDMC	Independent data monitoring committee
IFN	Interferon alpha
IMiDs®	Immunomodulatory drugs
IMWG	International Myeloma Working Group
IPD	Individual patient data
IRAC	Independent response adjudication committee
ISS	International Staging System
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews
LCHP	Log cumulative hazard plot
LD-Dex	Low-dose dexamethasone
LDH	Lactate dehydrogenase
LEN	Lenalidomide
LoDEX	Low-dose dexamethasone
LY	Life year
MAIC	Matched adjusted indirect comparison
MedDRA	Medical Dictionary for Regulatory Activities
MEL	Melphalan
MeSH	Medical Subject Headings
MGUS	Monoclonal gammopathy of undetermined significance

MHRA	Medicines and Healthcare Products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
ml	millilitre
MP	Melphalan + prednisone
MPT	Melphalan + prednisone + thalidomide
MR	Minimal response
MTC	Mixed treatment comparison
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCT	National clinical trial
NE	Not evaluable/ non estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NK	Natural killer
NMB	Net monetary benefit
NR	Not reported
ONS	Office of National Statistics
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAMT	Prior anti-myeloma therapy
PANO	Panobinostat
PAS	Patient access scheme
PBD	Panobinostat
PD	Progressive disease
PFD	Progression-free disease;
PFS	Progression-free survival
PI	Protease inhibitor
PK	Pharmacokinetic
POM	Pomalidomide
PPP	Pregnancy prevention programme
PPS	Post-progression survival
PR	Partial response
PRED	Prednisone
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
QALY	Quality-adjusted life year
QLQ	Quality of life questionnaire
QoL	Quality of life
RANKL	Receptor activator for nuclear factor kB ligand
RBC	Red blood cell
RCT	Randomised controlled trial

RDI	Relative dose intensity
RPSFTM	Rank preserving structure failure time model
RR	Relative Risk; Risk Ratio
RRMM	Relapsed and refractory multiple myeloma
RWE	Real world evidence
SAE	Serious adverse events
SC	Subcutaneous
sCR	Stringent complete response
SCT	Stem cell transplantation
SD	Standard deviation
StD	Stable disease
SF-36	Short form 36
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SPM	Second primary malignancies
STA	Single technology appraisal
TA	Technology appraisal
TEAEs	Treatment-emergent adverse events
THAL	Thalidomide
TNF	Tumour necrosis factor
Trt Phase Dis	Treatment phase discontinuation visit
TS	Two-stage method
TSG	Tumour suppressor gene
TTF	Time to treatment failure
TTP	Time to progression
TTR	Time to response
UK	United Kingdom
VEGF	Vascular endothelial growth factor
VGPR	Very good partial response
VTE	Venous thromboembolism
WHO	World Health Organisation
WTP	Willingness to pay

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The patient population described in the final scope issued by the National Institute for Health and Care Excellence (NICE) was '*Adults with relapsed and refractory multiple myeloma who have had at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and whose disease progressed on the last therapy*'. Panobinostat in combination with bortezomib and dexamethasone (PANO+BOR+DEX) was a comparator for patients who had two or more prior therapies. Bendamustine and conventional chemotherapy regimens are comparators at fourth line of treatmentor greater, i.e. patients who have received at least three prior treatements. Outcomes included overall survival, progression free survival, response rates, adverse effects of treatment and health-related quality of life.

The decision problem in the company submission (CS) is broadly in line with the final scope. However the main direct evidence submitted in the CS (the MM-003 trial) compares pomalidomide in combination with low dose dexamethasone (POM+LoDEX) with high dose dexamethasone (HiDEX) which is no longer considered representative of conventional chemotherapy regimens. Furthermore, the trial is not representative of third line treatment with pomalidomide as only 17 out of 455 patients had received exactly two prior treatments. The median number of prior treatments received by patients in the MM-003 study was five (interquartile range = 4 to 6, minimum = 2, maximum = 17). Any conclusions on the role of pomalidomide at third line would be based on an assumption of a better response in less treated patients rather than robust evidence.

1.2 Summary of clinical effectiveness evidence submitted by the company

Direct evidence

The company conducted a systematic review to inform the submission. The aim of the systematic review was '*to understand the relative efficacy and safety of POM+LoDEX compared to alternative therapies for adult patients with RRMM who were previously treated with LEN and BOR.*'

The company identified four randomised controlled trials (RCTs) and nine non-RCTs of pomalidomide. The company also described '*a retrospective real world data collection project on prescribing of BEN, BOR retreatment and POM+LoDEX at third line onwards with the aim of increasing the comparator evidence available to NICE.'*

The main evidence presented was the MM-003 randomised controlled trial as this was the only study that compared POM+LoDEX with any of the comparators listed in the final scope. This trial compared POM+LoDEX to HiDEX which the company considered a proxy for conventional chemotherapy. It included 455 participants and was a multinational trial including participants recruited in 93 study sites, 68 of which are located in Europe. The number of centres located in the United Kingdom (UK) and patients recruited in the UK was unclear.

Using the latest data cut-off of MM-003 (1 September 2013, investigator assessment) at 15.4 months follow-up, there was an increase in median survival with pomalidomide. Overall survival (OS) was significantly better for patients treated with POM+LoDEX compared to those receiving HiDEX (13.1 months vs. 8.1 months, hazard ratio (HR) 0.72, 95% CI: 0.56 to 0.92). POM+LoDEX significantly extended progression-free survival (PFS) compared to HiDEX (4 months vs. 1.9 months, HR 0.50, 95% CI: 0.41 to 0.62).

Almost all of the patients across the trial had at least one adverse event (99% POM+LoDEX, 99.3% HiDEX). The company found that 247 of 300 patients (82.3%) in the POM+LoDEX group had at least one adverse event (AE) considered by the investigator to be related to POM. Furthermore 190 patients (63.3%) had Grade 3-4 treatment-emergent adverse events (TEAEs) considered related to POM. However the company stated that '*with dose modifications and supportive care the safety profile was predictable, manageable and generally well tolerated.*' Events occurring more frequently in the POM+LoDEX group included neutropaenia (51.3% versus 20.0% for neutropenia and 9.3% versus 0% for febrile neutropenia). The main cause of treatment discontinuation was progressive disease and discontinuations related to adverse events were uncommon. There were more dose interruptions in the POM group than in the HiDEX group (67% vs. 30%).

Indirect evidence

Limitations of the available studies precluded a conventional mixed treatment comparison (MTC) or indirect meta-analysis. There were no studies that directly compared POM+LoDEX with either bendamustine (BEN) or PANO+BOR+DEX. Furthermore, there were no studies that could provide a common comparator to support indirect comparison or MTC. As a consequence the company selected individual treatment arms from the available studies and performed separate analyses comparing POM+LoDEX to each of the comparators independently. These were as follows:

1. Comparison of individual patient data (IPD) from the POM+LoDEX arms of the MM-003, MM-002 and MM-010 studies with IPD from the MUK-One, Gooding and Tarant studies of bendamustine using regression models to adjust for factors thought to be prognostic of OS and PFS. In the base case analysis covariate adjustment had little impact on the relative effect of POM+LoDEX compared to bendamustine+thalidomide+dexamethasone (BTD) on OS. The unadjusted hazard ratio was 0.55 (95% CI 0.38 to 0.81) compared to 0.58 (95% CI 0.36 to 0.94) in the covariate adjusted analysis. The median OS for patients receiving POM+LoDEX was 16.5 months (95% CI 12.6 to 19.8) in the unadjusted analysis and 16.6 months (95% CI 12.6 to 21.3) in the adjusted analysis. Similarly, for patients receiving BTD median OS in the unadjusted analysis was 8.1 months (95% CI 5.3 to 13.5) compared to 10.5 months (95% CI 6.1 to 12.4) in the adjusted analysis. Covariate adjustment also had little effect on PFS results. The unadjusted hazard ratio for POM+LoDEX relative to BTD was 0.76 (95% CI 0.56 to 1.05) compared to 0.79 (0.52 to 1.22) in the covariate adjusted analysis. The unadjusted median PFS for patients treated with POM+LoDEX was 4.2 months (95% CI 3.7 to 5.8) compared to 4.7 months (95% CI 3.7 to 6.6) in the adjusted analysis. The corresponding results for patients treated with BTD were 3.3 months (95% CI 2.5 to 5.5) in the unadjusted analysis and 3.7 months (95% CI 2.8 to 5.6) in the adjusted analysis.
2. Comparison of IPD from the POM+LoDEX arms of the MM-003, MM-002 and MM-010 studies with aggregate data from the single-arm PANORAMA-2 study of PANO+BOR+DEX using matching adjusted indirect comparison (MAIC) to adjust for adjust for factors thought to be prognostic of OS and PFS. As above this amounts to a direct comparison between two sets of observational studies. The application of the MAIC method resulted in a one month increase in median OS for patients receiving POM+LoDEX (13.4 months, 95% CI 11.4 to 15.6) compared to the unweighted analysis (12.4 months, 95% CI 11.1 to 13.4). In both cases the median OS was shorter than those patients receiving PANO+BOR+DEX (17.5 months, 95% CI 10.8 to 22.22). The hazard of death was reduced by a similar amount for patients receiving PANO+BOR+DEX compared to POM+LoDEX in both the unweighted analysis (HR=0.73, 95% CI 0.52 to 1.02) and in the MAIC (HR=0.78, 95% CI 0.56 to 1.09). The application of MAIC had little effect on the median PFS time of patients treated with POM+LoDEX (4.2 months, 95% CI 3.7 to 4.8) compared to the unweighted analysis (4.1 months, 3.7 to 4.6). The hazard of progression was increased by a similar

amount for patients receiving PANO+BOR+DEX compared to POM+LoDEX in both the unweighted analysis (HR=1.12, 95% CI 0.85 to 1.48) and in the MAIC (HR=1.18, 95% CI 0.89 to 1.56). These results show that POM+LoDEX reduced the risk of progression but increased the risk of death compared to PANO+BOR+DEX. It should be noted that the differences were not statistically significant and the evidence for PANO+BOR+DEX was based on only 55 patients compared to 886 patients receiving POM+LoDEX.

End of life

The company stated that POM+LoDEX is considered to meet the NICE end of life criteria in comparison to BEN and conventional chemotherapies. They stated that '*The estimated survival benefit compared to BEN and conventional chemotherapy is > 5 months in all comparisons (covariate adjusted and unadjusted, crossover adjusted and unadjusted). Modelled mean survival increase is 7 – 8 months*.'

They further stated that in relation to PANO that *'Evidence for end of life is less compelling in the comparison to PANO+BOR+DEX as no improvement was demonstrated in median outcomes for OS; difficulties in comparing to PANO+BOR+DEX are, however, considerable given the limited evidence available and lack of patient level data to correct for differences in patient population*.'

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The systematic review conducted by the company was appropriate to the scope of this submission. Although the ERG identified a number of problems in relation to searching for studies of clinical effectiveness, the ERG is satisfied that the evidence presented in the submission is the best available in this limited area. The ERG is further satisfied that a meta-analysis could not have been conducted as only one trial was deemed directly relevant to the decision problem (MM-003).

Although MM-003 was a reasonably large, well conducted multi-centre trial, the main comparator is no longer optimal in current practice. Therefore the comparator can only be viewed as a proxy for conventional chemotherapy which might constitute an alternative. Additionally, over 50% of patients in the trial are aged 65 or under so may reflect a younger population than that typically seen in practice. The ERG noted an under-representation of non-white participants. Under 1% were of Asian origin and 1.5% were of black or African American origin. The trial was in a heavily treated population who had received a median of five therapies (range 2 to 17). Results are presented for only 17 patients receiving two prior therapies thus the trial is not representative of POM as a third line therapy. It could be assumed that POM might perform better at third line in a less treated population but this is an assumption. Within these constraints, pomalidomide appears to extend OS and PFS in comparison with HiDEX in a heavily treated population who are refractory to bortezomib (BOR) and lenalidomide (LEN). The adverse event profile appears to be manageable with appropriate dose reductions and interruptions. However the slightly higher incidence of serious adverse events (grade 3 and 4) attributed to pomalidomide is drawn to the attention of the committee along with the more frequent occurrence of neutropaenia.

There were limited data available to inform the comparison of POM+LoDEX with treatments other than HiDEX. There were no studies that directly compared POM+LoDEX with either BTD or PANO+BOR+DEX. In addition the available studies did not include a common comparator that would permit an indirect comparison or MTC. As a result the company presented evidence based on comparisons of observational data. The ERG noted that the covariate adjusted results were very similar to the unadjusted results in terms of both PFS and OS for the base case and the sensitivity analysis of POM+LoDEX compared to BTD indicating that the differences between studies in the selected covariates (patient characteristics) have relatively little impact on the outcomes observed. The selection of different datasets for POM+LoDEX does alter the results for OS. Results suggested that the survival

benefit of POM+LoDEX was less for patients in the MM-003 and MM-010 studies than for patients in the MM-002 study of pomalidomide.

For the comparison with PANO+BOR+DEX the matching adjusted results for patients receiving POM+LoDEX were similar to the unadjusted results in terms of OS and PFS As in the comparison with BTD, the matching adjustment does not substantially alter the results which implies that the differences between studies in the selected covariates have relatively little impact on the outcomes observed.

Although the evidence reported by the company is limited, the ERG recognises that the lack of appropriate data excluded many of the standard alternatives. In the absence of any new direct head to head studies these results are likely to represent the best estimates of relative effectiveness that could be obtained given the limitations of the existing studies.

In terms of end of life criteria, the ERG 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, normally less than 24 months. Hence the first criterion for end of life has been met. As regards the second criteria, the ERG agrees that POM+LoDEX appear to meet end of life criteria of increasing survival in relation to BTD and HiDEX. However, the evidence suggests that POM+LoDEX does not meet this criteria compared to PANO+BOR+DEX. It is noted, though, that the evidence for PANO+BOR+DEX is based on a small number of patients (n=55) and the analysis was limited by the lack of studies comparing these treatments. Given that the patient population for this appraisal represents a heavily pretreated population who have progressed on multiple previous lines of therapy and the limited alternatives available for this population the committee will need to decide whether or not this second criteria has been met.

1.4 Summary of cost effectiveness submitted evidence by the company

In order to provide the evidence base for this resubmission, the company performed an update of the systematic review of cost effectiveness studies which was conducted for the previous NICE technology appraisal (TA338) in December 2013. Three health technology appraisals (HTAs) were included for data extraction: the original NICE appraisal of POM+LoDEX (TA338), and the equivalent submissions for Scottish Medicines Consortium (SMC) and for All Wales Medicines Strategy Group (AWMSG). From these, only the key-issues from the previous appraisal (TA338) were extracted and summarised.

A model was developed in Microsoft® Excel 2010 using a semi-Markov partitioned survival structure. The objective of the developed economic model was to present and analyse the cost effectiveness of pomalidomide (POM) in combination with low-dose dexamethasone (LoDEX) for the treatment of 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. The model compares POM+LoDEX with bendamustine+thalidomide+dexamethasone (BTD), panobinostat + bortezomib + dexamethasone (PANO+BOR+DEX), and conventional chemotherapy (CC).

The model has four health states: a pre-progressive state split into on treatment and off treatment, a post-progression state (progressive disease), and death. These health states were defined in relation to disease progression and whether or not patients were receiving treatment prior to progression. The model has a cycle length of one week (considered sufficient to capture the rapid progression of RRMM) and a time horizon of 15 years (when virtually every patient in the model has already died, i.e. lifetime). The model considers a NHS and personal social services perspective and discounts costs and utilities using a 3.5% discount rate.

Transition of patients through the model was estimated using data from the MM-003, MM-002, and MM-010 studies for POM+LoDEX. For the comparators, data from various sources was used. As no

connected network could be used, and some data sources were observational, various adjustment methods were required to assess POM+LoDEX versus all comparators.

Utilities for each health state were found using a regression model that was also used in TA338. That regression model was based on the EQ-5D data that was collected as part of the 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.

Costs of comparator treatments were based on list prices. The model assumed that a treatment interruption of less than 28 days would not lead to cost savings, as it is unlikely that the remaining drugs could be recovered by the NHS. However, for interruptions longer than 28 days it was assumed that costs could be saved as less medication is dispensed. For the monitoring costs, concomitant medication costs, 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.

The model presents the following outcomes: costs, life years (LYs) and quality-adjusted life years (QALYs). The model functionality includes deterministic and probabilistic sensitivity analysis. The company did not provide a full incremental analysis including all comparators. Instead incremental cost effectiveness ratios (ICERs) of POM+LoDEX versus each comparator are presented: £39,665 (versus BTD); £141,793 – SW quadrant[1] (versus PANO+BPR+DEX), and £44,811 (versus CC).

Probabilistic analysis which included the uncertainty around curve fit choice indicated the following probabilities of cost effectiveness for each comparison: 92.8% versus BTD, 100% versus PANO+BOR+DEX (at list price for PANO), 56.9% versus CC at a willingness-to-pay threshold of £50,000/QALY.

The one-way sensitivity analysis showed that the parameters with the greatest impact on model outcomes were the coefficients used within the regression analysis for utilities for the comparison against BTD and CC, and the HRs (OS and PFS) used to model comparative effectiveness for the comparison to PANO+BOR+DEX. The model is relatively insensitive to the majority of parameters.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The economic model described in the CS is considered by the ERG to meet the NICE reference case and is largely in line with the decision problem specified in the scope. However, in the scope of the current appraisal, NICE requested that at third line POM+LoDEX versus PANO+BOR+DEX would be assessed and at fourth line onwards versus all comparators (BTD, PANO+BOR+DEX and CC). In the CS, the cost effectiveness analyses were not stratified into third line and fourth and later lines. The ERG considers this acceptable, as data would be lacking for such stratification.

The ERG assessment indicated that the model was generally well presented and reported. However, one of the major concerns of the ERG is that even though efforts were made to correct for differences in baseline covariates between data sets, there can be still some unmeasured confounders or other factors

[1] ICERs in the south-west quadrant of the cost effectiveness plane (less effectiveness at lower costs) should be above the threshold in order to be deemed cost effective

that add uncertainty to the treatment effectiveness results of the CS. As a consequence, the results of the cost effectiveness analyses should be interpreted with caution.

Additionally, in the CS a different dataset is used for each of the three comparisons. The ERG considers that this pairwise approach is not that informative, because it implies a slightly different population for each comparison, without being able to clearly define these sub populations. Thus, the decision for POM+LoDEX should be based on a fully incremental analysis. Therefore, the ERG requested the company to provide a full incremental analysis using a single source of data. This approach not only sustains the consistency among comparisons, it also strengthens the POM+LoDEX vs. BTD comparison, as it is based on a larger dataset (in the base case, this comparison used the MM-002 only and BTD trials dataset instead of pooled data from all POM+LoDEX [MM-002, MM-003 and MM-010] and all BTD trials).

The ERG also has some concerns related to the implementation of AEs. The AE rates observed for POM+LoDEX were also used for the comparators, though multiplied by correction factors. These correction factors were based on the ratio of the TEAE discontinuation rate for each comparator and the TEAE discontinuation rate of POM+LoDEX in the MM-003 study. The TEAE discontinuation probabilities for each comparator were derived from disconnected parallel trials without any adjustments for baseline characteristic differences. Additionally, the approach above would mirror the frequency order of the AEs of POM+LoDEX (MM-003 trial) for each of the comparators, in the same magnitude. The ERG considers this assumption not to be plausible, because each drug has different working mechanisms and different safety profiles, and it is unlikely that the AE frequency order would be mirrored for other comparators, in the same magnitude.

The approach taken by the company to include health-related quality of life (HRQoL through a regression model) is largely the same as the approach used for TA338. In line with the conclusion of the previous ERG report, the use of this regression model is still deemed appropriate. Thus, the ERG did not encounter any major issues with the approach used to include quality of life in the model. Nevertheless, the data about the covariates that are included in the regression model (i.e. best overall response rate, hospitalisation and adverse events) has its limitations. For example, the proportions of patients who require a hospitalisation were only available for POM+LoDEX and HiDEX, so the hospitalisation rate for HiDEX was assumed to apply to the comparators. Also, some inconsistencies within the categorisation of best overall response rate were found. This might cause bias in the estimation of utilities. Therefore the ERG explored a scenario-analysis in which only disease progression varies across treatments in the estimation of utilities, whereas all other covariates are held equal across treatments. Due to the uncertainty about the estimated utility decrement associated with intravenous or subcutaneous treatment, the ERG also explored a scenario in which no utility decrement is assumed for IV treatments.

The current submission has re-estimated various types of resource use compared to TA338. For example, monitoring costs are now based on an extensive questionnaire filled in by six clinical experts, whereas TA338 used values from TA228. An important error was found in the electronic model submitted by the company in the transformation of yearly resource use for monitoring to weekly numbers. As a result, in the CS the monitoring costs are underestimated for all treatments, and since the extent of the underestimation varies by treatment, the ICERs in the CS are also incorrect. The impact of correcting this error is shown in section 5.3. Moreover, input parameters derived from the resource use questionnaire should be considered with care, since the questionnaire is quite long and detailed and thus might have been difficult to fill in, and also only six clinical experts completed the questionnaire.

Another important issue is that the model allows for a decrease in treatment costs based on treatment interruptions lasting longer than 28 days. The pertinent data were available for POM+LoDEX, and this was used to also estimate the cost decrease for panobinostat. However, dose interruptions of BOR (within PANO+BOR+DEX), BTD and conventional chemotherapies were not taken into account at all, creating a potential inconsistency. To assess the impact of this, the company altered the model, in response to the clarification letter, so that a scenario could be run where the costs of BOR, BTD and conventional chemotherapies are decreased at the same rate as panobinostat.

Regarding the costs of subsequent treatment, the ERG does not agree with the base-case choice to not include these costs. As stated in the CS, the effects of these subsequent treatments are implicitly incorporated in the OS results, and thus it would be rational to also include the costs required to achieve those effects. However, the two estimates of these costs provided in the CS for scenario analyses differ greatly. Which of these estimates should be preferred is difficult to determine based on the information provided in the CS.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company's submission contained a systematic review which addressed the scope issued by NICE. Searches were carried out broadly in line with NICE guidance. The submission and response to clarification provided sufficient details for the ERG to appraise the submission.

The ERG recognises the quality of the MM-003 trial (the main direct evidence) which at the time of recruitment was based on a suitable comparator for pomalidomide. The ERG acknowledges the company's attempts to provide comparative data with bendamustine and panobinostat through adjusted comparisons in the absence of direct evidence or any evidence to conduct a mixed treatment comparison. The company has made a reasonable attempt to extract the maximum information from the limited evidence available in this area.

The model used a common model structure, used in other STAs as well, and was also used in TA338. The structural model uncertainty (in terms of choice of parametric functions for OS and PFS) was reflected in the probabilistic sensitivity analysis.

Even though there were no data based on direct randomised evidence, substantial effort was made to statistically derive the comparative effectiveness input for the model. Also, a good regression model, based on EQ-5D measurements in the MM-003 trial, was used to estimate utilities for all health states per treatment. Compared to the previous TA, more effort was made to estimate the resource use associated with the treatments and the disease.

1.6.2 Weaknesses and areas of uncertainty

Although the ERG is satisfied that the company attempted to identify all relevant evidence to support the submission, there were some limitations in the way in which the literature searches were conducted. These included the use of overly restrictive search filters and limitations with the use of indexing terms. Of concern for the cost effectiveness review is that no resource use or health care cost searches were conducted and that data were therefore not systematically retrieved.

The main limitation of the submission is the lack of direct randomised evidence comparing pomalidomide to all relevant comparators in the scope. The only direct comparison is through the MM-003 trial of pomalidomide versus HiDEX, a proxy for conventional chemotherapy. The evidence in relation to bendamustine is based on comparisons of observational data. The ERG identified differences between the bendamustine and panobinostat studies including lines of prior therapy. Additionally

numbers receiving panobinostat treatment in the comparisons were small. The comparisons of pomalidomide to bendamustine and panobinostat are not as robust as direct evidence in the form of a randomised trial.

A further weakness is the lack of evidence for pomalidomide at the third line of treatment. In the main MM-003 trial only 5% of patients had received exactly two prior treatments. Any conclusions on the role of pomalidomide at third line would be based on an assumption of a better response in less treated patients.

The trials used in the effectiveness data were not connected and even though adjustment techniques were used, it was not clear whether the data was appropriate to use for informing the effectiveness and cost effectiveness of POM+LoDEX.

The pairwise comparisons that were conducted in company base-case gave inconsistent results, e.g. different outcomes for the same treatment (POM+LoDEX) in different comparisons, thus making it difficult to interpret these pairwise results. It might be reasonable to have three different estimates if they related to three different populations. However, in this situation it is not possible to define an exact subgroup for whom only POM+LoDEX vs BTD is relevant as opposed to any of the other comparators. Moreover, there is no convincing reason *why* different relevant patient populations should be considered for different comparisons, e.g. for POM+LoDEX vs BTD and for POM+LoDEX vs PANO+BOR+DEX.

The model makes many assumptions surrounding adverse events. In essence, it is assumed that the frequency order of the adverse events for POM+LoDEX is mirrored in other comparators, which may bias both the estimates of costs and disutility associated with AE.

A distinct weakness of the CS is that many modelling errors were found, some with a clear impact on the results.

The model assumed that all oral drugs would only be dispensed per full package per cycle, thus including wastage of part of a package in each cycle. This is unlikely to berealistic.

Finally, the ERG is of the opinion that the costs of subsequent treatment should be included in the model as the effects of these subsequent treatments are implicitly incorporated in the OS results, and thus it would be rational to also include the costs required to achieve those effects. However, the two estimates of these costs provided in the CS for scenario analyses differ greatly and which should be preferred is difficult to determine based on the information provided in the CS.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

After the clarification letter, a new model was submitted, in which the errors identified by the ERG were corrected. In the newly submitted model, the ERG identified additional errors. After these additional errors were corrected, the base case analyses of the company were repeated with the ERG-corrected model. The ICER results were around £45,000 per QALY gained for BTD, £143,000 per QALY gained for PANO+BOR+DEX -SW quadrant- and £49,000 per QALY gained for CC.

After the base-case analyses of the company were repeated, the ERG conducted a full incremental analysis, in which the effectiveness of BTD and POM+LoDEX treatments were based on the pooled dataset of MM-002, MM-003, MM-010 and all other BTD trials. Corrected group prognosis as covariate adjustment method was used. For PANO+BOR+DEX, the HR obtained from the MAIC is applied on top of POM+LoDEX curve; and similarly for CC, the HR from the ITT analysis of the OS data from MM-003 trial is applied on top of POM+LoDEX curve.

In this full incremental analysis, CC was the cheapest treatment option, however it was dominating BTD. The ICER of POM+LoDEX vs. CC was around £81,000 per QALY gained and the ICER of PANO+BOR+DEX vs. POM+LoDEX was around £143,000 per QALY gained.

When the two stage HR was used instead of ITT HR, BTD was not dominated by CC anymore, but was extendedly dominated by POM+LoDEX. The ICER of POM+LoDEX vs. CC was around £55,000 per QALY gained the ICER of PANO+BOR+DEX vs. POM+LoDEX was around £143,000 per QALY gained.

Finally, the ERG defined their preferred approach, i.e. with two stage HR, when instead of the CGP method, the mean covariate adjustment method was selected, (using not trial data but real world data from UK centres). The ICERs slightly increase, but the main message stays the same. BTD was extendedly dominated by POM+LoDEX. The ICER of POM+LoDEX vs. CC was around £59,000 per QALY gained and the ICER of PANO+BOR+DEX vs. POM+LoDEX was around £146,000 per QALY gained.

Some additional scenario analyses were conducted on the ERG preferred model (with two stage HR and mean covariate adjustment used to adjust for baseline differences). In these scenario analyses, the ICERs of POM+LoDEX vs. BTD were between £52,000 and £59,000 per QALY gained; for POM+LoDEX vs. PANO+BOR+DEX, the ICER was in the range of £117,000 and £146,000 – in the SW quadrant – and for POM+LoDEX vs. CC, the ICER was between £57,000 and £61,000.

From the full incremental analyses, POM+LoDEX does not seem to be a cost effective treatment option. The pairwise comparison of POM+LoDEX vs. PANO+BOR+DEX would yield the conclusion that POM+LoDEX is acceptable given the common NICE thresholds of £20,000 to £50,000. However the results should be interpreted cautiously as the effectiveness data was not based on a network of randomised trials, the PAS prices of some of the comparators were not included and there were many uncertainties in the model.

2. BACKGROUND

This report provides a review of evidence submitted by Celgene in support of pomalidomide (trade name (Imnovid®) for patients with relapsed and refractory multiple myeloma (RRMM) who have had at least two prior treatment regimens including both lenalidomide (LEN) and bortezomib (BOR). In addition to the main CS the ERG received a patient/carer organisation submission[1] and a joint expert statement from healthcare professionals.[2] These documents will be discussed where appropriate.

The background section of the report by the Evidence Review Group (ERG) outlines and critiques the company's description of the underlying health problem and the company's overview of current service provision. The information is taken from Chapter 3 of the company submission (CS) with sections referenced as appropriate.[3]

2.1 Critique of company's description of underlying health problem.

The underlying health problem is relapsed and refractory multiple myeloma. Table 9 of the company submission defines relapsed and refractory as '*Disease that is nonresponsive while on salvage therapy, or progresses within 60 days of last therapy in patients who have achieved minimal response or better at some point previously before then progressing in their disease course'*.[4] The company submission focuses on patients who have received *'at least 2 prior treatment regimens, including both lenalidomide (LEN) and bortezomib (BOR), and whose disease progressed on the last therapy*', i.e. patients who are eligible for third line therapy or greater (Section 3 of the CS).[3]

Multiple myeloma represents approximately 1% of all incident cancers globally and results in more than 43,000 deaths annually worldwide.[5] The company reported 4,652 new cases of myeloma in England in 2014, 4,703 cases in 2013 and 4,190 cases in 2012 based on figures from the UK office of National Statistics.[6-8] The CS described multiple myeloma as a disease of the elderly with almost two-thirds of patients aged 65 and over at the time of diagnosis. The main symptoms are '*skeletal destruction – which arises from activation of osteoclasts by multiple myeloma cells and leads to lytic bone lesions (80% of patients), pathological fractures (26%), bone pain (58%), mobility problems, osteoporosis (23%), impaired bone marrow function, hypercalcaemia (symptomatic or asymptomatic; 10-30% of patients), anaemia (75% of patients) and general ill health.[9-12] Secretion of M-proteins by plasma cells results in renal impairment (up to 50%) and kidney failure, and patients are also more susceptible to recurrent infections, due to a compromised B-cell lineage.[9, 12-14]'*(Section 3.1 of the CS).[3]

The CS highlighted that the course of the disease is not uniform for all patients and can vary according to the following factors:

- '*the patient, such as age, frailty and renal function* [CS ref 8][CS ref 55]
- tumour load, assessed by International Staging System (ISS) as well as Durie and Salmon stages of classification[CS ref 75][CS ref 76]
- cytogenetic anomalies, including translocations (4;14) and (14;16), and deletion 17p77, 78 (these high-risk cytogenic anomalies were incorporated into a revised ISS staging system in 2015)[CS ref 79]
- sensitivity of the tumour to treatment[CS ref 55]'

The CS describes the course of the disease as a series of cycles of remission and relapse with a decreasing duration of response (DOR) for each subsequent line of treatment ultimately leading to refractory disease.[3]

In section 3.2 of the CS the company described the impact of the disease on patients, carers and society. The company emphasised the challenge of '*balancing prolonging survival while optimising quality of*

life (QoL) with effective supportive care measures'[3] The company cited a European study assessing the emotional impact of multiple myeloma in 50 patients who had a clinical relapse of multiple myeloma. '*Patients reported a substantial decline in their emotional well-being at diagnosis, which improved following initial treatment, only to decline at first relapse. Patients reported feeling scared, depressed, worried, confused, frustrated and powerless. Some patients reported that multiple relapses were associated with loss of hope and increasing distress as they felt that they were exhausting treatment options and 'getting closer to the end'*[15]

The CS cited a study showing that multiple myeloma and the associated treatment has an impact on employment. '*As a result of intensive multiple myeloma treatment, many patients are no longer able to return to work, and some decide to take early retirement. One study showed that only half of patients who underwent intensive multiple myeloma treatment were still employed after diagnosis, with a mean age of 61 years.*

Caregivers are also affected; treatment for multiple myeloma often involves, weeks or months away from home, requiring a large time commitment from caregivers as well as patients themselves.'[16] In addition, '*caregivers can suffer financial difficulties as a result of a relative being diagnosed with multiple myeloma; they may suffer from loss of wages, difficulty in paying bills, lack of sick leave and premature use of retirement funds'*[17]

ERG comment: The ERG agrees with the company's description of the underlying health problem.

2.2 Critique of company's overview of current service provision

The company summarised the current clinical care pathway for patients with multiple myeloma in Table 10 of the CS, reproduced in Table 2.1 below. Section 3.3 of the CS states that '*for the majority of patients, POM+LoDEX will be placed as a fourth-line treatment, although some patients who have received prior LEN and BOR as part of first- or second-line combinations may be eligible to receive POM+LoDEX at third line. Examples of patients who may be eligible for POM+LoDEX at third line include those who received LEN at first line within a clinical trial setting and those who received LEN at second line whilst this was funded by the Cancer Drugs Fund (CDF)*'[3]

The company summarised the recommendations from previous NICE technology appraisals for treatment of multiple myeloma up to the fourth line of treatment in Table 11 of the CS.[3] These recommendations are reproduced in Table 2.2 below.

Table 2.1: Clinical pathway of care for patients with multiple myeloma

	Transplant eligible patients with MM	Transplant ineligible patients with MM
1st Line (NICE TA311[18]; NICE TA228[19])	BOR+DEX or BOR+THAL+DEX induction followed by ASCT[18]	THAL+ alkalyting agent + steroid (e.g. MPT) BOR+MP (THAL intolerant /contraindicated)[19]
	Note some patients may have received LEN as part of clinical trials	
2nd Line (NICE TA129[20])	BOR ± DEX having received 1 prior therapy[20] Conventional chemotherapy (including cyclophosphamide and melphalan) ± steroid[a] A minority of patients may receive a second ASCT Some patients may have initiated (and still be receiving) LEN from when this was funded by the CDF	
3rd Line onwards (NICE TA171[21]; TA380[22]; CDF[23])	Potential placement: POM+LoDEX[b] LEN+DEX[21] PANO+BOR+DEX[c22] Conventional chemotherapy (including cyclophosphamide and melphalan) ± steroid ± THAL re-treatment[d] BEN combinations[23] (via CDF)[e]	

Source: Based on Table 10 of the CS[3]
NICE TA311[18], 2014; NICE TA228, 2011[19]; NICE TA129, 2007[20]; NICE TA171, 2009[21]; NICE TA380, 2016[22]; NHS CDF List, 2016[23]
Notes: [a] Primarily received by patients who cannot tolerate THAL, have received BOR at first-line and have recently initiated 2nd line treatment as BOR retreatment is no longer funded by the CDF therefore availability is limited; [b] In patients who have received ≥2 prior lines of treatment including LEN & BOR; [c] PANO+BOR+DEX is reimbursed in patients who have received ≥2 prior lines of treatment including BOR + IMiD (either THAL, LEN or POM); [d]THAL retreatment can only be used in patients who are THAL eligible (i.e., not those who are THAL intolerant or contraindicated); [e] BEN is usually used at 4th line onwards (via the CDF).
ASCT, autologous stem cell transplant; BEN, bendamustine; BOR, bortezomib; CDF, National Cancer Drugs Fund; DEX, dexamethasone; LEN, lenalidomide; LoDEX, low dose dexamethasone; MP, melphalan, prednisone; MPT, melphalan, prednisone, thalidomide; NICE, National Institute for Health & Care Excellence; PANO, panobinostat; POM, pomalidomide; THAL, thalidomide.

Table 2.2: NICE recommendations in multiple myeloma

Source	Recommendation
First line	
TA311 (April 2014)[18]	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)[19]	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. This guidance is now on the static list. '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 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 multiple myeloma 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 (October 2007)[20]	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 under the following circumstances: 'The response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in people who have a complete or partial response (PR; that is, reduction in serum M protein of 50% or more or, where serum M protein is not measurable, an appropriate alternative biochemical measure of response) and; the company rebates the full cost of bortezomib for people who, after a maximum of four cycles of treatment, have less than a PR (as defined above).' This guidance is now on the static list.
Third line	
TA171 (June 2009)[21]	LEN+DEX recommended as an option for people who have received two or more prior therapies, with the condition that the drug cost of LEN for people who remain on treatment for >26 cycles would be met by the company. This guidance is now on the static list.
TA380 (January 2016)[22]	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, when the company provides PANO with the discount agreed in the patient access scheme.

Source	Recommendation
Fourth line	
TA338 (February 2015)[24]	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. Submission currently under reconsideration under ID985 in this submission.

Source: Based on Table 11 of the CS[3]

Notes: a, Three NICE technology appraisals are also currently ongoing in the second line setting: Appraisal of LEN after 1 prior treatment with BOR (ID667 [part review of TA171]);[25] appraisal of carfilzomib with LEN+DEX or with DEX after 1 prior treatment (ID934)[26]; and the appraisal of ixazomib citrate with LEN+DEX after 1 prior treatment (ID807).[27]

BOR, bortezomib; DEX, dexamethasone; LEN, lenalidomide; NICE, National Institute of Health and Care Excellence; PANO, panobinostat; POM, pomalidomide; PR, partial response; SCT, stem cell transplantation; THAL, thalidomide.

The CS also cited several other sources of guidance including the British Committee for Standards in Haematology (BCSH) 2014 guideline which stated that '*there is no standard approach for treatment at relapse based on disease heterogeneity and variability in patient-specific factors including co-morbidities and the persistence of toxicities related to previous therapy*'.[9] The BSCH guideline further states that '*the agents most often used in treating relapsed patients are THAL, BOR and LEN, generally in combination with corticosteroids and sometimes with an alkylating agent. They also recommend that a second autologous SCT may be considered in patients who had a good response to their initial transplant (≥18 months to disease progression). No recommendations are provided in the indication under consideration in this submission*'[9]

The European Society for Medical Oncology 2013 guideline states that '*choice of therapy in the relapse setting depends on age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options and the interval since the last therapy*'[28] The CS stated that '*these guidelines make no specific recommendation surrounding treatment in patients who have progressed on LEN and BOR, but they were published before POM was approved in Europe*' (CS section 3.5.2).[3]

The company referred to the recent National Comprehensive Cancer Network (NCCN) 2016 guidelines which recommended '*POM+DEX as a Category 1 option (i.e. based on high-level evidence, with uniform NCCN consensus that the intervention is appropriate) for treatment of patients with multiple myeloma who have received at least two prior therapies, including an immunomodulating agent and BOR, and have demonstrated disease progression on or within 60 days of completion of the last therapy*'.[CS ref 104]

The company also referred to guidance from the International Myeloma Working Group (IMWG) which recommended '*POM-containing regimens (usually with LoDEX but potentially combined with other agents such as BOR) and carfilzomib-containing regimens (preferably in combination with LEN and LoDEX) specifically for treatment of multiple myeloma that is refractory to both LEN and BOR'*.[29] The same IMWG guidance also suggested '*considering PANO+BOR+DEX for these patients, but it is not presented as the first option of choice*'.[29]

ERG comment: The company's description of the treatment options was based on existing NICE guidance which is appropriate and relevant to the decision problem. The company also cited supporting guidance from several sources. It is notable that the guidance from the BSCH and the European Society for Medical Oncology did not recommend pomalidomide based treatments whereas the more recent US (NCCN) and international (IMWG) guidance both supported the use of pomalidomide in patients who progressed on both BOR and LEN. The final scope issued by NICE specified the population for this appraisal as those patients who had received at least two prior treatment regimens (i.e. third line or greater) including both LEN and BOR.[30] Current NICE guidance only recommends LEN at third line[21] therefore the only patients who could have received two prior treatments where one of the treatments was LEN were those who had received LEN at first or second line in clinical trials or under the Cancer Drug Fund (CDF). In other words the number of patients who meet the eligibility criteria to receive POM at third line may be quite small. It is likely that the earliest most patients would be eligible for POM based treatment is at fourth line.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company presents its response to the decision problem in Section 1.1 of the CS.[3] This is reproduced below.

Table 3.1: Summary of the decision problem

	Final scope issued by NICE[30]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	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	As defined in scope	N/A
Intervention	Pomalidomide (POM) in combination with dexamethasone (DEX)	As defined in scope	N/A
Comparator(s)	For people who have had 2 prior therapies: • Panobinostat (PANO) in combination with BOR and DEX For people who have had 3 or more prior therapies: • PANO in combination with BOR and DEX • Bendamustine (BEN) (not appraised by NICE but funded via the Cancer Drugs Fund; does not currently have a marketing authorisation in the UK for this indication) • Conventional chemotherapy regimens (for example, melphalan and cyclophosphamide)	As defined in scope: • PANO+BOR+DEX • BEN ± THAL retreatment ± steroid • Conventional chemotherapy (including cyclophosphamide & melphalan) ± THAL retreatment ± steroid	N/A

	Final scope issued by NICE[30]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • Overall survival (OS) • Progression-free survival (PFS) • Response rates • Adverse effects of treatment • Health-related quality of life (HRQL)	As defined in scope with the addition of time to treatment failure (TTF)	Time to treatment failure added as this is used to inform the economic model
Economic Analysis	Reference case	As per reference case	N/A
Subgroups to be considered	None specified in final scope	N/A	N/A
Special considerations including issues related to equity or equality	None specified in final scope	N/A	N/A

Source: Based on Table 1 of the CS[3]

BEN, bendamustine; BOR, bortezomib; DEX, dexamethasone; HRQL, health-related quality of life; LEN, lenalidomide; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; POM, pomalidomide; RRMM, relapsed and refractory multiple myeloma; THAL, thalidomide; TTF, time to treatment failure

3.1 Population

The patient population defined in the final scope is '*Adults with relapsed and refractory multiple myeloma who have had at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and whose disease progressed on the last therapy*'[30]

In the CS the company states that the population is '*as defined in the scope*'[3]

ERG comment: The patient population for the comparison of POM+LoDEX with HiDEX which forms the main focus of the submission is based on the MM-003 study. Evidence from the MM-002 and MM-010 studies was also included in Section 4.10 of the CS to inform the comparison of POM+LoDEX with bendamustine (BEN) or with panobinostat+bortezomib+dexamethasone (PANO+BOR+DEX).

In the MM-003 study the median number of prior anti-myeloma therapies was five with a range from 2 to 17.[31]This implies that 50% of patients in the study received POM+LoDEX as sixth line treatment or greater. This is higher than the two prior therapies specified in the scope.[30]

The MM-002 study was an open label randomised phase II study comparing POM with POM+LoDEX in adults with RRMM who had received at least two prior therapies and had undergone prior treatment with at least two cycles of lenalidomide and two cycles of bortezomib. The median number of prior lines of therapy actually received by patients in MM-002 was 5 (range 1 to 13).[32]

The MM-010 study was an open label, single arm observational study to assess the efficacy and safety of POM+LoDEX in patients with RRMM who had received ≥ 2 prior treatment lines, including ≥ 2 cycles of lenalidomide and bortezomib (alone or in combination). The median number of prior lines of therapy actually received was five (range 2-18).[33]

In Section 3.1 the CS states that '*With increasing lines of therapy, there is a decreasing DOR and ultimately development of refractory disease*'[34] therefore the population in the MM-003, MM-002 and MM-010 studies may underestimate the treatment effect relative to the population specified in the scope.[30]

3.2 Intervention

Pomalidomide '*in combination with dexamethasone is indicated in 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. The recommended starting dose of Imnovid is 4 mg once daily taken orally on Days 1 to 21 of repeated 28 day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on Days 1, 8, 15 and 22 of each 28day treatment cycle. '*[35]

The intervention in the MM-003 study was '*28-day cycles of POM (4 mg/day orally on days 1-21) + LoDEX (40 mg/day orally on days 1, 8, 15, and 22)*'.[31]

The intervention arm of the MM-002 study was '*POM (4 mg/day on days 1-21 of each 28-day cycle)*' with '*LoDEX (40 mg/week)*'.[32]

In the MM-010 study '*Patients were administered pomalidomide 4 mg on days 1-21 of a 28-day cycle. Patients also received low-dose dexamethasone 40 mg (if aged ≤ 75 years old) or 20 mg (if aged > 75 years old) on days 1, 8, 15, and 22 of a 28-day cycle*'[33]

The intervention specified in the scope was '*Pomalidomide in combination with dexamethasone*'[30]

ERG comment: The intervention arms of all three pomalidomide studies were consistent with the scope.[30]

3.3 Comparators

The comparators listed in the scope specified by NICE were:

'*For people who have had 2 prior therapies:*

- *panobinostat in combination with bortezomib and dexamethasone*

For people who have had 3 or more prior therapies:

- *panobinostat in combination with bortezomib and dexamethasone*
- *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)*
- *conventional chemotherapy regimens (for example, melphalan and cyclophosphamide)*'[30]

In the previous submission there was limited evidence available for these comparators. In this resubmission the company presented evidence from the PANORAMA-2 study for panobinostat in combination with bortezomib and dexamethasone. The company also presented evidence for bendamustine from the MUK-One study, the Gooding study and the Tarant study. The company stated in the CS that data from the high dose dexamethasone (HiDEX) arm could be considered a proxy for other conventional therapy regimens.[3]

ERG comment: The ERG agrees that the design of the available studies was such that neither standard direct comparisons nor network meta-analyses could be carried out to compare the intervention and the comparators. The ERG recognises the company's efforts to identify all available evidence and consider a variety of different analyses to obtained estimates of effectiveness for the intervention relative to the comparators. These analyses are discussed in detail in Section 4.4.

The company justified the choice of HiDEX as the control arm in the MM-003 study on the basis that it was standard anti-myeloma therapy at the time the trials were initiated. The company also presented a comparison of OS and PFS for patients receiving HiDEX and patients receiving three alternative conventional chemotherapy regimens from the IFM 95-01 study.[36] This study was conducted in patients receiving second line treatment therefore these results may not be applicable to the patient population for this appraisal. The median overall survival for patients receiving HiDEX was similar to those on other conventional chemotherapy regimens. Patients receiving HiDEX had shorter PFS but longer survival post progression compared to patients on other conventional chemotherapy regimens.

3.4 Outcomes

All outcomes listed in the scope specified by NICE[30] were reported in the CS. In addition, time to treatment failure was added by the company as this was a key input to the economic model.[3]

3.5 Other relevant factors

[redacted]

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company conducted a systematic review to inform the submission. The aim of the systematic review was '*to understand the relative efficacy and safety of POM+LoDEX compared to alternative therapies for adult patients with RRMM who were previously treated with LEN and BOR.*' (appendix 2 of the CS).[37]

The CS also stated that '*An SLR focusing on adult patients previously treated with LEN and BOR was performed and updated for the previous NICE submission (TA338) and this was updated again for this resubmission*' (section 4.1 of the CS).[3]

The following updates were noted by the company.

- '*Update to patient population:*

  This submission included studies where at least 75% of adult RRMM patients had received both BOR and LEN to focus the evidence base to a comparable patient population

- *Update to comparators:*

  The updated SLR was restricted to the latest relevant comparators within UK clinical practice, as specified by the NICE scope. Therefore, PANO was added as an additional comparator, and carfilzomib, LEN and vorinostat were removed from the searches.'[3]

ERG comment: The ERG asked the company to clarify the reason for including only studies where 75% of participants had received BOR and LEN and to report if any studies were excluded based on this criterion. The company stated that '*for the presented evidence to be consistent with the population of interest, only studies where the majority of patients met this criterion were included in the submission*'.[38] The company listed the studies that were excluded based on this criterion. Whilst this cut-off appears arbitrary, the ERG considered that the studies were appropriately excluded and unlikely to affect results as numbers of participants receiving both BOR and LEN, where reported, were very small.

The update to comparators was appropriate given the scope issued by NICE.[30]

4.1.1 Searches

The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies, was used to inform this critique.[39] The submission was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[40] The ERG has presented only the major limitations of each search strategy in the main report.

Clinical effectiveness

The CS states that a previous systematic literature review (SLR) was updated in March 2016 to identify relevant studies on adult patients with relapsed and refractory multiple myeloma previously treated with LEN and BOR published since December 2013 (Section 4.1). Due to changes in the scope between the original and current submission there were some differences in the methods used for the original and updated SLRs, including changes to the patient population and the comparators included. PANO was added as an additional comparator, and carfilzomib, LEN and vorinostat were removed from the searches. The CS also states (page 52) that additional terms were added to the search strategies around study design in order to make the searches more comprehensive, in response to concerns raised by the ERG in the original NICE review (TA338).

Searches were reported for MEDLINE, MEDLINE In-Process, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and Database of Abstracts of Reviews of Effects (DARE), and were undertaken in March 2016. In addition online congress abstracts for the annual meetings of the American Society of Hematology (ASH), the American Society of Clinical Oncology (ASCO), the European Hematology Association (EHA) were searched for 2014-2015 and the International Myeloma Workshops for 2013/2015. The following UK HTA websites were searched: National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG). These meet the requirements specified in current best practice guidance as detailed in the NICE guide to the methods of technology appraisal.[41]

Search strategies for the database searches were provided in the Appendix 2 of the CS and are well reported and reproducible. Strategies for the conference proceedings searches were not included in the CS, however full details were provided following a clarification request. The host provider for each database was listed, and the date span of the databases searched and the specific date the searches were conducted were provided. The database searches were clearly structured and documented. No language limits were applied.

Free text and indexing terms were used to search for the population, intervention and comparators. These could have been extended to include drug brand names (such as Imnovid), and a broader range of search terms in the 'relapse' facet, however this is unlikely to have greatly affected the recall of results.

The ERG notes that both MEDLINE and Embase were searched via the Embase.com interface, however only EMTREE (Embase) indexing terms were used. Although some mapping between indexing terms does take place on Embase.com it is possible that relevant MEDLINE indexing terms (MeSH) will not be included in the search, and potentially relevant records missed.

As with the previous SLR and its ERG comments, the ERG still has concerns about the study design filters used for the MEDLINE and Embase searches. There do not appear to be many new terms added to the study design filter - the ERG was only able to identify two additional terms - and this could still result in the search being unnecessarily restrictive. Combining the MEDLINE and Embase searches within the Embase.com interface, as outlined above, with the use of only EMTREE indexing terms also places additional limits on the recall of the strategy.

The ERG therefore considered that it was possible that some relevant evidence may not have been identified as a consequence of the study design limits used and the indexing term searches on Embase.com. Unfortunately the ERG was unable to undertake independent searches and review the results within the STA timeline, as this would be outside of the ERG remit.

Of concern to the ERG was the search for the comparator PANO, which was introduced in this update. Searches for the update were limited to 2013 – 2016, so references pre-2013 for PANO will not have been identified by the strategy conducted. In response to clarification the company states that *'a full systematic literature review (SLR) is available for evidence for panobinostat + bortezomib + dexamethasone (PANO+BOR+DEX) within the NICE submission for TA380. The searches for this SLR were conducted in June 2013, with updates in May and December 2014, and therefore covers the period prior to the conduct of our SLR (i.e. pre-2013). It was therefore not considered necessary to run additional searches for literature published on PANO+BOR+DEX before 2013.'*

The ERG believes that were these searches comprehensive, then that would be sufficient to provide relevant pre-2013 studies. However, as details of the full search strategies referred to in the response to clarification were not provided in the submission, it is not possible to assess their quality.

Indirect and mixed treatment comparisons
The clinical effectiveness searches reported in Section 4.1 and Appendix 2 of the CS were used to inform the indirect and mixed treatment comparisons.[3, 37] In utilising the same strategies, the limitations reported above will apply.

Non-randomised and non-controlled evidence
The clinical effectiveness searches reported in Section 4.1 and Appendix 2 of the CS were used to identify non-randomised and non-controlled evidence.[3, 37] In utilising the same strategies, the limitations reported above will apply.

Adverse events
The clinical effectiveness searches reported in Section 4.1 and Appendix 2 of the CS were used to identify studies reporting safety data.[3, 37] In utilising the same strategies, the limitations reported above will apply.

Summary of clinical effectiveness searching
The searches in the CS were well documented and easily reproducible; searches were carried out in line with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.[41] The ERG expressed concerns on the use of search filters to limit the results by study design and the lack of relevant MeSH indexing terms on Embase.com, and was unable to comment on the searches conducted pre-2013 for panobinostat.

4.1.2 Inclusion criteria

The appendices of the CS described the selection process of the review '*Primary screening of abstracts and secondary screening of full-texts were conducted by two independent reviewers to ensure everything is quality checked.*'[37]

The eligibility criteria for the systematic review are presented in Table 4.1.

Table 4.1: Eligibility criteria used in search strategy for RCT and non-RCT evidence

Criteria	Inclusion	Exclusion
Population	Adult patients with RRMM previously treated with LEN and BOR	Healthy volunteers Children (age <18 years) Newly diagnosed MM Patients who have not received prior treatment with LEN and BOR
Intervention / comparator	Studies assessing at least one of the interventions listed below: POM+DEX using the licensed dosing regimen BEN (Levact®) with or without steroids / standard chemotherapy agents BOR (Velcade®) with or without steroids / standard chemotherapy agents PANO (LBH589®, Farydak®, Faridak®) in combination with BOR and steroids Standard chemotherapy agents in combination with each other or steroids Standard chemotherapy agents included:	Studies where patients have received SCT in combination with any of the interventions listed under inclusion criteria Studies that do not assess at least one of the interventions listed under inclusion criteria

Criteria	Inclusion	Exclusion
	CYC (Cytoxan®, Endoxan®, Neosar®, Procytox®, Revimmune®) Etoposide (Etopophos®, Vepesid®) Liposomal doxorubicin (Caelyx®, Myocet®) Methylprednisolone (Medrol®) THAL (Thalidomid®) MEL	
Study design	Systematic reviews/meta-analysis RCT Non-RCT Single arm studies Observational studies	Non-systematic reviews, letters, comments and editorials Case reports and case series
Language	Studies published in English	Studies published in non-English languages

BOR, bortezomib; BEN, bendamustine; CYC, cyclophosphamide; DEX, dexamethasone; LEN, lenalidomide; MEL, melphalan; non-RCT, non-randomised controlled trial; PAN, panobinostat; POM, pomalidomide; RCT, randomised controlled trial; RRMM, relapsed and refractory multiple myeloma; SCT, stem cell therapy; THAL, thalidomide.

The company further stated that '*The outcomes of interest were progression free survival (PFS), overall survival (OS), overall response rate (ORR), time to progression (TTP), time to response (TTR), event-free survival (EFS), duration of response (DOR), time to treatment failure (TTF), duration of treatment (DOT), health related quality of life (HRQL) measures and safety measures*.'

ERG comment: The population and outcomes of the review reflected the scope issued by NICE.[30] All interventions and comparators were included and conventional chemotherapy was further specified. The inclusion of non-RCT evidence is appropriate due to the lack of RCTs in this area. Restriction to English language only studies raises the possibility that relevant studies were excluded. However we do not believe this to be likely.

4.1.3 Critique of data extraction

In Appendix 24 of the CS (HRQoL SLR methods) it was stated that '*Data extraction and quality appraisal from the included full-text of articles were also performed independently by two reviewers*'.[37]

ERG comment: Although the company stated that two reviewers were involved in the selection, data extraction and quality assessment of studies, it was unclear how discrepancies were resolved (e.g. use of a third reviewer). Although it is good practice to include this detail when reporting a systematic review, we believe that overall the review was carried out appropriately.

4.1.4 Quality assessment

Quality assessment for RCTs was adapted from the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care.[42] Elements assessed were randomisation, allocation concealment, comparability of groups, blinding of care providers, patients and outcome assessors and drop out, selective reporting of outcomes and use of intention to treat analysis and appropriate methods for dealing with missing data. Non-RCTs were assessed based on the Downs and Black checklist.[43]

ERG comment: Study quality appeared to have been assessed using appropriate tools.

4.1.5 Evidence synthesis

The company stated that *'a meta-analysis was not conducted as there were no additional RCTs identified in a comparable population to MM-003.'*[3]

ERG comment: The ERG agrees that no meta-analysis was possible as there was only one study (MM-003) that compared POM+LoDEX to any of the included comparators. The synthesis of the indirect evidence is discussed in Sections 4.3 and 4.4 of this report.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Overview of the evidence in the submission

The company identified four RCTs[31, 32, 44, 45] of pomalidomide relevant to the submission, see Table 4.2. They identified nine non-RCTs[33, 46-53]which will be described in Section 4.2.7. The company also conducted a retrospective real world data collection project to compare BEN, BOR and POM+LoDEX at third line (Section 4.11.2 of the CS).[3] This will also be described in Section 4.2.7.

Table 4.2: Table of RCTs of pomalidomide

Study	Intervention	Comparator	Population
MM-003[31]	POM+LoDEX	HiDEX	Patients with refractory or RRMM with ≥2 lines of previous therapy including LEN and BOR
MM-002[32]	POM+LoDEX	POM	Patients with RRMM with ≥2 lines of previous therapy including LEN and BOR
IFM 2009-02: Leleu et al., 2013[45]	POM (21/28 day)+LoDEX	POM (28/28 day)+LoDEX	Relapsed MM ≥1 previous therapy
Baz et al., 2016[44]	POM+DEX	POM+DEX+CYC	Patients with RRMM with ≥2 prior therapies and LEN refractory

BOR, bortezomib; CSR, clinical study report; CYC, cyclophosphamide; DEX, dexamethasone; HiDEX, high-dose dexamethasone; LEN, lenalidomide; LoDEX, low-dose dexamethasone; MM, multiple myeloma; POM, pomalidomide; RRMM, relapsed and refractory multiple myeloma.

Furthermore, the company identified two ongoing trials, MM-008 and MM-013[54, 55] and provided details of these for information purposes only. One was a phase I trial designed to assess the pharmacokinetics and safety of POM+LoDEX in patients with normal or impaired renal function (due to complete Feb 2022).[54] The other was a phase II study to assess the safety and efficacy of patients with moderate or severe renal impairment due to complete in June 2021.[55]

The main evidence presented in the clinical effectiveness section was the MM-003 trial which compared POM+LODEX with HiDEX.[31] HiDEX was assumed to be a proxy for conventional chemotherapy. Most of our critique will be focused on the MM-003 trial but a brief overview of the three supporting trials is provided in section 4.2.6.

ERG comment

- The ERG examined the list of excluded studies and considered all of them to have been appropriately excluded.
- The ERG is satisfied that no data from the ongoing trials could have been used to inform the CS.
- None of the included RCTs compared pomalidomide with a comparator outlined in the scope.[30]

- The main evidence presented in the clinical effectiveness section was the MM-003 trial which compared POM+LODEX with HiDEX.[31] HiDEX was assumed to be a proxy for conventional chemotherapy. The evidence supporting this assumption is discussed in Section 4.3.

4.2.2 Overview of the direct evidence: MM-003

According to the CS '*The Phase III study MM-003 was a multicentre, randomised, open-label study, which took place in 93 centres in Europe (including the UK), Russia, Australia, Canada and the United States. The trial was designed to compare the efficacy and safety of POM+LoDEX versus high-dose dexamethasone (HiDEX) in patients with RRMM who have received at least two prior treatment regimens, including both LEN and BOR.*'[3] An overview of the trial is given in Table 4.3.

In MM-003 455 participants either received pomalidomide (4 mg/day) plus dexamethasone (40mg on Days 1, 8, 15 and 22 of a 28-day cycle) (POM+LoDEX) or 40mg dexamethasone on Days 1 through 4, 9 through 12 and 17 through 20 of a 28-day cycle HiDEX. See Table 4.3.

Median follow-up was 15.4 months. The primary outcome was progression-free survival defined as *'Time from randomisation until documented disease progression, or death, whichever occurred earlier.'* The main measure used International Myeloma Working Group (IMWG) response criteria[56] as assessed by an independent adjudication committee. Progression-free survival was also assessed using European Society for Blood and Marrow Transplantation (EBMT) criteria[57] and by investigators.

Overall survival was assessed along with other efficacy and safety outcomes outlined in Table 4.3 and defined more fully in Table 4.4.

Table 4.3: Overview of MM-003

	MM-003
Trial Design	Multi-centre, open-label, randomised (in a 2:1 ratio) controlled trial
Participants	N = 455 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. Following treatment discontinuation patients were assessed at 28 days then until death or five years after randomisation. 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
Pre-planned subgroups	≤ 75 years of age and > 75 years of age

	MM-003
	disease population (refractory patients versus relapsed and refractory patients versus refractory / intolerant patients) number of previous myeloma treatments (2 versus >2) gender race baseline Eastern Cooperative Oncology Group (ECOG) Performance Status baseline cytogenetic categories (high risk versus non-high risk) parameters of prognostic significance (e.g., baseline renal impairment), refractoriness to selected prior anti-myeloma therapies patients randomised at least 6 months prior to the data cut-off
Notes: *The DEX dose on both arms was reduced to 20mg in patients > 75 years of age; $ Treatment was continued until progressive disease or unacceptable toxicity BOR, bortezomib; ECOG, Eastern Cooperative Oncology Group; HiDex, high-dose dexamethasone; LEN, lenalidomide; Lo-DEX, low-dose dexamethasone; POM, pomalidomide; RRMM, Relapsed and refractory multiple myeloma	

Table 4.4: MM-003 outcome definitions

Endpoint type	Measure	Description
Primary endpoint	PFS	Time from randomisation until documented disease progression, or death, whichever occurred earlier. PFS was assessed by IRAC using IMWG response criteria based on the ITT population [a58] As a secondary analysis, PFS was assessed: by IRAC based on EBMT criteria,[57] and by Investigator based on IMWG criteria[a58]
Secondary outcomes	OS	Time from randomisation to death from any cause based on the ITT population
	Response rate	The primary response analysis was based on the assessments by the IRAC using IMWG response criteria [a58] Response was also assessed by investigator using IMWG criteria. The overall confirmed myeloma response rate (ORR; ≥PR) together with the relative proportions in each response category were examined for IRAC and investigator assessments An analysis of response assessments judged by the EBMT criteria was performed, with response categories of CR, PR, MR, StD, and PD.
	TTP	TTP was calculated as the time from randomisation to the first documented progression confirmed by the IRAC.
	TTR	TTR was calculated as the time from randomisation to the initial documented response (PR or better) based on IMWG or EBMT criteria.
	DOR	The duration of time from when response criteria for CR, VGPR or PR were first met to PD or death, whichever occurred first[a]
	TTF	Time from randomisation to discontinuation of study treatment for any reason including disease progression, toxicity and death[a]
Other	HRQL	QLQ-C30, QLQ-MY20, EQ-5D
Safety	Safety	Evaluation of AEs, physical examination (including vital signs/neurological examination), clinical laboratory evaluations (including haematology), electrocardiogram, concomitant medications/therapies, a pregnancy testing and pregnancy prevention risk management plan and incidence of SPM

Source: Table 16 of the CS[3]

Notes: a 01 March 2013 data cut was assessed by IRAC and 01 September 2013 data cut was assessed by the study investigator.

AEs, adverse events; CR, complete response; DOR, duration of response; EBMT, European Society for Blood and Marrow Transplantation; EQ-5D, 5-dimension European Quality of Life questionnaire; HRQL, health-related quality of life; IMWG, International Myeloma Working Group; IRAC, Independent Response Adjudication Committee; ITT, intention to treat; MR, minimal response; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QLQ-C30, Quality of Life Questionnaire – Core 30; QLQ-MY20, Quality of Life Questionnaire – Multiple Myeloma 20; SPM, second primary malignancy; StD, stable disease; TTF, time to treatment failure; TTP, time to progression; TTR, time to treatment response; VGPR, very good partial response.

All patients needed to have documented disease progression during or within 60 days of completing their most recent myeloma therapy. Patients had to have failed both bortezumab (BOR) and lenalidomide (LEN) regimens. Definitions of treatment failure are given in Table 4.5. The main exclusion criteria as stated by the company were: patients who were eligible for SCT, patients who had CrCl <45ml/min, patients who demonstrated resistance to HiDEX in the most recent line of therapy and patients who had peripheral neuropathy of Grade 2 or higher, see Table 4.5.

Table 4.5: Inclusion and exclusion criteria for MM-003

Inclusion criteria	Exclusion criteria
The key patient eligibility criteria for study MM-003 were as follows: Patients must have had either refractory or relapsed and refractory disease defined as documented disease progression during or within 60 days of completing their most recent myeloma therapy All patients must have received at least two consecutive cycles of previous treatment that included LEN and BOR, either alone or in combination Patients must have received adequate previous alkylator therapy All patients must have demonstrated *failure of both LEN and BOR,* using the following criteria for refractoriness that made the patient eligible for the study All patients must have had *treatment failure* with the *most recent LEN-containing regimen* in *one* of the following ways: documented PD during or within 60 days of completing treatment with LEN; *or* in case of previous response (≥PR) to LEN, patients must have relapsed within 6 months after stopping treatment with LEN-containing regimens All patients must have had *treatment failure* with the most *recent BOR-containing regimen* in using the same criteria described for LEN, *or*: patients who had not had at least a minimal response (MR) and had developed intolerance/toxicity after a minimum of two cycles of a BOR-containing regimen, for example ≥Grade 2 peripheral neuropathy or ≥Grade 2 painful neuropathy. Peripheral neuropathy must have resolved to Grade 1 before study entry Women of childbearing potential must have agreed to comply with conditions of a pregnancy prevention programme and male patients were required to follow specified contraceptive measures	The main exclusion criteria applied to: Patients who were eligible for SCT; Patients who had CrCl <45ml/min; Patients who demonstrated resistance to HiDEX used in the most recent line of therapy; or Patients who had peripheral neuropathy of Grade 2 or higher.
BOR, bortezomib; CrCl, creatinine clearance; HiDex, high-dose dexamethasone; LEN, lenalidomide; MR, minimal response; POM, pomalidomide; PR, previous response; SCT, stem cell transplantation	

The study characteristics of MM-003 as detailed in Section 2.8 of the CS appendices[37] are reproduced in Table 4.6. It was noted by the company that '*Baseline characteristics of the study populations in both treatment groups were well balanced in terms of age, age distribution, sex, disease stage, performance status, cytogenic risk, median time since diagnoses, median number of prior anti-myeloma regimens, and previous treatments. Patients were also well balanced for baseline beta-2-microglobulin, baseline distribution of beta-2-microglobulin, baseline albumin, baseline distribution of albumin, baseline renal function and baseline ECG.*'[3]

Participants in MM-003 had a mean age of 63.7 years of age. Most (92%) participants were under 75 years old. The trial had a predominantly white population, where stated. Over 60% of participants

had international staging system (ISS) stage of I or II and approximately 80% had an ECOG performance status of 0 or 1. Over 80% of the participants were classified as 'Disease population group 1' which represents refractory patients who have progressed on or within 60 days of both LEN and BOR based treatments. See Table 4.6.

Table 4.6: Full baseline characteristics of MM-003

	POM+LoDEX (N=302)	HiDEX (N=153)
Age (years)		
Mean (SD)	63.6 (9.3)	63.7 (9.6)
Median (range)	64.0 (35.0-84.0)	65.0 (35.0-87.0)
Age distribution n (%)		
≤65	167 (55.3)	81 (52.9)
>65	135 (44.7)	72 (47.1)
Stratification factor 1: Age, n (%)		
≤75 years old	278 (92.1)	141 (92.2)
>75 years old	24 (7.9)	12 (7.8)
Sex n (%)		
Male	181 (59.9)	87 (56.9)
Female	121 (40.1)	66 (43.1)
Race n (%)[b]		
White	244 (80.8)	113 (73.9)
American Indian or Alaska Native	0 (0.0)	0 (0.0)
Asian	4 (1.3)	0 (0.0)
Black or African American	4 (1.3)	3 (2.0)
Native Hawaiian or Other Pacific Islanders	0 (0.0)	0 (0.0)
Other	2 (0.7)	2 (1.3)
Not Collected	48 (15.9)	35 (22.9)
Durie Salmon Stage (before Study Entry), n (%)		
I	21 (7.0)	12 (7.8)
II	94 (31.1)	37 (24.2)
III	178 (58.9)	103 (67.3)
Missing	9 (3.0)	1 (0.7)
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)

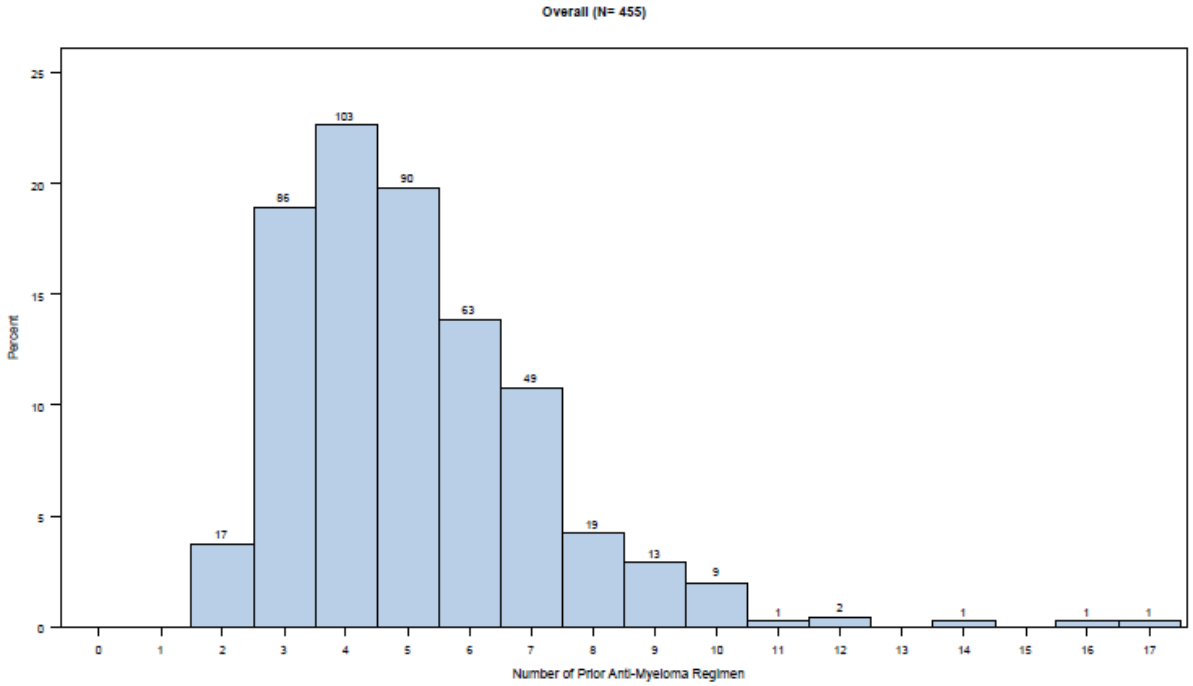
	POM+LoDEX (N=302)	HiDEX (N=153)
3	0 (0.0)	3 (2.0)
Missing	2 (0.7)	3 (2.0)
Time from first pathologic diagnosis (years)		
Mean (SD)	6.2 (4.0)	6.5 (3.6)
Median (min, max)	5.3 (0.6, 30.0)	6.1 (0.9, 21.1)
Cytogenetic risk, n (%)		
High risk [c]	130 (43.0)	57 (37.3)
Non high risk	91 (30.1)	47 (30.7)
Modified high risk [d]	77 (25.5)	35 (22.9)
Missing	81 (26.8)	49 (32.0)
Presence of bone lesions	205 (67.9)	101 (66.0)
Presence of plasmacytoma	28 (9.3)	13 (8.5)
Baseline beta-2-microglobulin (mg/L)		
n	289	146
Mean (SD)	5.3 (3.3)	5.4 (3.4)
Median (min, max)	4.6 (1.6, 31.8)	4.4 (1.6, 30.0)
Baseline distribution of beta-2-microglobulin, n (%)		
<3.5mg/L	92 (30.5)	44 (28.8)
3.5 - <5.5mg/L	104 (34.4)	47 (30.7)
≥5.5mg/L	93 (30.8)	55 (35.9)
Missing	13 (4.3)	7 (4.6)
Baseline renal function (CrCl)		
<30ml/min	2 (0.7)	3 (2.0)
30 - <45ml/min	28 (9.3)	15 (9.8)
45 - <60ml/min	65 (21.5)	41 (26.8)
60 - <80ml/min	97 (32.1)	41 (26.8)
≥80ml/min	108 (35.8)	52 (34.0)
Missing	2 (0.7)	1 (0.7)
Number of prior anti-myeloma therapies		
Mean (SD)	5.0 (2.0)	5.2 (2.2)
Median (min, max)	5.0 (2.0, 14.0)	5.0 (2.0, 17.0)
Stratification factor 2: Disease population[a], n (%)		
Disease population group 1	249 (82.5)	125 (81.7)
Disease population group 2	8 (2.6)	5 (3.3)
Disease population group 3	45 (14.9)	23 (15.0)
Stratification factor 3: Number of prior anti-myeloma therapies, n (%)		
2 prior anti-myeloma therapies	17 (5.6)	8 (5.2)
>2 prior anti-myeloma therapies	285 (94.4)	145 (94.8)

	POM+LoDEX (N=302)	HiDEX (N=153)
Previous treatments, n (%)		
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)
Prior radiation therapies, n (%)	109 (36.1)	49 (32.0)
Prior cancer surgeries, n (%)	24 (7.9)	17 (11.1)
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)

Source: *Data were obtained from the CSR[59] except for ISS which was obtained from San Miguel 2013[60]
Notes: a Disease Population Group 1 is defined as refractory patients who have progressed on or within 60 days of both LEN and BOR based treatments. Disease Population Group 2 is defined as relapsed and refractory patients who achieved at least PR and progressed within 6 months after stopping treatment with LEN and/or BOR. Disease Population Group 3 is defined as refractory/intolerant patients who have developed intolerance/toxicity after a minimum of two cycles of BOR; bRace/ethnicity was not permitted to be collected by law in some regions; c High risk is defined as any cytogenetic abnormality in 13q14, 17p13, 4p16/14q32 or 14q32/16q23; d Modified risk is defined as any cytogenetic abnormality in 17p13 or 4p16/14q32.
BOR, bortezomib; CrCl, creatinine clearance; DEX, dexamethasone; ECG, electrocardiogram; 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 transplantion; SD, standard deviation; THAL, thalidomide.

The scope issued by NICE included an evaluation of pomalidomide for patients who have had two prior therapies and for those who have had three or more prior therapies.[30] The ERG noted that patients in MM-003 had received a median number of five prior treatments (range 2 to 17). The ERG asked the company to clarify the comparability of the patients in MM-003 to the total population in this appraisal. The company acknowledged that '*MM-003 has been conducted in an advanced and highly refractory population likely to have a poor prognosis, with a reduced ability to benefit from subsequent treatment*'.[38] Furthermore the company provided information on breakdown of numbers of prior therapies in MM-003. These are displayed in Figure 4.1.

Figure 4.1: Distribution of prior treatments in MM-003



It can be seen from the figure that most patients had received between three and seven prior treatments (median number of prior anti-myeloma treatments was five (IQR 4, 6)).

The ERG asked the company to provide results for all outcomes specified in the scope for patients who had had exactly two prior therapies. They provided results for 17 patients (25 are listed in the baseline characteristics) but stated that '*Due to the small numbers of patients….these results cannot be credibly interpreted.*'[38] We have not reproduced the results in this report for that reason.

ERG comment The randomised trial, MM-003, has several strengths and matches the NICE scope[30] in several ways:

- It is a relatively large trial (455 participants) and is well-conducted.
- It is an international and multicentre trial (including patients from the UK).
- The trial inclusion criteria matches the scope issued by NICE as it involves patients who have failed on both BOR and LEN treatments.
- The trial examined all outcomes relevant to the NICE scope and has an average follow-up of over 15 months. A range of subgroups were investigated to ascertain any differential effects of the drug. We note that the trial was stratified based on age, disease population and number of previous myeloma treatments.

There are a number of limitations in applying the results of the trial to the NICE scope.

- The major limitation of the trial is that the comparator HiDex as stated in the CS '*is no longer viewed as optimal treatment in this setting in the UK and is given at a lower dose mostly with palliative intent*' (p156 of the CS).[3] Since HiDEX is no longer considered conventional chemotherapy technically there is no direct evidence comparing POM+LoDEX with any of the comparators listed in the NICE scope.[30] The indirect comparisons which were conducted to address this limitation are discussed in Sections 4.3 and 4.4.
- Another limitation is that the trial is open label which means that subjective outcomes such as those related to quality of life may be subject to bias. However an independent outcome assessor

was used to determine progression-free survival and both investigator and independent assessor results are presented in the submission.

- Most importantly, the trial does not provide sufficient evidence for patients who have received only two prior therapies. Results were provided for 17 patients who had received exactly two therapies. However the results, as acknowledged by the company, are based on too small a number to be reliable. Hence the trial is not truly representative of third line treatment with pomalidomide. Any conclusions on the role of pomalidomide would be based on an assumption of a better response in less treated patients.
- The trial population is a heavily treated population. Participants had received an average of five prior treatments (most had received between three and seven).
- The trial population is a hard to treat population. Eighty-two per cent of the patients had disease progression on or within 60 days of both LEN and BOR based treatments.
- The ERG noted that 68 of the 93 study sites were based in Europe but could not identify from the main submission how many centres and how many individual patients were from the UK.
- The ERG noted that over 50% of patients in the trial are aged 65 or under so may reflect a younger population than that typically seen in practice.
- We also noted an under-representation of non-white participants. Under 1% were of Asian origin and 1.5% were of black or African American origin.
- The ERG noticed an inconsistency in relation to patients with renal insufficiency. It was noted in the company submission that patients with CrCl < 45ml/min were excluded from the trial. However the baseline characteristics showed that 48 of 455 (10.5%) patients had a baseline CrCl of < 45ml/m.

4.2.3 MM-003: Quality assessment

The quality rating of MM-003 as presented by the company is given in Table 4.7.

Table 4.7: Quality assessment of MM-003

Was randomisation carried out appropriately?	Yes. Patients were randomised in a 2:1 ratio by permuted block randomisation. Randomisation was undertaken using a validated interactive voice/web response system (IVRS/IWRS).
Was the concealment of treatment allocation adequate?	MM-003 is an open-label study.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Baseline characteristics of the study populations in both treatment groups were well balanced in terms of age, age distribution, sex, disease stage, performance status, cytogenic risk, median time since diagnoses, median number of prior anti-myeloma regimens, and previous treatments. Patients were also well balanced for baseline beta-2-microglobulin, baseline distribution of beta-2-microglobulin, baseline albumin, baseline distribution of albumin, baseline renal function and baseline ECG.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Although the study was open-label, the sponsor's study team was blinded to the study treatment code until the final analysis of the primary endpoint. An independent Response Adjudication Committee (IRAC) reviewed all efficacy data in a blinded manner, independent of investigator response to ensure an unbiased assessment of the data.
Were there any unexpected	No. The majority of patients in both treatment groups discontinued treatment due to progressive disease (61% of discontinuations for the POM+LoDEX group versus 62% for the HiDEX group). Similar percentages of patients in

imbalances in drop-outs between groups?	both treatment groups discontinued due to AEs or death. Similar percentages withdrew from the study, were lost to follow-up or withdrew due to other causes.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All treatment outcomes were reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The analysis included an ITT population, which was the most appropriate population as it included all randomised patients. A safety population, defined as all patients who took at least one dose of study medication, and an efficacy evaluable population, defined as all ITT patients who took at least one dose of study treatment and who had baseline disease measurement and at least one post-baseline efficacy assessment or PFS were also included. Appropriate censoring methods were used to account for missing data. Missing assessments or discontinuations due to reasons other than progressive disease were handled by censoring rules based on the EMA guidelines on the evaluation of anti-cancer medicinal products and Appendix 1.[61]
Source: Table 20 of the CS[3] AEs, adverse events; ECG, electrocardiogram; EMA, European Medicines Agency; HiDEX, high-dose dexamethasone; ITT, intention to treat; IVRS, interactive voice response system; IWRS, interactive web response system; LoDEX, low-dose dexamethasone; PFS, progression-free survival; POM, pomalidomide.	

ERG comment: We agree with the company's assessment of the quality of the trial. Implications of the open label design have been previously discussed.

4.2.4 MM-003: Efficacy results

An overview of the results is presented in Table 4.8. Using the latest cut-off (1 September 2013) of 15.4 months, POM+LoDEX significantly extended PFS based on investigator assessment. (4 months vs. 1.9 months, HR 0.50, 95% CI: 0.41 to 0.62). Overall survival was significantly better for patients treated with POM+LoDEX compared to those receiving HiDEX (13.1 months vs. 8.1 months, HR 0.72, 95% CI: 0.56 to 0.92). The CS stated that "*A total of 126 (41.7%) patients assigned to the POM+LoDEX arm and 52 (34.0%) patients initially assigned to the HiDEX arm were alive as of 01 September 2013.*"[3]All other effectiveness outcomes were significantly better for POM+LoDEX than for HiDEX at the latest time point.

Table 4.8: Overview of results in MM-003

Outcomes[a]	**01 March 2013 data cut[b]**		**01 September 2013 data cut[c]**	
	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 [*p*-value]	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 [*p*-value]	0.70 (95% CI: 0.54 to 0.92)		0.72 (95% CI: 0.56 to 0.92)	

Outcomes[a]	01 March 2013 data cut[b]		01 September 2013 data cut[c]	
	POM+LoDEX	HiDEX	POM+LoDEX	HiDEX
ORR, %	23.5	3.9	32	11
OR [*p*-value]	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 [*p*-value]	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 [*p*-value]	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 [*p*-value]	0.53 (95% CI: 0.19 to 1.51)		0.52 (95% CI: 0.29 to 0.95)	

Source: CS[3]
Notes: aValues in months have been converted from weeks (as they were reported in the MM-003 CSR and in the September 2013 data cut tables data on file) using the conversion factor of 0.22998 (calculated by 7/365.25*12); b 01 March 2013 data cut was from a pre-planned assessment by IRAC using IMWG criteria; c 01 September 2013 data cut was from a post-hoc analysis using investigator assessed outcomes by IMWG criteria.
DOR, duration of response; HiDEX, high-dose dexamethasone; HR, hazard ratio; IRAC, Independent Response Adjudication Committee; ITT, intention to treat; LoDEX, low-dose dexamethasone; NR, not reported; PFS, progression-free survival; OR, odds ratio; ORR; overall response rate; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; TTF; time to treatment failure; TTP, time to progression.

Treatment crossover

The CS stated that '*by the time of the 01 September 2013 data cut, 56% (85/153) of patients on the HiDEX arm received subsequent therapy with POM. 11 patients (7.2%) entered MM-003 companion study and received POM as they progressed on HiDEX. The remaining 74 patients (48.4%) received POM (with or without LoDEX) at the final analysis for PFS and the interim analysis for OS based on the IDMC recommendation that people in the HiDEX group who had not progressed should have the option to receive POM.*'[3]

The company adjusted for treatment crossover to provide a more reliable assessment of overall survival. The CS stated that '*two methods were used to account for treatment switching using the 01 March 2013 data cut; the two-stage method[62] and the rank preserving structure failure time model (RPSFTM) approach.(Table 24)*'

After adjustment for crossover from HiDEX to POM+LoDEX participant survival was noticeably lower in the HiDEX group. The two stage method shows the largest difference 7.0 (HR: 0.52; 95% CI: 0.39, 0.68). The results adjusted for crossover are presented in Table 4.9.

Table 4.9: Crossover adjusted results for OS in MM-003

Median OS in months	POM+LoDEX (n = 302)	HiDEX (n = 153)	Difference
Intent-to-treat, median OS	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)
After crossover adjustment, median OS, 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)
After crossover adjustment, median OS, 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: Morgan, 2015[CS ref 126]
CI, confidence interval; HiDEX, high-dose dexamethasone; HR, hazard ratio; LoDEX, low-dose dexamethasone; OS, overall survival; POM, pomalidomide; RPSFTM, rank preserving structure failure time model

Patients in both treatment groups in MM-003 went on to receive a range of other therapies as is typical in this population. Forty-four point four percent of the pomalidomide arm received at least one subsequent treatment compared to 60.1% of the HiDEX group. Patients in the HiDEX group were most likely to receive pomalidomide, see Table 4.10.

Table 4.10: Subsequent post-study anti-myeloma therapy (ITT population, 1 September 2013 data cut)

Subsequent therapy, n (%)[a]	POM+LoDEX (N = 302)	HiDEX (N = 153)
≥1 subsequent anti-myeloma drug	134 (44.4)	92 (60.1)
Pomalidomide	1 (0.3)	74 (48.4)[b]
Dexamethasone	88 (29.1)	36 (23.5)
Cyclophosphamide	64 (21.2)	17 (11.1)
Bortezomib	54 (17.9)	24 (15.7)
Bendamustine	34 (11.3)	13 (8.5)

Source: Data on file, 2016[63]
Note: [a] Patients may have received more than one of the subsequent treatments listed therefore numbers listed for individual drugs do not necessarily correlate with the total number of patients receiving ≥1 subsequent anti-myeloma drug. [b] An additional 11 patients crossed over to the POM+DEX arm during the study after IDMC review
HiDEX, high-dose dexamethasone; ITT, intention to treat; LoDEX, low-dose dexamethasone; POM, pomalidomide.

Quality of life

Three tools were used to assess quality of life: the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, the myeloma-specific EORTC QLQ-MY20 and the EQ-5D. Health-related quality of life (HRQL) results were based on data at 1 March 2013 (433 patients of 455). From these tools eight clinically relevant domains were selected following a workshop discussion with specialists on perceived clinical relevance results of multivariate regression analysis comparing domains with the EQ-5D utility index.[64] The domains of interest were QLQ-MY20 side effects, QLQ-MY20 disease symptoms, QLQ-C30 global health status, QLQ-C30 physical functioning, QLQ-C30 emotional functioning, QLQ-C30 fatigue, QLQ-C30 pain and EQ-5D health utility. The company reported both cross-sectional and longitudinal analyses, see Table 4.11.

Table 4.11: MM-003 HRQL results

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*

Source: CS[3]
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

Subgroups

The company conducted analyses based on age, disease population and number of prior therapies for overall survival and progression-free survival.

The company noted that '*Overall survival was generally consistent with the overall ITT population for both age groups (≤75 and >75 years old) and in patients with >2 prior anti-myeloma therapies. Patients having received 2 prior anti-myeloma therapies demonstrated lower OS for both the POM+LoDEX and HiDEX groups compared with the overall ITT population, however, care is required in the interpretation of these data as the patient pool is small*.'[3] As stated before, just 25 patients had received two prior therapies so this analysis is not likely to be reliable. Just 36 patients were over 75 so this analysis is also limited, see Table 4.12.

The progression-free survival subgroup results were noted by the company to be '*generally consistent with the ITT population*'[3] but are not duplicated here due to the small numbers of patients.

Table 4.12: OS in weeks by stratification factors of age (≤75 vs. >75 years old), disease population and number of previous anti-myeloma therapies (2 vs. >2)

Stratification factors	POM+LoDEX	HiDEX	2-sided p-value[d]
Stratification factor 1: Age			
≤75 Years Old	278	141	
Median [a] OS [two sided 95% CI [b]]	54.0 [45.1, 63.6]	36.6 [29.9, 44.0]	
HR [two sided 95% CI [c]]	0.75 [0.57, 1.00]		0.045
>75 Years Old	24	12	
Median [a] OS [two sided 95% CI [b]]	67.3 [31.6, NE]	18.1 [10.7, 35.3]	
HR [two sided 95% CI [c]]	0.34 [0.13, 0.87]		0.019
Stratification factor 2: Disease population			
Disease Population Group 1[e]	249	125	
Median [a] OS [two sided 95% CI [b]]	51.3 [42.4, 63.6]	34.0 [27.0, 39.9]	
HR [two sided 95% CI [c]]	0.72 [0.53, 0.96]		0.026
Disease Population Group 2[f]	8	5	

Stratification factors	POM+LoDEX	HiDEX	2-sided p-value[d]
Median [a] OS [two sided 95% CI [b]]	NE	NE	
HR [two sided 95% CI [c]]	NE		NE
Disease Population Group 3[g]	45	23	
Median [a] OS [two sided 95% CI [b]]	61.4 [48.3, 76.1]	36.6 [23.3, NE]	
HR [two sided 95% CI [c]]	0.58 [0.30, 1.14]		0.111
Stratification Factor 3: Number of Prior Anti-MM Therapies			
2 Prior anti-MM Therapies	17	8	
Median [a] OS [two sided 95% CI [b]]	47.9 [45.1, NE]	19.4 [15.4, NE]	
HR [two sided 95% CI [c]]	0.44 [0.14, 1.4]		0.155
>2 Prior anti-MM Therapies	285	145	
Median [a] OS [two sided 95% CI [b]]	54.0 [43.7, 63.6]	35.1 [29.9, 39.1]	
HR [two sided 95% CI [c]]	0.72 [0.55, 0.95]		0.020

Source: MM-003 CSR[59]

Notes: Data cut-off 1 March 2013. A The median is based on the Kaplan–Meier estimate; b 95% confidence interval about the median PFS; c Based on Cox Proportional hazards model comparing the hazard functions associated with treatment groups; d The p-value is based on unstratified log-rank test; e Disease Population Group 1 is defined as refractory patients who have progressed on or within 60 days of both LEN and BOR based treatments; f Disease Population Group 2 is defined as relapsed and refractory patients who achieved at least PR and progressed within 6 months after stopping treatment with LEN and/or BOR; g Disease Population Group 3 is defined as refractory/intolerant patients who have developed intolerance/toxicity after a minimum of 2 cycles of BOR.

BOR, bortezomib; CI, Confidence interval; HiDEX, high-dose dexamethasone; HR, hazard ratio; LEN, lenalidomide; MM, multiple myeloma. NE = Non estimable; POM+LoDEX, pomalidomide in combination with low-dose dexamethasone; OS, overall survival

ERG comment:

- POM+LoDEX improved survival, progression-free survival and other efficacy outcomes compared to HiDEX in a very heavily treated population but it should be reiterated that HiDEX is not the optimal comparator.
- Both results from independent assessors and investigators are presented but it should be noted that the most up to date data (1 September 2013) is investigator-derived. This is at greater risk of bias in an open-label trial for subjective outcomes.
- In the MM-003 trial a high proportion of patients crossed over to pomalidomide from the HiDEX group. Two methods of adjustment for treatment crossover for overall survival were chosen by the company with the two-stage method preferred. The ERG is satisfied that the company's adjustments were appropriate.[65]
- Results for all outcomes for participants who have received two therapies only are uncertain due to the small numbers in the analyses.
- Results for all outcomes for patients over 75 remains uncertain due to the small numbers of participants.

4.2.5 MM-003: Safety results

The tables below use information provided in Section 4.12.1 and Appendix 10 of the CS. Data presented are from the safety population which included patients who had received at least one dose of the medication. Safety data were from the data cut-off of 1 March 2013 unless otherwise stated.

Almost all of the patients across the trial had at least one adverse event (99% POM+LoDEX, 99.3% HiDEX). However the company stated that '*AEs were more likely to occur shortly after treatment initiation (within the first two cycles) and decreased in frequency thereafter*.'[3]

The company identified that 247 of 300 patients (82.3%) in the POM+LoDEX group had at least one AE considered by the investigator to be related to POM. Furthermore 190 patients (63.3%) had Grade 3-4 TEAEs considered related to POM. However the company stated that '*with dose modifications and supportive care the safety profile was predictable, manageable and generally well tolerated.*'[3]

The company stated '*the most common cause of death in both treatment groups was multiple myeloma: 100 patients (33.3%) in the POM+LoDEX group and 52 patients (34.7%) in the HiDEX group. The second most common cause of death was infection, which occurred less frequently in the POM+LoDEX group (14 of 300 patients [4.7%]) than in the HiDEX group (17 of 150 patients [11.3%]).*'[3]

The company further stated that '*There were 11 (4%) treatment-related deaths in the POM+LoDEX arm: eight cases of infections and infestations, two cases of multi-organ failure or sudden death and one nervous system disorder: There were seven (5%) in the HiDEX arm due to infections and infestations.*'[3]

An overview of adverse events is given in Table 4.13.

Table 4.13: Overview of adverse events in MM-003

Adverse events by patient	POM+LoDEX (n=300)	HiDEX[a] (n=150)
At least one AE	297 (99.0)	149 (99.3)
At least one Grade 3-4 AE	259 (86.3)	127 (84.7)
At least one AE related to study drug	247 (82.3)	115 (76.7)
At least one Grade 3-4 AE related to study drug	190 (63.3)	70 (46.7)
At least one Grade 5 AE	44 (14.7)	21 (14.0)
At least one serious AE	183 (61.0)	80 (53.3)
At least one serious AE related to study drug:	82 (27.3)	36 (24.0)
Death	146 (48.7)	84 (56.0)
Treatment-related death	11 (3.67)[b]	7 (4.67)[c]

Notes: a Data are before crossover to POM+LoDEX; b (8 infections and infestations, 2 multi-organ failure or sudden death and one nervous system disorder); c All infections and infestations
AE, adverse event; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide

The company provided details of treatment-emergent AEs that occurred in at least 10% of patients and corresponding Grade 3/4 TEAEs . These results are summarised in Table 4.14 below.

The company noted '*High levels of neutropenia and the presence of febrile neutropenia in the POM+LoDEX compared with the HiDEX group (51.3% versus 20.0% for neutropenia and 9.3% versus 0% for febrile neutropenia) were of particular interest, occurring mainly in the first few cycles of therapy. However, few neutropenic events were serious, only one patient discontinued therapy and no patients died due to neutropenia. Furthermore, in the group of patients that experienced neutropenia of Grade 3 and above, the majority of patients had no concurrent infection*.'[37]

The company acknowledged that rates of thrombocytopaenia were similar in both groups but that only 1% of patients discontinued and no patient died due to thrombocytopenia. In those patients with concurrent haemorrhage or bleeding haemorrhage was the cause of death for two patients in the POM+LoDEX group and one in the HiDEX group.

The company noted that levels of infection were high in both treatment groups but observed that patients in the POM+LoDEX group had a lower death rate from infections compared to those in the HiDEX group due to lower proportions of septic shock (0% vs. 4.0%).

The company stated that *'The most frequently occurring serious AEs in both treatment arms were pneumonia (13.0% in the POM+LoDEX arm and 8.7% in the HiDEX arm) and general physical health deterioration (8.7% and 8.0%, respectively).'*[3]

They stated that *'Grade 3/4 events that occurred more frequently in the POM+LoDEX arm than in the HiDEX arm included: neutropenia (48.3% versus 15.3%); febrile neutropenia (9.3% versus 0%); pneumonia (12.7% versus 8.0%); bone pain (7.3% versus 4.7%); decreased neutrophil count (4.7% versus 0.7%); and leukopenia (9.0% versus 3.3%.'*[3]

Table 4.14: MM-003: specific adverse events

	POM+LoDEX (n=300)	HiDEX[b] (n=150)	POM+LoDEX (n=300)	HiDEX[b] (n=150)
System organ preferred class[a]	**Total**	**Total**	**Grade 3/4**	**Grade 3/4**
Number of patients with at least one AE	297 (99.0)	149 (99.3)	259 (86.3)	127 (84.7)
Blood and lymphatic system disorders	**229 (76.3)**	**99 (66.0)**	**203 (67.7)**	**84 (56.0)**
Anaemia	156 (52.0)	77 (51.3)	98 (32.7)	58 (38.7)
Neutropenia	154 (51.3)	30 (20.0)	145 (48.3)	23 (15.3)
Febrile neutropenia	28 (9.3)	0 (0.0)	28 (9.3)	0 (0.0)
Thrombocytopenia	89 (29.7)	44 (29.3)	66 (22.0)	39 (26.0)
Leukopenia	38 (12.7)	8 (5.3)	27 (9.0)	5 (3.3)
General disorders and administration site conditions	**224 (74.7)**	**95 (63.3)**	**62 (20.7)**	**37 (24.7)**
Fatigue	101 (33.7)	41 (27.3)	16 (5.3)	9 (6.0)
Pyrexia	80 (26.7)	35 (23.3)	9 (3.0)	7 (4.7)
Oedema peripheral	52 (17.3)	17 (11.3)	4 (1.3)	3 (2.0)
Asthenia	50 (16.7)	27 (18.0)	11 (3.7)	10 (6.7)
General physical health deterioration	35 (11.7)	16 (10.7)	24 (8.0)	12 (8.0)
Infections and infestations	**203 (67.7)**	**79 (52.7)**	**90 (30.0)**	**36 (24.0)**
Upper respiratory tract infection	48 (16.0)	11 (7.3)	5 (1.7)	1 (0.7)

	POM+LoDEX (n=300)	HiDEX[b] (n=150)	POM+LoDEX (n=300)	HiDEX[b] (n=150)
System organ preferred class[a]	**Total**	**Total**	**Grade 3/4**	**Grade 3/4**
Pneumonia	45 (15.0)	16 (10.7)	38 (12.7)	12 (8.0)
Bronchitis	30 (10.0)	8 (5.3)	4 (1.3)	0 (0.0)
Gastrointestinal disorders	**178 (59.3)**	**62 (41.3)**	**24 (8.0)**	**10 (6.7)**
Diarrhoea	66 (22.0)	28 (18.7)	3 (1.0)	2 (1.3)
Constipation	65 (21.7)	22 (14.7)	7 (2.3)	0 (0.0)
Nausea	45 (15.0)	16 (10.7)	3 (1.0)	2 (1.3)
Musculoskeletal and connective tissue disorders	**162 (54.0)**	**83 (55.3)**	**49 (16.3)**	**30 (20.0)**
Back pain	59 (19.7)	24 (16.0)	15 (5.0)	6 (4.0)
Bone pain	54 (18.0)	21 (14.0)	22 (7.3)	7 (4.7)
Muscle spasms	46 (15.3)	11 (7.3)	1 (0.3)	1 (0.7)
Muscular weakness	9 (3.0)	19 (12.7)	2 (0.7)	5 (3.3)
Respiratory, thoracic and mediastinal disorders	**151 (50.3)**	**49 (32.7)**	**36 (12.0)**	**13 (8.7)**
Cough	60 (20.0)	15 (10.0)	2 (0.7)	1 (0.7)
Dyspnoea	59 (19.7)	22 (14.7)	15 (5.0)	7 (4.7)
Epistaxis	28 (9.3)	15 (10.0)	3 (1.0)	3 (2.0)
Nervous system disorders	**129 (43.0)**	**54 (36.0)**	**30 (10.0)**	**18 (12.0)**
Dizziness	37 (12.3)	14 (9.3)	4 (1.3)	2 (1.3)
Metabolism and nutrition disorders	**117 (39.0)**	**64 (42.7)**	**58 (19.3)**	**33 (22.0)**
Decreased appetite	38 (12.7)	11 (7.3)	3 (1.0)	2 (1.3)
Hypercalcaemia	21 (7.0)	16 (10.7)	13 (4.3)	7 (4.7)
Skin and subcutaneous tissue disorders	**94 (31.3)**	**26 (17.3)**	**9 (3.0)**	**1 (0.7)**
Psychiatric disorders	**88 (29.3)**	**56 (37.3)**	**17 (5.7)**	**15 (10.0)**
Insomnia	32 (10.7)	32 (21.3)	3 (1.0)	5 (3.3)
Investigations	**86 (28.7)**	**30 (20.0)**	**40 (13.3)**	**12 (8.0)**
Renal and urinary disorders	**52 (17.3)**	**24 (16.0)**	**22 (7.3)**	**8 (5.3)**

Source: CSR[59] Date cut-off: 01 March 2013

Notes: TEAEs are defined as any AE occurring or worsening on or after the first treatment of the study medication and within 30 days after the end date of study drug; a, System organ classes and preferred terms are coded using the MedDRA dictionary version 14.0. System organ classes and preferred terms are listed in descending order of

	POM+LoDEX (n=300)	HiDEX[b] (n=150)	POM+LoDEX (n=300)	HiDEX[b] (n=150)
System organ preferred class[a]	**Total**	**Total**	**Grade 3/4**	**Grade 3/4**
frequency of POM+LoDEX group. A patient with multiple occurrences of an AE is counted only once in the AE category; b, Data are before crossover to POM+LoDEX. AE, adverse event; DEX, dexamethasone; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide; TEAEs, treatment-emergent adverse events.				

The company noted that *'Venous (VTEs) and arterial (ATEs) embolic and thrombotic events occurred infrequently in both treatment groups and none of these events resulted in death.'*[3] These results are summarised in Table 4.15 below.

Table 4.15: MM-003: VTEs and ATEs

Adverse events by patient	POM+LoDEX (n=300)	HiDEX[b] (n=150)
At least 1 VTE	12 (4.0)	3 (2.0)
At least 1 Grade 3/4 VTE	3 (1.0)	0
Serious VTE	6 (2.0)	0
At least 1 ATE[a]	5 (1.7)	0
Source: CS[3] Notes: a embolism, ischaemic cerebral infarction and myocardial infarction each occurring in 2 patients; b before crossover to POM+LoDEX ATE, arterial thrombotic event; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide; VTE, venous thromboembolism		

Treatment discontinuations, dose reductions, interruptions and supportive care

The main cause of discontinuation was progressive disease (54% vs. 60.1%). Although adverse events were similarly common in both treatment groups discontinuations related to AEs were uncommon. The company noted that 8.6% of the POM group discontinued due to an adverse event (3.3% specifically drug-related) and 10.5% of the HiDEX group discontinued due to AE (6.0% drug-related).

There were more dose interruptions in the POM group than in the HiDEX group (67% vs. 30%). Rates of dose reductions were similar. There was a greater need for granulocyte colony stimulating factor for neutropaenia in the POM group (43% vs. 10%). The company further stated that '*neutropaenia and thrombocytopaenia were the most common reasons for dose interruptions and reductions of Pomalidomide in the POM + LoDEX arm.*'[3] See Table 4.16 for details.

Table 4.16: MM-003: treatment discontinuations, dose reductions, interruptions and supportive care

Patient event	POM+LoDEX	HiDEX
Discontinuation due to progressive disease	163 /302 (54.0)	92/153 (60.1)
Discontinuation due to AE	(8.6)	(10.5)
At least 1 dose reduction	(27.3)	(32.7)
At least 1 dose interruption	(67.0)	(30.0)
Need for granulocyte colony stimulating factor for neutropaenia	(43)	(10)
Need for anti-infectives	(86)	(79)
RBC transfusions	(50)	(54)
Platelet transfusions	(20)	(21)
AE, adverse event; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide; RBC, red blood cell		

ERG comment

- The ERG considers the adverse effect profile to be broadly similar to that of HiDEX. However the slightly higher incidence of grade 3/4/serious adverse events attributed to pomalidomide is drawn to the attention of the committee.
- Although treatment-related death is slightly lower in the pomalidomide arm, attention is drawn to the three causes of death not related to infection.
- The ERG draws the attention of the committee to the events that occurred more frequently in the Pom+LoDEX group particularly grades 3/4 **(**neutropenia, febrile neutropenia, pneumonia, bone pain, decreased neutrophil count and leukopenia).
- The higher incidence of VTE and ATE in the Pom+LoDEX arm is also drawn to the attention of the committee.
- The attention of the committee is drawn to the need for dose interruptions more frequently with POM+LoDEX. The need for supporting treatment particularly for neutropenia is also highlighted.

4.2.6 Overview of the supporting RCTs

The three supporting RCTs of pomalidomide shown in the Table 4.2 were MM-002, IFM 2009-02 and Baz 2016.[32]

The CS described MM-002 as '*an open-label, randomised Phase I/II study assessing the maximum tolerated dose (MTD) of POM and the safety and efficacy of POM + LoDEX in patients who had received two or more previous therapies including BOR and LEN and who had progressed within 60 days of the most recent therapy.'*[32] The phase I part of the study determined the maximum tolerated dose of pomalidomide. In the phase II part '*221 patients (median of five previous therapies [range 1-13]), were randomised to POM + LoDEX (n=113) or POM (n=108)*', i.e. the study compared POM monotherapy versus POM+LoDEX.[3]

The IFM 2009-02 study compared two different regimens of POM+LoDEX in patients who '*had relapsed MM after at least one prior regimen of myeloma treatment*'[45] '*Patients were considered to be nonresponders to the last line of lenalidomide and to the last line of bortezomib—at least two cycles of either drug—if they did not achieve a response as per International Myeloma Working Group (IMWG)*

criteria'.[45] Eligible patients were randomised to either pomalidomide 4 mg given orally on the first 21 days of each 28-day cycle (arm 21/28, n = 43) or pomalidomide 4 mg daily for each day of the 28-day cycle (arm 28/28, n = 41). All patients in both arms received 40 mg dexamethasone once per week.[45]

Baz 2016 was a Phase II study comparing POM+LoDEX with POM+LoDEX+cyclophosphamide in patients with RRMM who '*had received ≥2 prior lines of therapies to include a prior immunomodulatory drug, and patients were required to be refractory to lenalidomide (defined as progressive disease during active therapy or within 60 days of discontinuation of therapy).*' The study included an initial phase I period to determine the maximal tolerated dose of cyclophosphamide. In the phase II study eligible patients were randomised to either pomalidomide 4 mg on days 1 to 21 of a 28-day cycle plus dexamethasone 40 mg weekly (n = 36) or to the same regimen combined with 400 mg oral cyclophosphamide on days 1, 8 and 15 of a 28-day cycle (n = 34).[44]

ERG comment: Individual patient data from the POM+LoDEX arm of the MM-002 study were included in the indirect comparisons on the basis that the company considered this study to be the most comparable to the available studies for bendamustine (see Section 4.3 and 4.4).

The IFM 2009-02 study could not be included in any analysis. Only one of the two treatment arms in this study was comparable to the POM+LoDEX regimen in the MM-003 and MM-002 studies. The POM+LoDEX 21/28 arm is equivalent to the treatment regimen in the other pomalidomide studies however the study population was patients who had relapsed MM after at least one prior regimen of myeloma therapy (second line treatment) whereas the final scope issued by NICE specified '*Adults with relapsed and refractory multiple myeloma who have had at least 2 prior treatment regimens'*.[30]

The study population in Baz 2016 differed from the population defined in that all patients had RRMM, had received ≥2 prior lines of treatment and were refractory to lenalidomide but only 75% were also refractory to bortezomib. In the appendices to the CS the company reported that Baz 2016 was excluded from the indirect comparisons on the grounds that it was a '*Small investigator led study with only 1 arm looking at the licensed dose (n≤50) – did not add additional information, no access to patient level data*' (See Table 16, Appendix 4 of the CS).[37] The arguments that the study was small and investigator led are not relevant as there is no inherent reason why small investigator led studies cannot provide relevant evidence. The ERG agrees that the lack of IPD prevents the inclusion of this study in the comparisons of POM+LoDEX with either bendamustine or with PANO+BOR+DEX as the methods for both comparisons rely on the availability of IPD for patients receiving POM+LoDEX (see Section 4.4).

4.2.7 Overview of non-RCT evidence and real world evidence

The nine non-RCTs mentioned in the CS[3] are listed in Table 4.17.

Table 4.17: Non-RCTs of pomalidomide

Study	Intervention	Population	Objectives
STRATUS trial (MM-010)[33]	POM (4mg) administered days 1-21 of a 28-day cycle with LoDEX 40mg/day (20mg for patients aged >75 years) on days 1, 8, 15, and 22 until PD or unacceptable toxicity	Patients with refractory or relapsed and refractory disease (PD on or within 60 days of last prior treatment), treatment failure with BOR and LEN, and adequate prior alkylator therapy	Phase IIIb, single arm, open-label study to evaluate the safety and efficacy of POM+LoDEX in RRMM
Lacy 2014[48]	Group A: POM 2mg for 28/28 day with oral DEX 40mg daily on days 1, 8, 15 and 22 Group B: POM 4mg for 28/28 day with oral DEX 40mg daily on days 1, 8, 15 and 22 Group C: POM 4mg for 21/28 days with oral DEX 40mg daily on days 1, 8, 15 and 22	LEN refractory, relapsed MM patients from 5 sequential phase 2 trials	Long term follow up of LEN refractory, relapsed MM patients from 5 sequential phase II trials to compare efficacy, tolerability and long term outcomes between cohorts treated with 2mg or 4mg daily continuously and 4mg daily for 21/28 days
MM-011[49]	POM 4mg orally on days 1-21, and LoDEX orally on days 1, 8, 15 and 22 of each 28-day cycle. LoDEX was given at 40 or 20mg in patients aged ≤75 or >75 years, respectively. Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent	RRMM patients who had received ≥ 2 prior therapies, including ≥ 2 cycles of LEN and ≥ 2 cycles of BOR (either separately or in combination) and had developed PD on or within 60 days of the last prior therapy	Phase II study to evaluate the efficacy and safety of POM+LoDEX in Japanese patients with RRMM
Jimenez-Zepeda 2014[50]	Oral POM 2-4mg/day on days 1-21, and DEX 20mg or 40mg on a weekly basis. Two patients received POM at a dose of 3mg, one received 2mg and 28 received 4mg doses.	Relapsed or refractory MM patients after two or more prior therapies (including LEN, BOR or THAL); and had an ECOG performance status of 0 to 2	Observational study to evaluate the efficacy of POM+DEX for heavily-pretreated RRMM patients at Tom Baker Cancer Center

Study	Intervention	Population	Objectives
IFM 2010-02[51]	POM 4mg orally daily on days 1 to 21 of each 28-day cycle along with DEX 40mg, given orally to all patients on days 1, 8, 15, and 22 of each cycle. The treatment was given until progression.	Relapsed/refractory MM following at least 1 prior regimen of myeloma treatment and prior exposure to LEN (minimum 2 cycles)	Phase II study to determine the efficacy and safety of POM+DEX in early relapsed/refractory MM patients with del(17p) and/or t(4;14)
Maciocia 2015[46]	All patients received POM (2-4mg day 1-21) /DEX. Median no of cycles was 4 (range 1-32), and median dose 4mg. In those with starting GFR <45ml/min, 50% (7/14) received <4mg.	Relapsed/refractory MM patients with measurable disease (IMWG criteria) who had received at least 1 cycle of POM+DEX	To assess the real-world clinical efficacy of POM+DEX in several large UK centres
MM-004[52]	Patients in Cohort 1 received a single dose of POM 0.5mg seven days before the start of cycle 1 for PK evaluation. Beginning on the first day of cycle 1, patients in Cohort 1 received 2mg POM orally on day 1 and days 3–21 of a 28-day cycle. The study was constructed based on a 3+3 design to determine the tolerated dose, based on two dose levels. Following identification of the tolerated dose, both cohorts proceeded to the treatment phase, which consisted of POM 2mg/day (Cohort 1) or 4 mg/day (Cohort 2) on days 1–21 of a 28-day cycle and DEX 40mg/day (for patients aged ≤75 years) or 20mg/day (for patients aged >75 years) on days 1, 8, 15, and 22 of a 28-day cycle. The median treatment duration was 6.1 months in Cohort 1.	Refractory or RRMM patients who had measurable disease (serum M-protein ≥0.5 g/dL or urine M-protein ≥200 mg/day) and were ineligible for SCT. All patients previously received ≥2 lines of antimyeloma therapy and had documented disease progression during or within 60 days of completing their last prior treatment. Prior therapy must have included ≥2 cycles of LEN and ≥2 cycles of BOR, as well as adequate alkylator therapy; induction therapy followed by SCT was counted as a single therapy. Patients were required to have an ECOG performance status of ≤2.	Phase I, open-label, dose-escalation study designed to determine the tolerated dose (recommended dose) of POM in Japanese patients with RRMM based on the observed maximum tolerated dose of POM (4mg) in the MM-002 trial and assess the safety, efficacy, and pharmacokinetic of POM alone or in combination with LoDEX.
Miles 2015[47]	POM was given with DEX as per licence until evidence of disease progression or unacceptable toxicity.	All patients had initially received LEN and BOR as prior treatment	Observational study to compare the 'real-world' POM outcomes across four UK

Study	Intervention	Population	Objectives
	The median number of POM cycles received was 4 (60% at standard 4mg dose). Importantly 5 patients received more than 15 cycles of POM with treatment ongoing at the end of the study period.		regional hospitals against data from the MM-003 trial.
Montes-Gaisan 2015[53]	Preapproval dose in the first 10 patients were 2mg in 5 patients and 4mg in other 5 patients (cycles 1-21/28) with DEX 40mg weekly.	Patients treated with POM from 2010 to 2015 (13 patients with refractory MM and 1 with PCL)	Observational study to analyse the effectiveness of POM in MM considering previous treatments, response rate, side effects, TTP and follow-up of the patients.

BOR, bortezomib; DEX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; GFR, glomerular filtration rate; IMWG, International Myeloma Working Group; LEN, lenalidomide; LoDEX, low-dose dexamethasone; MM, multiple myeloma; PCL, plasma cell leukaemia; PD, progressive disease; POM, pomalidomide; RCT, randomised controlled trial; RRMM, relapsed and refractory multiple myeloma; SCT, stem cell transplantation; THAL, thalidomide; TTP; time to progression

ERG comment: Of the nine non-RCTs one, MM-010, was used to inform the indirect comparisons and the economic model in addition to providing supporting efficacy and safety data.[33] We will focus our attention on this non-RCT only.

The CS described MM-010 as '*single-arm, open-label, European Phase IIIb study, which evaluated the safety and efficacy of POM+LoDEX in patients with RRMM.[33] Patients (≥18 years) were included if they were refractory to last prior therapy, had received ≥2 prior therapies (including ≥2 consecutive cycles of LEN and BOR, alone or in combination and adequate prior alkylator therapy) and had previous BOR and LEN treatment failure (defined as progressive disease on or within 60 days of treatment [refractory], progressive disease ≤ 6 months after achieving a PR [relapsed], or intolerance to BOR)*'[3]

The company also conducted a retrospective real world data collection project to compare BEN, BOR and POM+LoDEX at third line (Section 4.11.2 of the CS).[3]

The company's real world evidence (UK RWE) project was '*a retrospective real world data collection project on prescribing of BEN, BOR retreatment and POM+LoDEX at third line onwards with the aim of increasing the comparator evidence available to NICE.*'[3] The inclusion criteria for this study are summarised in Table 4.18 below.

Table 4.18: Inclusion/exclusion criteria for UK RWE

Inclusion criteria	Exclusion criteria
All patients must have received at least 2 prior treatments ≥ 2 consecutive cycles of LEN and BOR (alone or in combination) Adequate prior alkylator treatment (SCT or ≥6 cycles or PD after ≥2 cycles) All patients must have progressed on BOR and LEN All patient should have been prescribed and progressed on one of the following at 3rd line onwards BEN BOR (retreatment) POM+LoDEX	BEN+BOR (in combination) BEN or BOR retreatment patients who have received POM as part of the treatment pathway POM: any indication outside of the licensed indication
Source: Based on Table 36 of the CS[3] BEN, bendamustine; BOR, bortezomib; CS, company submission; LEN, lenalidomide; LoDEX, low-dose dexamethasone; PD, progressive disease; POM, pomalidomide; RWE, real world evidence; SCT, stem cell therapy; UK, United Kingdom	

The CS reported that UK RWE '*did not provide additional evidence to allow assessment of comparative effectiveness due to issues with data collection, which led to the outcomes collected not being sufficiently comparable to those available from the POM+LoDEX trials*'[3] The CS presented the following reasons why data from the UK RWE project were not comparable to data from the RWE studies'

- *Definition of progression being different across participating centres and poor input of information on serum-M protein preventing recalculation of PFS according to the IMWG criteria used in the POM+LoDEX trials – this lack of comparability of outcomes is immediately apparent when the PFS estimated for POM+LoDEX (8 months in the study) is compared to the outcomes from all other studies using IMWG criteria (approximately 4 months)*
- *Presence of crossover to POM: 17/58 patients on the BEN arm received subsequent POM, which is likely to confound OS outcomes*

- *Per protocol lack of collection of data from patients who did not complete treatment within the dataset: this eliminates responders with a durable response from data collection, which is most likely to bias against POM+LoDEX*
- *High levels of missing covariate data precluding the use of statistical techniques to adjust for the substantial differences in patients treated with POM+LoDEX and other therapies at the time*
- *Having spoken to the clinicians involved in data collection, it has been confirmed that the short PPS* [Post Progression Survival] *seen with POM+LoDEX and the limited amount of subsequent treatment given after POM+LoDEX in this dataset is not reflective of clinical practice, and indicates that the treatment has been used with palliative intent in many of the centres participating in data collection compared to treatment with BEN, which was used earlier in the treatment pathway with active intent. Clinicians stated that at the time POM+LoDEX became available on the CDF 'patients had been in a holding pattern waiting for POM to be made available.'*[3]

The characteristics of patients enrolled in UK RWE at the time of initiating third or later line treatment were reported in Table 37 of the CS. These data are reproduced in Table 4.19 below alongside the characteristics in a pooled dataset of patients from the MM-002 and MM-003 trials as reported in the Schey 2016 slide presentation of the UK RWE study provided with the references to the CS.[66]

Table 4.19: Patient characteristics in UK RWE study at initiation of third or later line treatment

Characteristic	POM+LoDEX (n=54)	BEN (n=58)	BOR (n=38)	POM + LoDEX from MM-002 + MM-003 (n=415)
Median age, years (range)	69 (47 - 84)	65 (46 - 76)	67 (39 - 86)	64 (34 -88)
Age category				
>70 yrs	24 (44.4)	14 (24.1)	11 (28.9)	105 (25.3)
>75 yrs	10 (18.5)	1 (1.7)	4 (10.5)	39 (9.4)
Median time from diagnosis, years (range)	5.1 (0.9 - 15.5)	4.8 (0.9 - 16.4)	4.5 (1.7 - 12.7)	5.3 (0.6 -30)
ISS stage, n (%)				
I	1 (1.9)	3 (5.2)	1 (2.6)	81 (19.5)
II	2 (3.7)	4 (6.9)	0 (0.0)	116 (28.0)
III	4 (7.4)	4 (6.9)	1 (2.6)	93 (22.4)
Missing	47 (87.0)	47 (81.0)	36 (94.7)	125 (30.1)
ECOG-PS, n (%)				
0	4 (7.4)	4 (6.9)	1 (2.6)	144 (34.7)
I	7 (13.0)	9 (15.5)	5 (13.2)	205 (49.4)
II	2 (3.7)	9 (15.5)	0 (0.0)	65 (15.7)
III	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)
IV	1 (1.9)	1 (1.7)	1 (2.6)	0 (0.0)
Missing	40 (74.1)	35 (60.3)	30 (78.9)	1 (0.2)

CrCL, n (%), < 60 ml/min	4 (7.4)	4 (6.9)	3 (7.9)	20 (4.8)
Cytogenetic risk, n (%): Missing	54 (100)	58 (100)	38 (100)	81 (19.5)
Median (range) number of previous treatments	4 (2 -9)	3 (2 -9)	3 (2 -7)	5 (2 -14)
Previous treatments				
DEX	54 (100)	58 (100)	38 (100)	415 (100)
THAL	44 (81.5)	43 (74.1)	30 (78.9)	250 (60.2)
LEN	54 (100)	58 (100)	38 (100)	415 (100)
BOR	54 (100)	58 (100)	38 (100)	415 (100)
BEN	12 (22)	0 (0)	5 (13)	71 (17)
Previous SCT, n (%)	35 (64.8)	30 (51.7)	23 (60.5)	298 (71.8)
Refractory to LEN*, n (%)	47 (87)	52 (89.7)	34 (89.5)	345 (83.1)
Refractory to BOR*, n (%)	37 (68.5)	36 (62.1)	12 (31.6)	282 (68)
Refractory to LEN & BOR*, n (%)	32 (59.3)	33 (56.9)	12 (31.6)	235 (56.6)

Source: Based on Table 37 of the CS[3] and slide 13 of Schey 2016[66]
*Refractory progressed on or within 60 days of treatment in real world clinical practice.
Key: BEN, bendamustine; BOR, bortezomib; DEX, dexamethasone; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; ISS, International Staging System; LEN, lenalidomide; POM+LoDEX, pomalidomide plus low-dose dexamethasone; SCT, stem cell transplant; T0, time when treatment of interest was initiated; THAL, thalidomide.

The results for patients in the UK RWE study are summarised in Table 4.20 compared to a pooled analysis of data from the MM-002 and MM-003 pomalidomide RCTs.[66]

Table 4.20: PFS, PPS and OS results from the UK RWE study

	BEN in UK RWE (n=58)	**BOR in UK RWE (n=38)**	**POM + LoDEX in UK RWE (n=54)**	**POM + LoDEX in MM-002 + MM-003 (n=415)**
Progression-free survival				
No. of Events	47	33	36	352
Median PFS in months (95% CI)	5.5 (3.8 to 7.3)	6.3 (4.6 to 8.4)	8.0 (4.3 to 13.2)	4.0 (3.7 to 4.7)
Post progression survival				
No. of Events	31	23	25	199
Median PPS in months (95% CI)	8.1 (7.5 to 20.4)	6.9 (3.4 to 18.0)	2.9 (2.2 to 6.4)	8.8 (7.2 to 10.9)
Overall Survival				
No. of Events	41	27	36	273
Median OS in months (95% CI)	13.2 (9.0 to 24.2)	14.4 (9.3 to 24.8)	8.6 (6.5 to 17.6)	13.6 (12.4 to 16.2)

Source: Based on slides 16-18 of Schey 2016[66]
BEN, bendamustine combination chemotherapy; BOR, bortezomib combination chemotherapy; CI, confidence interval; PFS, progression-free survival; POM, pomalidomide; PPS, post-progression survival

ERG comment: Individual patient data from the MM-010 were included in the indirect comparisons on the basis that '*the full trial dataset (MM-002, MM-003 and MM-010) was most comparable to the*

data for PANO+BOR+DEX'.[3] This study is discussed in more detail in Sections 4.3 and 4.4 in the context of the indirect comparisons.

The ERG agrees that the data from the UK RWE study are not comparable to the data from the pomalidomide RCTs and therefore could not be used to provide additional evidence for the comparator treatments. The differences in the definition disease progression alone could be considered sufficient reason not to combine these data. There were also differences in the patient population between the POM+LoDEX group and the both the BOR and BEN groups in UK RWE. The POM+LoDEX group included a higher proportion of older patients and had received more previous lines of therapy compared to both the BOR and BEN groups. The POM+LoDEX group included 44.4% of patients >70 years old and 18.5% of patients >75 years old. In the BEN group there were 24.1% of patients > 70 years old and 1.7% of patients >75 years old. In the BOR group there were 28.9% of patients >70 years old and >10.5% of patients >75 years old. The patients in the POM+LoDEX group had received a median of four previous lines of therapy (range, 2 to 9). Patients in the BEN group had received a median of three previous lines (range, 2 to 9) and patients in the BOR group also had a median of three previous lines (2-7).

The observation that patients receiving BEN or BOR based treatment could then receive POM after disease progression whereas patients who initially received POM did not have this option could lead to patients in the BEN or BOR groups surviving longer after progression. This may partially explain the short PPS time seen in the POM+LoDEX group.

It should be noted that the outcomes for patients receiving POM+LoDEX in UK RWE differ from those receiving POM+LoDEX in the pooled analysis of MM-002 and MM-003. However these differences are likely to be attributable to the differences in study design and data collection between UK RWE and MM-002/MM-003.

The methods used to compare POM+LoDEX to the other comparators depend on the availability of data on key prognostic factors to adjust for differences between studies in patient characteristics and study design (see Section 4.4). The ERG agrees that the high proportion of patients in UK RWE with missing data for key prognostic factors would severely limit any analysis based on these data.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company did not report any indirect comparison or multiple treatment comparison. The selection of studies for inclusion in the quantitative analysis was based on '*study size (only studies with >50 patients were considered given the large body of evidence available), study population (studies analysing comorbidity subgroups were not considered), generalisability and comparability to comparator studies and availability of patient level data for analysis*'.

Bendamustine

The CS states that '*The systematic review did not identify any comparator RCTs allowing the formation of a traditional network meta-analysis*'.[3] The systematic review identified one RCT (MUK-one) that compared 60 mg/m^2 bendamustine with 100 mg/m^2 bendamustine in patients with RRMM. All patients in both arms of MUK-one received oral thalidomide 100 mg on days 1-28 and oral dexamethasone 20 mg on days 1, 8, 15 and 22 of each 28 day cycle.[67] The company also included data from a subset of RRMM patients in the Gooding study who were refractory to both bortezomib and lenalidomide and who had received bendamustine+thalidomide+dexamethasone (BTD).[68] Furthermore, data were included from the Tarant study in patients who had progressive disease or were intolerant after having sequentially received thalidomide based, bortezomib based and lenalidomide based combination therapy.[69]

Individual patient data (IPD) were obtained from each of the MUK-one, Gooding and Tarant studies. Patient data were selected for inclusion in the analysis if they had received bendamustine based treatment, were refractory to prior bortezomib and lenalidomide and reported data for all of a set of key prognostic factors (Section 4.10.2 of the CS).[3] The procedure for selecting a set of prognostic factors and the final set are discussion in Section 4.4. The final number of patients included in the analysis and the characteristics of those patients are summarised in Table 4.21 below alongside the corresponding data from the three POM+LoDEX studies. The CS reports that '*A total of 191 patients were included in the base case analysis (113 POM+LoDEX, 78 BEN), arising from four separate data sources.*'[3]

Table 4.21: Baseline characteristics of patients in bendamustine and POM+LoDEX studies

Study	Treatment	N	Age, mean (SD)	Number of prior lines of therapy mean (SD)	Receipt of prior THAL (% yes)	Refractory to LEN (% yes)	Previous SCT (% yes)	Disease duration (years), mean (SD)	ISS stage (%) (1, 2, 3, NR)
Tarant	BEN	4	57.5 (12.6)	3.5 (0.6)	50.0	25.0	75.0	8.3 (3.6)	50.0, 25.0, 0.0, 25.0
MUK-One	BEN	57	63.4 (8.7)	3.8 (0.8)	100.0	24.6	71.4 [N=56]	6.4 (3.3) [N=56]	26.3, 29.8, 42.1, 1.8
Gooding	BEN	17	63.6 (8.3)	3.9 (0.8)	88.2	17.6	58.8	4.3 (2.1) [N=15]	0, 0, 0, 100
MM-010	POM+LoDEX	682	65.4 (9.1)	4.9 (2.1)	54.5	95.9	66.1	6.2 (3.6)	21.4, 39.3, 34.6, 4.7
MM-002	POM+LoDEX	113	64.4 (9.2)	5.6 (2.4)	68.1	77.9	74.3	6.2 (3.6)	0, 0, 0, 100
MM-003	POM+LoDEX	302	63.6 (9.3)	5.1 (2.0)	57.3	94.7	70.9	6.2 (4.0)	26.8, 38.4, 30.8, 4.0

Source: Based on Table 31 of the CS[3]

BEN, bendamustine; ISS, International Staging System; LEN, lenalidomide; LoDEX, low-dose dexamethasone; MM, multiple myeloma; NR, not reported; POM, pomalidomide; SCT, stem cell transplantation; SD, standard deviation; THAL, thalidomide

ERG comment: The MUK-one contributed 57 of the 78 bendamustine treated patients therefore this study is likely to have the largest impact in the analysis (see Section 4.4). In comparison, the Tarant study reported a lower proportion of patients who had received prior thalidomide (50%) and a higher proportion patients at ISS stage 1 (50%) relative to MUK-one (100% and 26.3% respectively) however given that the Tarant study contributed only four patients this unlikely to significantly influence the results. The Gooding study had a lower proportion of patients who had received previous SCT (58.8%) and patients had a shorter duration of disease (4.3 years, SD=2.1) compared to the MUK-one study (71.4% and 6.4 years, SD = 3.3 respectively).

All three bendamustine studies had a lower percentage of patients who were refractory to lenalidomide compared to studies of POM+LoDEX. The proportions of patients who were refractory to lenalidomide were 25% in Tarant, 24.6% in MUK-one and 17.6% in Gooding. This compares to 95.9% in MM-010, 77.9% in MM-002 and 94.7% in MM-003 (see Table 4.22). There was also a difference in the number of prior lines of therapy between bendamustine studies and POM+LoDEX studies. In the bendamustine studies the mean (SD) number of prior lines of therapy were 3.5 (SD = 0.6) in Tarant, 3.8 (SD = 0.8) in MUK-one and 3.9 (SD = 0.8) in Gooding. This compares to 4.9 (SD = 2.1) in MM-010, 5.6 (SD = 2.4) in MM-002 and 5.1 (SD = 2.0).

The licensed indication for pomalidomide requires that patients have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy. Given the difference in the number of prior lines of therapy and the low proportion of lenalidomide refractory patients in the bendamustine studies it is unclear that the patients in the bendamustine studies are comparable to those in the POM+LoDEX studies. The ERG recognises that there is a lack of available data in this area and that these data may be the best available evidence despite the limitations.

Panobinostat

The systematic review did not identify any relevant RCTs and only one non-randomised study reported information suitable for inclusion in quantitative analysis.[3] The CS states that '*The PANORAMA 2 trial of PANO+BOR+DEX was identified as the most relevant and comparable study to trials of POM+LoDEX based on similar but not identical patient characteristics. Patients in this trial are most comparable to those within the trials for POM+LoDEX, all patients have received prior BOR and the vast majority (94%) of patients have also received prior LEN, additionally all patients are refractory to prior BOR. There are, however, still differences in the patient populations included; in particular the number of prior lines of treatment received (median 4 lines vs. 5 lines in the POM+LoDEX trials) and lack of reporting of refractoriness to LEN, which limit the ability to make a valid comparison*'[3]

The PANORAMA-2 study was a '*two-stage, single-arm, open-label multicentre study of oral panobinostat in combination with bortezomib and dexamethasone*' in '*adult patients>18 years of age with relapsed and bortezomib-refractory MM (progressed on or within 60 days of the last bortezomib-containing regimen) who had received at least 2 prior lines of therapy and had been exposed to an IMiD* [immunomodulatory drug]'. In stage 1 patients received '*8 three-week cycles of oral panobinostat (20 mg) 3 times per week on weeks 1 and 2, bortezomib (1.3 mg/m^2 intravenously) 2 times per week on weeks 1 and 2, and oral dexamethasone (20 mg) 4 times per week on weeks 1 and 2 on days of and after bortezomib use*.' In stage 2 '*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; and dexamethasone on the days of and after bortezomib*'[70] The baseline characteristics of the patients in the PANORAMA-2 study are summarised in Table 4.22 alongside the characteristics of the pooled dataset from the POM+LoDEX studies.

The CS also notes that '*The PANORAMA 1 trial[71] which forms the main basis of the PANO+BOR+DEX submission to NICE (TA380), was not identified within the SLR as this represents a much less advanced patient population (as evidenced by the inclusion of LEN as a NICE comparator): only 19% of patients had received prior LEN in the study, and in the licensed subgroup (≥2 prior regimens including BOR and an IMiD) reporting for patients receiving prior IMiD still fails to meet the inclusion criteria for the SLR (86% of patients had received prior THAL versus 38% receiving prior LEN). There is a high likelihood of confounding of OS results from use of subsequent LEN in this trial within a patient population who have not received, let alone become refractory to, this treatment, which rules out use of this study when comparing to the POM+LoDEX trials*'[3]

Table 4.22: Comparison of baseline characteristics between the pooled trial dataset for POM+LoDEX (pomalidomide arm) and PANORAMA-2 (panobinostat arm)

	Panobinostat (PANORAMA-2)	Pomalidomide Combined MM-002, MM-003 and MM-010 datasets (subgroup refractory to bortezomib but not primary refractory)
N	55	886
Age: Median (range)	61 (41-88)	66 (34-88)
ECOG (%) 0 1 2 3	 47.3 (26/55) 45.5 (25/55) 7.3 (4/55) 0 (0)	 40.1 47.0 12.9 0.1
ISS stage (%) 1 2 3 Missing	 33.3 (18/54) 42.6 (23/54) 24.1 (13/54) 1/55	MM-003 and MM-010*: 23.5 (373/1588) 41.0 (651/1588) 35.5 (564/1588) 78/1666
Prior lines of therapy Median (range)	 4 (2-11)	 5 (2-18)
Prior thalidomide therapy (%)	69.1	56.9
Refractory to bortezomib (%)	100	100

Source: Based on Table 32 of the CS[3]
Note: * Not reported in MM-002
ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; POM, pomalidomide, LoDex, low-dose dexamethasone, MM, multiple myeloma.

ERG comment: The exclusion of the PANORAMA-1 study appears reasonable given the low percentage of patients who had received prior lenalidomide in this study (19%). In order to be eligible to receive pomalidomide patients are required to be refractory to both bortezomib and lenalidomide. Since 81% of patients in PANORAMA-1 had not received lenalidomide these patients would not be considered comparable to patients who are eligible to receive pomalidomide.

The patients in the PANORAMA-2 study appear to meet the eligibility criteria to receive pomalidomide and PANORAMA-2 provides the best available evidence to inform the comparison of pomalidomide

and panobinostat although there are limitations. The ERG agrees that there is a key difference between the PANORAMA-2 study and the pomalidomide studies in terms of the number of lines of prior therapy. Patients in the PANORAMA-2 study had received one fewer prior lines of therapy on average than those in the pomalidomide studies. Patients in the PANORAMA-2 study had received a median of four (range 2-11) previous lines of therapy compared to median=5 (range 2-18) in MM-003, median=5 (range 2-13) in MM-002[32] and median=5 (2-18) in MM-010.[33] The patients in the PANORAMA-2 study were clearly defined as being refractory to bortezomib and the CS states '*the vast majority (94%) of patients have also received prior LEN'*.[3] The main publication of the PANORAMA-2 study reports that '*All except 1 patient had received prior lenalidomide (n = 54; 98.2%)'*.[70] The difference between 94% and 98.2% in a sample of 54 patients corresponds to three patients. The more relevant point is that although most patients had received lenalidomide it is not clear whether these patients were refractory to lenalidomide.

Conventional chemotherapy

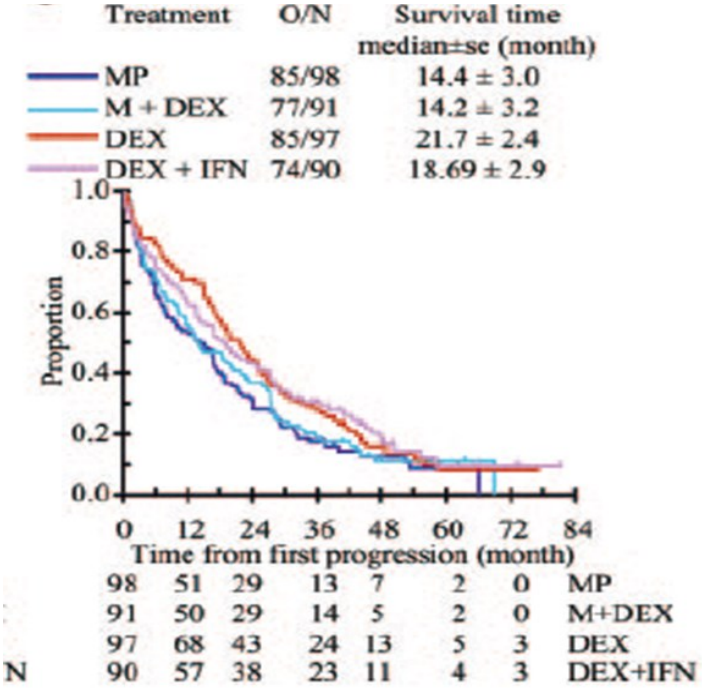
In Section 4.10.4 the CS states that '*Although three studies were identified from the original SLR of clinical evidence presenting data on conventional chemotherapy in patients with RRMM, none of these studies have been included in the submission nor can be used to inform a statistical comparison. As stated above, the reason for this is that they are conducted in patient populations not comparable to the population in MM-003.*

However, HiDEX data can be used as a proxy for other conventional chemotherapy regimens. In using HiDEX as a proxy, we can assume that the efficacy and safety results observed in the MM-003 study for POM+LoDEX versus HiDEX are equivalent for all conventional chemotherapy regimens. This is considered reasonable as patients on the HiDEX arm of the MM-003 trial receive HiDEX for only a short time period (TTF = 1.8 months) with the majority (60.1%) of patients going on to receive subsequent alternative active treatment'[3]

The company further argued that '*HiDEX was adopted as the control arm as it represented a standard anti-myeloma therapy for the treatment of subjects with relapsed or refractory disease at the time the trials were initiated*.'[3]

The company reported evidence from the IFM 95-01 study to demonstrate the similarity in patient outcomes between HiDEX and conventional chemotherapy regimens.[36] This study was conducted in first line patients. The company justified this on the grounds that '*this represents the only study available comparing outcomes in patients receiving conventional chemotherapy compared with HiDEX'*[3] In the IFM 95-01 study patients were randomised to one of four chemotherapy regimens. The MP regimen was 12 6-week cycles of melphalan (0.25 mg/kg) and prednisone (2 mg/kg) which were given orally for four days. The DEX regimen was 12 6-week cycles of dexamethasone, 40 mg/d, for four days beginning on days 1, 9, and 17 for the first 2 cycles and 40 mg/d for four days beginning on day 1 for the next 10 cycles. The M-DEX regimen was 12 6-week cycles of melphalan (0.25 mg/kg) given orally for four days combined with dexamethasone, 40 mg/d, for four days beginning on days 1, 9, and 17 for the first two cycles and 40 mg/d for four days beginning on day 1 for the next 10 cycles. The DEX-IFN regimen was IFN alpha-2b administered subcutaneously at 3.0 MU three times weekly. Treatment was started alongside dexamethasone as discontinued on day 42 of the last dexamethasone cycle. The dexamethasone component was delivered as for the DEX regimen above. The company reproduced results from the IFM 95-01 study showing overall survival form the time of first progression in Figure 26 of the CS which is presented below (Figure 4.2).

Figure 4.2: Overall survival from the time of first progression in the IFN 95-01 study



Source: Based on Figure 26 of the CS[3] which was reproduced from Facon 2006[36]

The IFM 95-01 study also reported results for overall survival and progression free survival both measured from the time entry to the trial. These results are summarised in Table 4.23 below.

Table 4.23: OS and PFS for HiDEX compared to conventional chemotherapy in the IFM 95-01 study

	Progression free survival from time of entry		Overall Survival from time of entry	
Treatment	**Number of events/Total**	**Survival time in months, median (SE)**	**Number of events/Total**	**Survival time in months, median (SE)**
MP	120/122	21.1 (1.7)	106/122	34.0 (3.6)
M + DEX	112/118	22.9 (2.0)	97/118	39.6 (3.1)
DEX	123/127	12.2 (1.0)	110/127	33.4 (2.0)
DEX + IFN	118/121	15.2 (2.7)	102/121	32.0 (5.3)
Source: Figure 1 of Facon 2006[36] DEX = dexamethasone; M = melphalan; MP = melphalan + prednisone; IFN = interferon alpha 2b, SE = standard error				

ERG comment: The results presented in Figure 26 of the CS (Figure 4.2 above) actually report overall survival time after the first disease progression in first line patients in the IFM 95-01 study.[3] These results show that OS after first progression is similar but not identical for patients receiving DEX compared to other conventional chemotherapy regimens. Patients receiving DEX in the IFM 95-01 study had a median OS from the time of first progression of 21.7 months (SE=2.4) compared to 14.4 months (SE=3.0) for MP, 14.2 months (SE=3.2) for M + DEX and 18.69 months (SE=2.9).

When OS in the IFM 95-01 study was measured from time of study entry the median OS for patients receiving DEX (33.4 months, SE=2.0) was similar to the median OS for patients receiving MP

(34.0 months, SE=3.6), M+DEX (39.6 months, SE=3.1) or DEX + IFN (32.0 months, SE=5.3). The results of the IFM 95-01 study for PFS measured from time of entry to the study showed that patients receiving DEX had a shorter median time to progression (12.2 months, SE=1.0) compared to patients receiving DEX + IFN (15.2 months, SE=2.7), MP (21.1 months, SE=1.7) or M + DEX (22.9 months, SE=2.0).

In combination these results suggest that patients receiving DEX have a shorter time to progression but survive longer after first progression than patients on other conventional chemotherapy regimens. This may introduce different biases in PFS results and OS results respectively. Patients receiving DEX have a shorter time to progression than patients on other chemotherapy regimens therefore 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, assuming that POM+LoDEX increases time to disease progression. In contrast, OS measured from time of study entry was similar for patients receiving DEX compared to other conventional chemotherapy regimens. As a result the HiDEX arm of the MM-003 study may be a reasonable proxy for conventional chemotherapy when assessing OS but may bias the comparison in favour of POM+LoDEX when assessing PFS.

It should be emphasised that these results are based on a study of patients receiving first line treatment. These results may not be applicable to the patient population defined in the scope for this appraisal[30] however the ERG recognises the company's argument that this study represents the only available evidence comparing high dose dexamethasone. The uncertainty in this area is compounded by the lack of an agreed definition for what constitutes 'conventional chemotherapy'.

The comparison of POM+LoDEX with conventional chemotherapy may be of lower importance in clinical practice. The clinical expert statement submitted on behalf of UK Myeloma Forum /Guys and St. Thomas' NHS Foundation Trust states that '*Cyclophosphamide, melphalan, high dose dexamethasone and thalidomide would generally be considered as a palliative approach rather than an active approach (in comparison to the treatments outlined above). These are NOT appropriate comparators. There is no evidence to support these agents at this stage of therapy in the modern era of myeloma therapy (other than as palliative treatments).*'[2]

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The limitations of the available studies precluded a conventional mixed treatment comparison (MTC) or indirect meta-analysis. There were no studies that directly compared POM+LoDEX with either bendamustine or PANO+BOR+DEX. Furthermore, there were no studies that could provide a common comparator to support indirect comparison or MTC.

ERG comment: The available evidence did not support a comparison of POM+LoDEX with bendamustine and with PANO+BOR+DEX in the same analysis. As a consequence the company selected individual treatment arms from the available studies and performed separate analyses comparing POM+LoDEX to each of the comparators independently. In other words, there was no evidence from randomised studies to support these comparisons therefore the company presented evidence based on comparisons of observational data. There were three main analyses:

1. Comparison of individual patient data (IPD) from the POM+LoDEX arms of the MM-003, MM-002 and MM-010 studies with IPD from the MUK-One, Gooding and Tarant studies of bendamustine using regression models to adjust for factors thought to be prognostic of OS and PFS. This is described in the CS as an indirect comparison however in practice this is equivalent to a direct comparison between two sets of observational studies. The randomisation of the RCTs is broken by selecting single treatment arms. There is no common comparator to link the two sets of studies which would make this an indirect comparison.

2. Comparison of IPD from the POM+LoDEX arms of the MM-003, MM-002 and MM-010 studies with aggregate data from the single-arm PANORAMA-2 study of PANO+BOR+DEX using matching adjusted indirect comparison (MAIC) to adjust for adjust for factors thought to be prognostic of OS and PFS. As above this amounts to a direct comparison between two sets of observational studies
3. Comparison of POM+LoDEX with HiDEX based on the MM-003 trial. In the CS the company argue that HiDEX can be used as a proxy for conventional chemotherapy. The evidence base for this assumption is discussed in Section 4.3. The results of the MM-003 trial are described in Section 4.2.

The details of these analyses are described below. The ERG recognises that although the evidence supporting the comparisons with bendamustine and with PANO+BOR+DEX is limited this is likely to be the best that could be achieved given the available studies.

4.4.1 Selection of studies for statistical analysis – POM+LoDEX

The CS stated that '*the decision whether to include or exclude studies for POM+LoDEX from quantitative analysis of comparative effectiveness was taken on the basis of study size (only studies with >50 patients were considered given the large body of evidence available), study population (studies analysing comorbidity subgroups were not considered), generalisability and comparability to comparator studies and availability of patient level data for analysis. Based on these criteria, three studies were considered for inclusion in analyses: the MM-003 Phase III trial, the MM-002 Phase II trial and the MM-010 Phase IIIb trial.*'[3] The MM-003 and MM-002 studies are described in section 4.2. The MM-010 study was '*an open-label, single-arm phase 3b study undertaken at 91 centers in 19 countries across Europe*'.[33] In the MM-010 study '*Patients were administered pomalidomide 4 mg on days 1-21 of a 28-day cycle. Patients also received low-dose dexamethasone 40 mg (if aged ≤ 75 years old) or 20 mg (if aged > 75 years old) on days 1, 8, 15, and 22 of a 28-day cycle*'.[33]

According to the CS the dataset for each analysis was selected '*based upon comparability with the available comparator datasets. The MM-002 Phase II trial represented the trial that was the most comparable to available comparator studies for BEN, whereas the full trial dataset (MM-002, MM-003 and MM-010) was most comparable to the data for PANO+BOR+DEX. The comparison to the pooled dataset of all three studies (MM-002, MM-003 and MM-010) is also presented as sensitivity analysis for comparison to BEN.'*[3]

4.4.2 Comparison of POM+LoDEX and bendamustine

The CS states that '*The systematic review did not identify any comparator RCTs allowing the formation of a traditional network meta-analysis: no RCTs have been run in this setting by any of the therapies listed within the NICE decision problem except for the MUK-one trial, which compared two doses of BEN.*'

The company obtained patient level trial data from the MUK-one study which compared 60 mg/m^2 bendamustine with 100 mg/m^2 bendamustine in patients with RRMM. All patients in both arms received oral thalidomide 100 mg on days 1-28 and oral dexamethasone 20 mg on days 1, 8, 15 and 22 of each 28 day cycle.[67] These data were supplemented by patient level data on 14 patients from the Gooding and Tarant datasets.[68, 69] Based on these data the company constructed a series of covariate adjusted IPD regression models to compare the relative effects of POM+LoDEX and bendamustine.

4.4.3 Selection of covariates

The CS reports that prognostic factors to be considered as potential covariates in the regression model were identified based on three sources of information:

- *'A SLR of prognostic factors in RRMM*
- *Consultation with clinical experts at a recent advisory board to gain their insight into which factors they expected to influence prognosis for patients at this line of therapy*
- *Covariates included in the analysis submitted in TA338 (determined via a review of prognostic factors within the MM-003 trial and clinical input derived as part of the original submission)'*[3]

A summary of all prognostic factors considered for inclusion was provided in Table 29 of the CS. In response to a request for clarification for the ERG this table was updated and further details of the selection procedure were provided. The updated table is reported as Table 4.24 below. Covariates for which the multicollinearity column is blank in Table 4.24 were not captured in the bendamustine studies and therefore could not be included in the analysis.[38] In response to the clarification letter the company stated that '*availability of the data was assessed first, correlation was assessed in the second instance, and then clinical rationale was used in order to select the final set of covariates*'.[38] Correlation between prognostic factors was assessed using Pearson's product moment correlation coefficients. For those covariates that showed evidence of statistically significant correlation clinical rationale was used to select which covariates to include in the final model. The correlation coefficients and p-values from this assessment are reported in Table 4.25 below.

There was evidence of correlation between treatment arm and number of prior lines of therapy, receipt of prior thalidomide and refractory to LEN however all three covariates were retained in the final *'as it was believed that these were all clinically important/relevant prognostic factors and the values of Pearson's product moment correlation coefficients were not too high (correlation=-0.18 and correlation=0.21 respectively).'*[38] There was evidence of statistically significant correlation between prior stem cell therapy (SCT) and age. In the response to clarification the company stated that '*Due to statistically significant correlation between prior SCT and age, together with clinical consideration of the two covariates, prior SCT was not included in the statistical model.*'[38] There was also evidence of correlation between disease duration and number of prior lines of therapy. The company stated '*due to the significant correlation between disease duration and number of prior lines of therapy, together with clinical consideration of the two covariates, disease duration was not included in the statistical model.'*[38]

Table 4.24: Prognostic factor selection

Covariate	Identified as influential on median survival time in prognostic factor SLR?		Included in TA338?	Identified as relevant by clinicians?	Issues with multicollinearity?	Data availability
	OS (reports/ significance)	PFS (reports/ significance)				
Treatment arm	N/A	N/A	Current care = 1	Y	N	All
Age at start of treatment	11 / 5	11 / 2	Y	Y	Correlated with prior SCT (Pearson's PMCC=-0.47)	All
Disease duration (time since diagnosis)	4 / 2	2 / 2	Y	N	Correlated with no of prior lines (Pearson's PMCC=0.43)	All
Prior lines of therapy	7 / 3	8 / 5	N	Y	Correlated with disease duration (Pearson's PMCC=0.43)	All
ISS stage	10 / 3	9 / 0	Y	Y	N	MM003, MM010, Tarant, MUK-one
Prior THAL	7 / 2	4 / 1	Y	Y	N	All
Prior SCT	9 / 2	10 / 0	Y	N	Correlated with age (Pearson's PMCC=-0.47)	All
Refractory to LEN	9 / 6 [a]	3 / 2 [a]	Y	Y	N	All
Refractory to BOR			Y	Y	N	MM003, MM010, MM002, Tarant, Gooding
ECOG status at start of treatment	4 / 3	2 / 0	N	Y	-	MM003, MM010, MM002
Creatinine clearance at start of treatment	NR, 5 /2 for renal function	8 / 1	N	Y	-	MM003, MM010, MM002
Cytogenetics (note difference categorisations used across papers)	19 / 9	18 / 13	N	N[b]	-	MM003, MM010, MM002

Covariate	Identified as influential on median survival time in prognostic factor SLR?		Included in TA338?	Identified as relevant by clinicians?	Issues with multicollinearity?	Data availability
	OS (reports/ significance)	PFS (reports/ significance)				
Disease history (extramedullary manifestations and osteolytic lesions)	2 / 0	NR	N	N		NR
Sex	7 / 2	8 / 1	N	N		All
Durie-Salmon Stage	3 / 1	2 / 1	N	N		MM003, MM010, MM002
Haemoglobin	6 / 4	3 / 1	N	N		MM003, MM010, MM002
LDH	8 / 6	3 / 1	N	N		MM003, MM010, MM002
Paraprotein class	8 / 0	7 / 0	N	N		MM003, MM010, MM002
Platelets	4 / 3	1 / 0	N	N		MM003, MM010, MM002
Beta 2 microglobulin	6 / 5	2 / 2	N	N		MM003, MM010, MM002
Albumin	NR	2 / 1	N	N		MM003, MM010, MM002
Light chain type	3 / 1	2 / 1	N	N		MM003, MM010, MM002

Source: Table 7 of the response to request for clarification[38]
Notes: a refractoriness / type relapse or progression, b Clinicians stated non informative and not used at this stage of disease.
Colour code used for prognostic SLR: Green: ≥5 reports and >50% were significant, Yellow: Either ≥5 reports or >50% of reports were significant, Orange: Neither of the above.
BOR, bortezomib; Pearson's PMCC, Pearson's Product Moment Correlation Coefficient; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; LDH, lactate dehydrogenase; LEN, lenalidomide; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival; SCT, stem cell transplantation; SLR, systematic literature review; TA, technical appraisal; THAL, thalidomide.

Table 4.25: Assessment of multicollinearity between prognostic factors

	Arm	Age	Prior lines of therapy	Receipt of prior THAL	Refractory to LEN	Prior SCT	Disease duration
Arm	NA						
Age	PMCC = 0.05 p=0.524	NA					
Prior lines of therapy	**PMCC =0.42** **p<0.001**	PMCC = -0.07 p=0.323	NA				
Receipt of prior THAL	**PMCC = -0.32** **p<0.001**	PMCC = -0.06 p=0.443	PMCC = 0.09 p=0.244	NA			
Refractory to LEN	**PMCC = 0.55** **p<0.001**	PMCC = 0.06 p=0.384	**PMCC = 0.21** **p=0.004**	**PMCC = -0.18** **p=0.015**	NA		
Prior SCT	PMCC = 0.06 p=0.422	**PMCC = -0.47** **p<0.001**	PMCC = 0.06 p=0.402	PMCC = 0 p=0.961	PMCC = 0.05 p=0.531	NA	
Disease duration	PMCC = 0.03 p=0.702	PMCC = -0.05 p=0.464	**PMCC = 0.43** **p<0.001**	PMCC = 0.14 p=0.056	PMCC = -0.03 p=0.713	**PMCC = 0.15** **p=0.046**	NA

Source: Based on Figure 5 in Appendix 12 of the CS[37] and Table 6 in the response to clarification[38]
Note: Bold denotes statistical significance at the 5% level
LEN, lenalidomide; NA, not applicable; PMCC, Pearson's product moment correlation coefficient; SCT, stem cell transplantation; THAL, thalidomide

Following this selection process the CS reported that the following covariates were included in the final analysis:

- *'Treatment arm [POM+LoDEX/BEN]*
- *Age at the start of treatment [continuous]*
- *Number of prior lines of therapy [continuous]*
- *Receipt of prior THAL [Yes/No]*
- *Refractory to LEN [Yes/No]*
- *ISS stage [1/2/3]'*[3]

In the original CS, the company reported that only covariates where data were available for at least 50% of patients were included in the analysis however in response to a request for clarification by the ERG the company stated that '*all covariates of interest were either well reported within each dataset with low levels of missing information or were entirely missing (i.e. not collected).*'[38]

ERG comment: The ERG initially questioned the procedure for covariate selection as reported in the CS. Based on the additional detail supplied in the clarification response the ERG is satisfied that the approach to covariate selection was reasonable.

Selection of study data

For the base case analysis the company selected only the POM+LoDEX arm of the MM-002 study as the data source for pomalidomide. According to the CS this decision was based on '*the lower levels of refractoriness exhibited within this trial (78%) compared to the remainder of the POM+LoDEX data (95%). This lower level of refractoriness was considered more comparable to the BEN data (18-25%) across sources. As this covariate was identified as most prognostically important by clinicians and is difficult to adjust for with the current datasets (given that the overlap between datasets is low) it was considered more important to select the more comparable dataset for analysis than to retain the maximum number of patients for analysis in the POM+LoDEX arm*'[3] A sensitivity analysis including data from all three POM+LoDEX studies (MM-002, MM-003, MM-010) was also reported to assess the impact of this decision (Sensitivity analysis 1). ISS stage was considered to be influential predictor of survival however this variable was not measured in all relevant studies. The company reported two additional sensitivity analyses either including ISS stage for those studies that reported it or excluding ISS stage entirely (Sensitivity analysis 2 and 3).

In Section 4.10.2 of the CS the company stated that '*Patients with missing data for any of the clinically-relevant prognostic factors were not included in the analyses'*[3] In response to an ERG request for clarification the reported that there were no patients with missing covariate data in either the base case or in sensitivity analysis 1.[38] The company also provided the following explanation of missing data is sensitivity analyses 2 and 3:

- *'Sensitivity analysis 2 – Tarant (n=1), MUK-One (n=1), Gooding (n=17), MM003 (n=12), MM002 (n=113), MM010 (n=32) – all missing data are due to lack of recorded ISS stage. Since this prognostic factor is missing at the study level for Gooding and MM002, these studies were not included in this sensitivity analysis.*
- *Sensitivity analysis 3 – no missing covariate data as the data set matches that used in sensitivity analysis 2 but ISS stage is not included in the analysis.'*[38]

ERG comment: The ERG initially questioned the rationale for including only patients with complete covariate data in the analysis. The additional detail supplied in the clarification response showed that this selection had no impact on the base case or the key sensitivity analysis pooling data from all POM+LoDEX studies.

Results

The company used covariate adjusted Cox proportional hazards regression to adjust for the differences between studies based on the set of covariates selected above. The company reported results for OS and PFS comparing POM+LoDEX in the base case and in three sensitivity analyses as described above. The results of these analyses are summarised in Table 4.26 below. For the base case and sensitivity analysis 1 the company reported adjusted and unadjusted results for both OS and PFS. For sensitivity analyses 2 and 3 only adjusted hazard ratios were reported.

In the base case analysis covariate adjustment had little impact on the relative effect of POM+LoDEX compared to BTD on OS. The unadjusted hazard ratio was 0.55 (95% CI 0.38 to 0.81) compared to 0.58 (95% CI 0.36 to 0.94) in the covariate adjusted analysis. The median OS for patients receiving POM+LoDEX was 16.5 months (95% CI 12.6 to 19.8) in the unadjusted analysis and 16.6 months (95% CI 12.6 to 21.3) in the adjusted analysis. Similarly, for patients receiving BTD median OS in the unadjusted analysis was 8.1 months (95% CI 5.3 to 13.5) compared to 10.5 months (95% CI 6.1 to 12.4) in the adjusted analysis.

Covariate adjustment also had little effect on PFS results. The unadjusted hazard ratio for POM+LoDEX relative to BTD was 0.76 (95% CI 0.56 to 1.05) compared to 0.79 (0.52 to 1.22) in the covariate adjusted analysis. The unadjusted median PFS for patients treated with POM+LoDEX was 4.2 months (95% CI 3.7 to 5.8) compared to 4.7 months (95% CI 3.7 to 6.6) in the adjusted analysis. The corresponding results for patients treated with BTD were 3.3 months (95% CI 2.5 to 5.5) in the unadjusted analysis and 3.7 months (95% CI 2.8 to 5.6) in the adjusted analysis.

The results of sensitivity analysis 1 showed that the inclusion of additional POM+LoDEX data from MM-003 and MM-010 reduced the benefit observed for patients treated with POM+LoDEX compared to BTD on OS. The covariate adjusted hazard ratio for POM+LoDEX relative to BTD was 0.64 (95% CI 0.45 to 0.91) compared to 0.58 (95% CI 0.36 to 0.94) in the base case. The unadjusted results were 0.68 (95% CI 0.51 to 0.92) in sensitivity analysis 1 and 0.55 (95% CI 0.38 to 0.81). The difference between the base case and the sensitivity analysis is also apparent in the median overall survival time. Patients treated with POM+LoDEX had a shorter median OS in sensitivity analysis 1 compared to the base case by approximately four months in both the adjusted and the unadjusted results. In contrast patients treated with BTD had a similar median OS in both the base case and the sensitivity analysis.

The inclusion of additional POM+LoDEX data from MM-003 and MM-010 did not substantially alter the results for PFS. The median PFS time was similar in the base case and in sensitivity analysis 1 for patients treated with POM+LoDEX and for patients treated with BTD regardless of covariate adjustment. In the unadjusted analysis the hazard ratios for PFS were similar in the base case (HR=0.76, 95% CI 0.56 to 1.05) and in sensitivity analysis 1 (HR=0.80, 95% CI 0.80, 95% CI 0.62 to 1.03). In the adjusted analysis of PFS POM+LoDEX showed a greater improvement relative to BTD in sensitivity analysis 1 (HR=0.61, 95% CI 0.45 to 0.84) compared to the base case (HR=0.79, 95% CI 0.45 to 0.84). Since the median PFS times remain similar between the adjusted and unadjusted analyses and given the fact that the confidence interval in sensitivity analysis 1 is contained entirely within the confidence interval for the base case this difference may not be clinically relevant.

Sensitivity analyses 2 and 3 were designed to assess the impact of including ISS stage as a prognostic factor in those studies where data were available. The MM-002 and Gooding studies did not report ISS stage therefore these studies were excluded from the analysis. The hazard ratios for overall survival were similar in both sensitivity analysis 2 which included ISS stage (HR=0.72, 95% CI 0.47 to 1.11) and sensitivity analysis 3 which excluded ISS stage (HR=0.82, 95% CI 0.53 to 1.27). The company highlighted that '*ISS stages two and three show an increased hazard of death versus stage one, and the*

effect increases as stage increases (HR 1.71, 95% CI [1.35, 2.18], HR 3.10, 95% CI [2.45, 3.92] for stage two versus one and stage three versus one, respectively).'[3]

The inclusion of ISS stage as a covariate had very little impact on the hazard ratios for PFS: HR=0.62 (95% CI 0.43 to 0.90) in sensitivity analysis 2 compared to HR=0.62 (95% CI 0.43 to 0.89) in sensitivity analysis 3. Similar to the analysis of OS the company highlighted that '*ISS stages two and three show an increased hazard of progression versus stage one, and the effect increases as stage increases (HR 1.25, 95% CI [1.04, 1.50], HR 1.80, 95% CI [1.49, 2.16] for stage two versus one and stage three versus one, respectively).*'[3]

It should be noted that this result shows that increasing ISS stage is predictive of an increased hazard of death or progression respectively not that the effect of treatment is different in patients with a different ISS stage.

ERG comment: The company only presented results for OS and PFS. There were no results reported for the other outcomes in the scope (response rates, adverse effects, HRQL).

Comparing the results of the base case and sensitivity analysis 1 showed that the magnitude of the relative effect of POM+LoDEX compared to BTD was dependent on the selection of data for inclusion in the analysis. The base case which included only data from MM-002 for POM+LoDEX showed a greater improvement in OS compared to sensitivity analysis 1 which included data from MM-002, MM-003 and MM-010 for POM+LoDEX. The dataset in the base case was chosen on the basis that '*the MM-002 Phase II trial represented the trial that was the most comparable to available comparator studies for BEN*'.[3]

The assessment of comparability between studies was based primarily on the percentage of patients refractory to lenalidomide in each study. The CS reported that '*The MM-002 trial alone was selected for use for POM+LoDEX within the base case analysis due to the lower levels of refractoriness exhibited within this trial (78%) compared to the remainder of the POM+LoDEX data (95%). This lower level of refractoriness was considered more comparable to the BEN data (18-25%) across sources. As this covariate was identified as most prognostically important by clinicians and is difficult to adjust for with the current datasets (given that the overlap between datasets is low) it was considered more important to select the more comparable dataset for analysis than to retain the maximum number of patients for analysis in the POM+LoDEX arm.'*[3]

As noted by the company the overlap between datasets is limited. Since the MM-002 study includes three to four times as many lenalidomide refractory patients as the BTD studies it is not clear that the gain in comparability justifies the exclusion of the MM-003 and MM-010 studies given how different the studies are to begin with. It should be noted that being refractory to lenalidomide did not significantly affect the OS results in either the base case or in sensitivity analysis 1. In the base case the HR for refractory to lenalidomide (Yes vs. No) was 1.102 (95% CI 0.74 to 1.65) compared to HR=1.174 (95% CI 0.89 to 1.54) in sensitivity analysis 1.[38] In contrast, being refractory to lenalidomide was a significant predictor of PFS in both the base case and in sensitivity analysis 1. Patients who were refractory to lenalidomide had an increased hazard of progression in both the base case (HR=1.58, 95% CI 1.09 to 2.28) and in sensitivity analysis 1 (HR=1.44, 95% CI 1.12 to 1.85).[38]

In this type of analysis a covariate for study is typically included in the model to allow for the fact that data on different treatments are derived from different studies. When the ERG queried why this was not done in this instance the response to clarification stated that '*We are unaware of any methods that may be applied to the data in order to adjust for both treatment and study variables, when both predictors are linearly dependent – i.e. each study only contains one treatment arm.*'[38] In other words, the

difference between studies cannot be separated from the difference between treatments because the two variables are exactly correlated.

The overall conclusion from these analyses is that POM+LoDEX appears to improve both OS and PFS compared to BTD. However there is some 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. The lack of data in this area means that although there are limitations to these analyses this is likely to be the best available evidence that could be obtained.

Table 4.26: Summary of the comparison of POM+LoDEX with BTD – OS and PFS

Outcome	Base-case		Sensitivity analysis 1		Sensitivity analysis 2		Sensitivity analysis 3	
	POM+LoDEX	BTD	POM+LoDEX	BTD	POM+LoDEX	BTD	POM+LoDEX	BTD
Overall Survival								
Included studies Study, N	MM-002, 113	Tarant, 4 Gooding, 17 MUK-one, 57	MM-002, 113 MM-003, 302 MM-010, 682	Tarant, 4 Gooding, 17 MUK-one, 57	MM-003, 290 MM-010, 650	Tarant, 3 MUK-one, 56	MM-003, 290 MM-010, 650	Tarant, 3 MUK-one, 56
Total N	113	78	1097	78	940	59	940	59
Median OS1 Unadjusted Adjusted	 16.5 (12.6, 19.8) 16.6 (12.6, 21.3)	 8.1 (5.3, 13.5) 10.5 (5.8, 13.5)	 12.6 (11.6, 13.8) 12.7 (11.9, 13.9)	 8.1 (5.3, 15.5) 8.1 (6.1, 12.4)	 NR NR	 NR NR	 NR NR	 NR NR
HR (95%CI) Unadjusted Adjusted	 0.55 (0.38, 0.81) 0.58 (0.36, 0.94)		 0.68 (0.51, 0.92) 0.64 (0.45, 0.91)		 NR 0.72 (0.47, 1.11)		 NR 0.82 (0.53, 1.27)	
Progression free survival								
Included studies Study, N	MM-002, 113	Gooding, 17 MUK-one, 57	MM-002, 113 MM-003, 302 MM-010, 682	Gooding, 17 MUK-one, 57	MM-003, 290 MM-010, 650	MUK-one, 56	MM-003, 290 MM-010, 650	MUK-one, 56
Total N	113	74	1097	74	940	56	940	56
Median PFS1 Unadjusted Adjusted	 4.2 (3.7, 5.8) 4.7 (3.7, 6.6)	 3.3 (2.5, 5.5) 3.7 (2.8, 5.6)	 4.3 (3.9, 4.7) 4.6 (3.9, 48)	 3.3 (2.5, 5.5) 2.8 (2.2, 3.8)	 NR NR	 NR NR	 NR NR	 NR NR
HR (95%CI) Unadjusted Adjusted	 0.76 (0.56, 1.05) 0.79 (0.52, 1.22)		 0.80 (0.62, 1.03) 0.61 (0.45, 0.84)		 NR		 NR	

Outcome	Base-case		Sensitivity analysis 1		Sensitivity analysis 2		Sensitivity analysis 3	
	POM+LoDEX	BTD	POM+LoDEX	BTD	POM+LoDEX	BTD	POM+LoDEX	BTD
					0.62 (0.43, 0.90)		0.62 (0.43, 0.89)	

Source: Based on CS Table 30, CS pages 102-110[3], CS Appendix 12 Tables 37 + 38[37], Clarification response page 19 and Tables 10-15[38]
1. Time in months (95% CI)
BTD, bendamustine + thalidomide + dexamethasone; CI, confidence interval; CS, company submission; HR, hazard ratio; OS. overall survival; PFS, progression free survival; POM + LoDEX, Pomalidomide + low dose dexamethasone

4.4.3 Comparison of POM+LoDEX and PANO+BOR+DEX

Selection of study data

There were two studies of PANO+BOR+DEX considered as potentially relevant for inclusion in the quantitative analysis: PANORAMA-1 and PANORAMA-2. The PANORAMA-1 study was excluded on the basis that '*this represents a much less advanced patient population (as evidenced by the inclusion of LEN as a NICE comparator): only 19% of patients had received prior LEN in the study, and in the licensed subgroup (≥2 prior regimens including BOR and an IMiD) reporting for patients receiving prior IMiD still fails to meet the inclusion criteria for the SLR (86% of patients had received prior THAL versus 38% receiving prior LEN). There is a high likelihood of confounding of OS results from use of subsequent LEN in this trial within a patient population who have not received, let alone become refractory to, this treatment, which rules out use of this study when comparing to the POM+LoDEX trials.*'[3]

The patients in the PANORAMA-2 study were considered the most comparable to those in the POM+LoDEX studies since '*all patients have received prior BOR and the vast majority (94%) of patients have also received prior LEN, additionally all patients are refractory to prior BOR.*'[3] The company acknowledged that there were still differences between the patient populations including '*the number of prior lines of treatment received (median 4 lines vs. 5 lines in the POM+LoDEX trials) and lack of reporting of refractoriness to LEN, which limit the ability to make a valid comparison.*'[3]

The company selected the pooled dataset from the MM-002, MM-003 and MM-010 studies as the base case for the comparison of POM+LoDEX with PANO+BOR+DEX. The CS stated that '*As the full population of PANORAMA 2 were refractory to BOR but not primary refractory, to aid comparability of the populations, the subgroup of patients (approximately 81%) in the POM+LoDEX trials that were refractory to BOR but not primary refractory were used for the MAIC*'[3]

The comparability of the patient characteristics between the POM+LoDEX studies and PANORAMA-2 study is discussed in Section 4.3.

Results

In the absence of patient level data for the PANORAMA-2 study the covariate adjustment methods used to compare POM+LoDEX with BTD could not be applied to the comparison of POM+LoDEX and PANO+BOR+DEX. The company used a matching adjusted indirect comparison (MAIC) to adjust for the differences in patient characteristics between studies. As reported by the company '*MAIC reweights patient level data for POM+LoDEX to reflect a population of similar baseline characteristics to the PANO+BOR+DEX population*'[3] The results of this analysis represent the difference between treatments that would have been observed if the PANO+BOR+DEX study had included a POM+LoDEX. The set of covariates included in the MAIC model was the same as those included in the comparison with BTD with the exception that '*refractoriness to LEN was not included as this variable was not reported in the paper for PANORAMA 2.*'[3] The CS reported that '*ISS stage was not collected in MM-002 and therefore could not be included as a covariate for the MAIC. This likely biases against POM+LoDEX given more patients in MM-003 and MM-010 are at ISS stage 3 than in PANORAMA 2 (35.5% vs. 24.1%).*'

The results of the MAIC of POM+LoDEX and PANO+BOR+DEX for OS and PFS are summarised in Table 4.27. The application of the MAIC method resulted in a one month increase in median OS for patients receiving POM+LoDEX (13.4 months, 95% CI 11.4 to 15.6) compared to the unweighted analysis (12.4 months, 95% CI 11.1 to 13.4). In both cases the median OS was shorter than those patients receiving PANO+BOR+DEX (17.5 months, 95% CI 10.8 to 22.22). The hazard of death was reduced by a similar amount for patients receiving PANO + BOR + DEX compared to POM + LoDEX in both

the unweighted analysis (HR=0.73, 95% CI 0.52 to 1.02) and in the MAIC (HR=0.78, 95% CI 0.56 to 1.09).

The application of MAIC had little effect on the median PFS time of patients treated with POM+LoDEX (4.2 months, 95% CI 3.7 to 4.8) compared to the unweighted analysis (4.1 months, 3.7 to 4.6). The hazard of progression was increased by a similar amount for patients receiving PANO+BOR+DEX compared to POM+LoDEX in both the unweighted analysis (HR=1.12, 95% CI 0.85 to 1.48) and in the MAIC (HR=1.18, 95% CI 0.89 to 1.56).

The CS states that '*These comparative effectiveness analyses produce clinically non-plausible results for OS, given that both UK clinicians and the NCCN assess POM+LoDEX to be the more efficacious treatment based upon available data. This surprising result is not the case for PFS indicating that it is highly likely that an unknown confounder (such as differential use of subsequent therapy) is having an impact on outcomes.*'[3]

Table 4.27: Summary of the comparison of POM+LoDEX with PANO+BOR+DEX – OS and PFS

Outcome	Base-case	
	POM+LoDEX	**PANO+BOR+DEX**
Overall Survival		
Included studies	MM-002 MM-003 MM-010	PANORAMA-2
Total N	886	55
Median OS[1] 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)[2] Unweighted Weighted		 0.73 (0.52 to 1.02) 0.78 (0.56 to 1.09)
Progression free survival		
Included studies	MM-002 MM-003 MM-010	PANORAMA-2
Total N	886	55
Median PFS[1] 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)[2] Unweighted Weighted		 1.12 (0.85 to 1.48) 1.18 (0.89 to 1.56)

Source: Based on Tables 33-34 of the CS[3]
Notes: 1. Time in months (95% CI); 2. Hazard ratios were reported in the CS for PANO + BOR + DEX relative to POM + LoDEX
CI, confidence interval; CS, company submission; HR, hazard ratio; NA, Not applicable; OS, overall survival; PANO + BOR + DEX, Panobinostat + bortezomib + dexamethasone; PFS, progression free survival; POM + LoDEX, Pomalidomide + low dose dexamethasone

ERG comment: The company only presented results for OS and PFS. There were no results reported for the other outcomes in the scope (response rates, adverse effects, HRQL).[30]

As there was no common comparator to link the POM+LoDEX studies with the PANO+BOR+DEX studies the MAIC is technically a matching adjusted direct comparison of two separate sets of observational data, patients receiving POM+LoDEX in the MM-002, MM-003 and MM-010 compared to patients receiving PANO+BOR+DEX in the PANORAMA-2 study.

These results indicate that there is little difference in the effectiveness of POM+LoDEX and PANO+BOR+DEX in terms of OS or PFS. As noted by the company there are modest differences in the relative effects (hazard ratios) however the median OS and median PFS are very similar for POM+LoDEX and PANO+BOR+DEX in both the unweighted results and in the MAIC. The median OS for patients treated with POM+LoDEX was increased by one month in the MAIC compared to the unweighted result. There is also an increase in the uncertainty surrounding this result as shown by the increase in the width of the confidence interval. Although the median OS for patients treated with POM+LoDEX was shorter than that for patients treated with PANO+BOR+DEX the confidence intervals for these results overlap entirely with the confidence interval for the median OS in patients treated with PANO+BOR+DEX. This may be partly due to the high degree of uncertainty surrounding the median OS on PANO+BOR+DEX since this result is based on only 55 patients.

The PFS results show the same pattern. For patients treated with POM+LoDEX the median PFS is very similar in both the MAIC and the unweighted analysis. The confidence intervals are also very similar. In addition the confidence intervals for patients treated with POM+LoDEX overlap entirely with the confidence interval for patients treated with PANO+BOR+DEX which suggests there is little difference between the two treatments.

The evidence supporting the comparison of POM+LoDEX and PANO+BOR+DEX is limited by the small number of patients receiving PANO+BOR+DEX and the lack of either a direct head to head trial or a common comparator to form an indirect comparison. Collectively the results presented here suggest that the effectiveness of the two treatments is quite similar.

4.4.4 Comparison of POM+LoDEX and conventional chemotherapy

The CS argues that '*HiDEX data can be used as a proxy for other conventional chemotherapy regimens. In using HiDEX as a proxy, we can assume that the efficacy and safety results observed in the MM-003 study for POM+LoDEX versus HiDEX are equivalent for all conventional chemotherapy regimens.*'[3]
The comparison of POM+LoDEX versus HiDEX was reported in the MM-003 study which is described in detail in Section 4.2.

ERG comment: The evidence supporting the assumption that HiDEX can act as a proxy for conventional chemotherapy is discussed in Section 4.3. It should also be noted that the relevance of conventional chemotherapy regimens as appropriate comparators was questioned in the clinical expert statement submitted on behalf of UK Myeloma Forum /Guys and St. Thomas' NHS Foundation Trust which states that '*Cyclophosphamide, melphalan, high dose dexamethasone and thalidomide would generally be considered as a palliative approach rather than an active approach (in comparison to the treatments outlined above). These are NOT appropriate comparators. There is no evidence to support these agents at this stage of therapy in the modern era of myeloma therapy (other than as palliative treatments).*'[2]

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The company conducted a systematic review to identify studies comparing pomalidomide to comparators outlined in the NICE scope.[30] Although a number of limitations were identified in relation to the systematic review of evidence (particularly in relation to the search for studies), overall the ERG is satisfied that all the relevant evidence has been presented. The evidence is limited as patients had to have received previous treatment with BOR and LEN. The main evidence in the submission came from the MM-003 trial which compares POM+LoDEX to HiDEX. Although this was a reasonably large, well conducted multi-centre trial, the main comparator is no longer optimal in current practice. Therefore the comparator can only be viewed as a proxy for conventional chemotherapy which might constitute an alternative. The trial was in a heavily treated population who had received a median of five therapies (range 2 to 17). Only 25 patients had received two prior therapies only, thus the trial is not representative of POM as a third line therapy. It could be assumed that POM might perform better at third line in a less treated population but this is an assumption. At third line patients can be offered PANO and there is no direct evidence comparing the two treatments. Within these constraints, pomalidomide appears to extend OS and PFS in comparison with HiDEX in a heavily treated population who are refractory to BOR and LEN. The adverse event profile appears to be manageable with appropriate dose reductions and interruptions. The ERG has drawn attention to those adverse events occurring more frequently in the POM arm, notably neutropaenia.

There were limited data available to inform the comparison of POM+LoDEX with treatments other than HiDEX. There were no studies that directly compared POM+LoDEX with either BTD or PANO+BOR+DEX. In addition the available studies did not include a common comparator that would permit an indirect comparison or mixed treatment comparison (MTC). As a result the company presented evidence based on comparisons of observational data.

In the base case the POM+LoDEX arm of the MM-002 study was compared to BTD arms from the MUK-one, Gooding and Tarant studies. The company also reported a sensitivity analysis that included POM+LoDEX data from MM-002, MM-003 and MM-010. The company used covariate adjusted Cox proportional hazards regression to adjust for the differences between studies in patient characteristics. The covariate adjusted results were very similar to the unadjusted results in terms of both PFS and OS for the base case and the sensitivity analysis. This indicates that the differences between studies in the selected covariates (patient characteristics) have relatively little impact on the outcomes observed.

The selection of different datasets for POM+LoDEX does alter the results for OS. In the base-case using only the MM-002 study the median OS in the covariate adjusted analysis was 16.6 months (95% CI 12.6 to 19.8) for patients receiving POM+LoDEX. In the sensitivity analysis based on data from MM-002, MM-003, MM-010 the median OS in the covariate adjusted analysis was 12.7 months (95% CI 11.9 to 13.9) for patients receiving POM+LoDEX. The median OS for patients receiving BTD was similar in both the base-case and the sensitivity analysis. As a result the covariate adjusted relative effect of POM+LoDEX versus BTD was reduced in the sensitivity analysis (HR=0.64, 95% CI 0.45 to 0.91) compared to the base-case (HR=0.58, 95% CI 0.36 to 0.94). In combination these results suggest the survival benefit of POM+LoDEX was less for patients in the MM-003 and MM-010 studies than for patients in the MM-002 study.

For the comparison with PANO+BOR+DEX the POM+LoDEX arms of the MM-002, MM-003 and MM-010 studies were compared with the PANO+BOR+DEX arm of the PANORAMA-2 study in a matching adjusted indirect comparison. The matching adjusted results for patients receiving POM+LoDEX were similar to the unadjusted results in terms of OS and PFS. The matching adjusted median OS for patients receiving POM+LoDEX was 13.4 months (95% CI 11.4 to 15.6) compared to 12.4 months (95% CI 11.1 to 13.4) in the unadjusted results. The matching adjusted PFS for patients

receiving POM+LoDEX was 4.2 months (95% CI 3.7 to 4.8) compared to 4.1 months (95% CI 3.7 to 4.6) in the unadjusted results. As in the comparison with BTD the matching adjustment does not substantially alter the results which implies that the differences between studies in the selected covariates have relatively little impact on the outcomes observed.

Although the evidence reported by the company is limited the ERG recognises that the lack of appropriate data excluded many of the standard alternatives. In the absence of any new direct head to head studies these results are likely to represent the best estimates of relative effectiveness that could be obtained given the limitations of the existing studies.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

5.1.1 Objective of cost effectiveness review

The CS states that a systematic literature review (SLR) was conducted to identify and summarise the relevant economic evidence for adult patients with RRMM previously treated with LEN and BOR reporting outcomes for POM+LoDEX versus relevant comparators (Section 5.1). Updated searches were carried out to identify literature published since the last SLR, between 1 December 2013 and 3 March 2016.

Searches were reported for MEDLINE, MEDLINE In-Process, Embase, Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database. In addition, online congress abstracts for the annual meetings of the American Society of Hematology (ASH), the American Society of Clinical Oncology (ASCO) and the European Hematology Association (EHA) were searched for 2014-2015 and the International Myeloma Workshops for 2013/2015. The UK HTA websites NICE, SMC and AWMSG were also searched. These meet the requirements specified in current best practice guidance as detailed in the NICE guide to the methods of technology appraisal.[41]

Search strategies were provided in Appendix 17 of the CS and are well reported and reproducible. The host provider for each database was listed, and the date span of the databases searched and the specific date the searches were conducted were provided. The database searches were clearly structured and documented. No language limits were applied.

Free text and indexing terms were used to search for the population, intervention and comparators. These could have been extended to include drug brand names (such as Imnovid), and a broader range of search terms in the 'relapse' facet, however this is unlikely to have greatly affected the recall of results.

The ERG notes that both MEDLINE and Embase were searched via the Embase.com interface, however only MeSH (MEDLINE) indexing terms were used in the economics search filter applied. Although some mapping between indexing terms does take place on Embase.com it is possible that relevant Embase indexing terms (EMTREE) will not be included in the search, and potentially relevant records missed. The ERG therefore considered that it was possible that some relevant evidence may not have been identified. Unfortunately the ERG was unable to undertake independent searches and review the results within the STA timeline, as this would be outside of the ERG remit.

Measurement and value of health effects

The CS states that a systematic literature review (SLR) which formed part of the previous NICE submission (TA338) was updated in order to capture new utility studies for RRMM patients. Literature searches aimed to identify studies published between 1 December 2013 and 3 March 2016.

Searches were reported for MEDLINE, MEDLINE In-Process, Embase, Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database. In addition, online congress abstracts for the annual meetings of the American Society of Hematology (ASH), the American Society of Clinical Oncology (ASCO) and the European Hematology Association (EHA) were searched for 2014-2015 and the International Myeloma Workshops for 2013/2015. The NICE website was also searched. These meet the requirements specified in current best practice guidance as detailed in the NICE guide to the methods of technology appraisal.[41]

Search strategies were provided in Appendix 24 of the CS, and are well reported and reproducible.[37] The host provider for each database was listed, and the date span of the databases searched and the specific date the searches were conducted were provided. The database searches were clearly structured and documented. No language limits were applied.

Free text and indexing terms were used to search for the population. A broader range of search terms could have been included in the 'relapse' facet, however this is unlikely to have greatly affected the recall of results. Search terms were used to limit the results to HRQoL studies. Although a validated filter does not appear to have been used or referenced, a wide range of relevant terms was included.

Cost amd healthcare resource use identification, measurement and valuation

The CS states that '*the cost and resource use SLR conducted as part of this submission did not identify any treatment specific resource use*' (Section 5.5.1), however no search strategies or details of search methods are included in the CS. In response to a request for clarification the company states: *'No additional formal literature searches were performed to identify resource use or health care costs for this resubmission. The original literature searches, as is often the case, found no information that could be directly used within the economic model. The types of resource use required to be included within the economic model were agreed within the previous appraisal for POM+LoDEX. Resource use was therefore instead gathered by directly contacting UK clinicians to determine what their resource requirements are on a treatment-specific basis.'*

The NICE document Single technology appraisal: User guide for company evidence submission template[72] states that a systematic search should be conducted to identify relevant cost and healthcare resource use data, and search strategies used should be provided. The ERG therefore believes that although relevant data may have been identified through other means for inclusion in the model, this approach does not meet with NICE requirements.

5.1.2 Inclusion/exclusion criteria used in the study selection

Table 5.1 presents an overview of inclusion and exclusion criteria used for the review.

Table 5.1: Inclusion and exclusion criteria used for the cost effectiveness review

Criteria	Inclusion	Exclusion
Population	Adult patients with RRMM previously treated with LEN and BOR	Patients having disease other than RRMM and not previously treated with LEN and BOR
Intervention	POM+LoDEX	Studies not assessing POM+LoDEX in any of the intervention arm
Comparators	Bendamustine (Levact®) with or without steroids/standard chemotherapy agents Bortezomib (Velcade®) with or without steroids/standard chemotherapy agents Panobinostat (LBH589®, Farydak®, Faridak®) in combination with bortezomib and steroids Standard chemotherapy agents in combination with each other or steroids Standard Chemotherapy Agents:	Studies were excluded if patients have received stem cell therapy in combination with the listed intervention/comparators

Criteria	Inclusion	Exclusion
	Cyclophosphamide (Cytoxan®, Endoxan®, Neosar®, Procytox®, Revimmune®) Etoposide (Etopophos®, Vepesid®) Liposomal doxorubicin (Caelyx®, Myocet®) Methylprednisolone (Medrol®) Thalidomide (Thalidomid®) Melphalan	
Study type	Full economic evaluations, such as: Cost–consequence Cost-minimisation Cost-effectiveness Cost–utility Cost–benefit	Burden of illness and non-modelling studies
Outcome	ICER Costs (unit and total) QALYs LYs/LYG Incremental costs Incremental QALYs/LYs Model inputs (e.g. transition probabilities, % of patients at fibrosis stage etc.) Sensitivity analyses results	No specific exclusion criteria
Time limits	Publication timeframe: December 2013 onwards	Studies were excluded before December 2013
Language	Studies published in English were included	Studies published in languages other than English were not included
Source: Based on Table 44 of the CS Appendix 17[37] BOR, bortezomib; CS, company submission; ICER, incremental cost effectiveness ratio; LEN, lenalidomide; LoDEX, low-dose dexamethasone; LYs, life years; LYG, life years gained; POM, pomalidomide; QALYs, quality-adjusted life years; RRMM, relapsed and/ or refractory multiple myeloma.		

5.1.3 Included/excluded studies in the cost effectiveness review

In the CS it was mentioned that 454 studies were identified in the SLR. Four duplicates were removed and the screening of titles and abstracts against the pre-specified inclusion and exclusion criteria was performed for the remaining 450 records. After screening, only three HTAs were included for data extraction: the original NICE appraisal of POM+LoDEX (TA338)[73], and the equivalent submissions for Scottish Medicines Consortium (SMC)[74] and for All Wales Medicines Strategy Group (AWMSG)[75]. According to the CS, the limitations raised by the AWMSG and SMC coincided with those raised by NICE. Therefore, they only listed the key issues raised by the ERG and the Appraisal Committee during the appraisal (TA338) as below[73]:

- *Comparative effectiveness data:* The Committee considered that all data available at the time had been included in the submission; however, very few data were identified for current care, which left the Committee unable to fully assess the cost effectiveness of POM+LoDEX vs. its comparators.

- *Assumptions regarding equivalence of comparators:* The Committee disagreed with the company's equal effectiveness assumption for all comparators with regard to OS, PFS and TTF, which the ERG found unjustified by the evidence.
- *Relative benefit of current care vs. HiDEX:* There were concerns about the modelling assumptions in the submission, which led to the situation where the current standard of care had a lower survival estimate compared to HiDEX. This was deemed implausible because HiDEX was considered a sub-optimal treatment for RRMM patients.
- *Adjustment of trials to provide comparable estimates:* Differences in patient characteristics indicated that the populations in the studies included for analysis were not considered comparable. The ability to adjust for differences in patient characteristics was questionable, due to the limited sample size available.
- *Adverse Events:* The Committee considered that the cut-off point to include disutility values only for AEs that occurred in more than 2% of patients on the POM+LoDEX arm to be arbitrary. Further, the ERG identified an error in the modelling, which led to an underestimation of the utility decrement due to adverse events and subsequently an underestimation of the ICER for POM+LoDEX versus its comparators.
- *Dosing:* The Committee had concerns on the assumption that unused tablets of POM+LoDEX due to non-protocol interruptions were fully recovered by the NHS, as it may not hold in clinical practice

ERG comment In the Final Appraisal Documentation (FAD) of TA338[73], many other issues than the list of 'key' issues provided in this submission were mentioned, including the overestimation of the overall survival for POM+LoDEX and underestimation of the overall survival of its comparators, number of bortezomib cycles, disutility due to subcutaneous and intravenous therapies, potential 'over-fitting' of the data and residual confounding. It was not clear to the ERG how the 'key issues' were selected from all the issues mentioned in the FAD of TA338.[73]

5.1.4 Conclusions of the cost effectiveness review

Besides the list of key issues from the previous appraisal (TA338), no specific conclusions from the economic review were provided in the CS.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.2 presents a summary of the de novo economic model developed by the company.

Table 5.2: Summary of the company submission economic evaluation

	Approach	Source/Justification	Signpost (location in CS)
Model	A semi-Markov partitioned survival model for RRMM patients, who were previously treated with LEN and BOR was used. Time horizon in the base case was 15 years (in effect lifetime).		Section 5.2.2 (p. 166)
States and events	Four health states including: a pre-progressive state (split into on-treatment and off-treatment), a post-progression state (progressive disease), and death. Disease progression was based on the Independent Response Adjudication Committee (IRAC) review by International Myeloma Working Group (IMWG) criteria. The proportion of patients on treatment is calculated using time to treatment failure (TTF) rates. TTF is defined as the earliest of progression, death, treatment discontinuation or withdrawal. From the pre-progression state, a transition is possible to the post-progression state or death state. From post-progression, patients can only move to the death state and a transition back to the pre-progression state following progression is not possible.	The model structure and the health states are typical in the modelling of advanced/metastatic oncology and have been previously utilised in numerous NICE STAs and MTAs.	Section 5.2.2 (p. 166)
Comparators	PANO+BOR+DEX BTD CC (including cyclophosphamide & melphalan) ± THAL retreatment ± steroid	Based on NICE Scope.	Section 5.2.3 (p. 168)
Natural History	The majority of patients that enter the model have been treated with thalidomide, bortezomib and lenalidomide in previous lines.		

	Approach	Source/Justification	Signpost (location in CS)
Treatment effectiveness	Treatment influences time on treatment, PFS and OS. Adverse event rates and utilities are also treatment specific.	For the POM+LoDEX vs. BTD comparison, PFS and OS estimates of POM+LoDEX were based on adjusted parametric survival functions fitted to MM-002 trial data[32] and the PFS and OS estimates of BTD were based on adjusted parametric survival functions fitted to the pooled data from Gooding et al [68], Tarant et al [69] and MUK-ONE[67] trials. For the POM+LoDEX vs. PANO+BOR+DEX comparison, PFS and OS estimates of POM+LoDEX were based on adjusted parametric survival functions fitted to combined data from MM-002[32], MM-003[59] and MM-010[33]trials and the PFS and OS estimates of PANO+BOR+DEX were obtained by applying the hazard ratios derived from the matched adjusted indirect comparison (MAIC) methods, using data from the PANORAMA-2 trial.[70] For the POM+LoDEX vs. conventional care (CC) comparison, PFS and OS estimates of both POM+LoDEX and CC were based on parametric survival functions fitted to data from the POM+LoDEX and HiDEX arms of the MM-003 trial, respectively.[59]	Section 5.3 (p. 168)
Adverse events	41 different AEs of severity grade 3 or 4 were included in the model. The AE rates were derived from the MM-003 trial.[59]	In the CS, it was mentioned that all grade 3-4 treatment emergent adverse events that occurred at least in 2% of the POM+LoDEX patients of the MM-003	Section 5.3.16 (p. 191)

	Approach	Source/Justification	Signpost (location in CS)
		trial dataset were included. The CS did not take MM-002 and MM-010 into consideration, as those trials did not have that level of granularity for adverse event data.	
Health related QoL	The economic model uses a regression model based on data from MM-003 trial.[59] Disease progression, best overall response, hospitalisation, baseline EGOG and the presence of adverse events were the main regression coefficients.	In the CS, it was mentioned that the HRQL data were not included in the MM-002 and MM-010 trials.	Section 5.4 (p. 194)
Resource utilisation and costs	Treatment cost (e.g. technology acquisition and administration costs of POM+LoDEX and other comparators, monitoring costs and tests) and other monitoring/tests costs, concomitant medication costs, subsequent medication therapy and terminal care costs and other costs for adverse events.	Based on literature, expert opinion and UK reference costs.	Section 5.5 (p. 210)
Discount rates	A 3.5% discount rate was used for both costs and effects.	According to NICE reference case	Section 5.2.3 (p.168)
Sensitivity analysis	One-way deterministic sensitivity analysis, scenario analyses and probabilistic sensitivity analysis	Ranges based on observed confidence intervals and assumptions.	Section 5.8 (p. 241)

AE, Adverse event; BOR, bortezomib; BTD, Bendamustine + thalidomide + dexamethasone; CC, conventional chemotherapy; DEX, dexamethasone; HiDEX, High-dose dexamethasone; ICER, incremental cost effectiveness ratio; LEN, lenalidomide; LoDEX, low-dose dexamethasone; LYs, life years; LYG, life years gained; PANO, Panobinostat; POM, pomalidomide; QALYs, quality-adjusted life years; RRMM, relapsed and/ or refractory multiple myeloma; THAL, Thalidomide

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.3: Comparison of the CS model with the NICE reference case

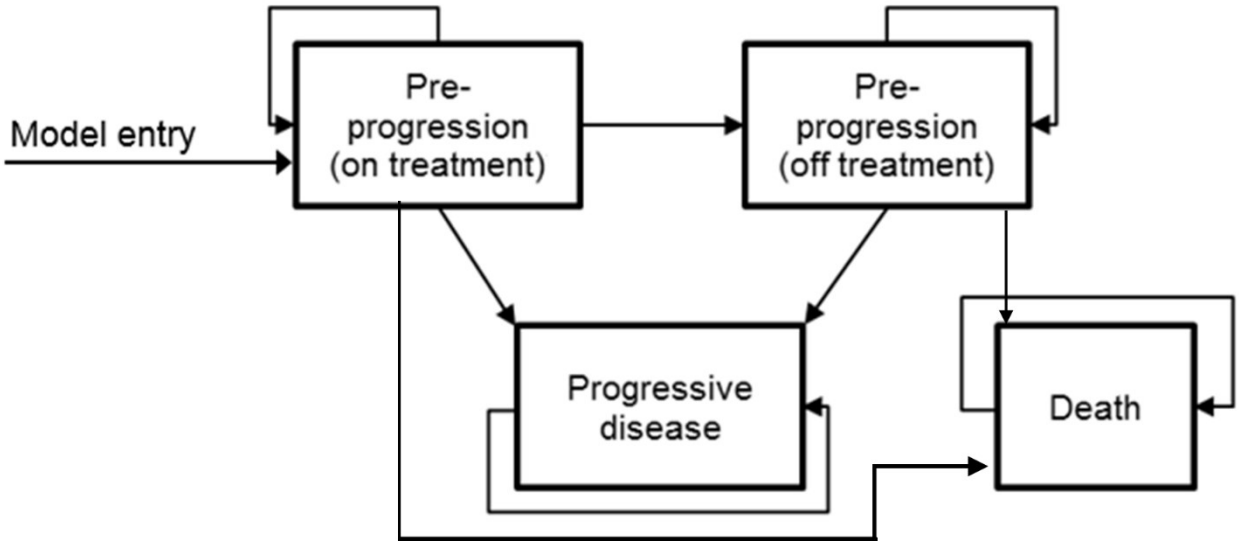
Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de novo evaluation meets requirements of NICE reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes	Mostly in line with the scope, though efficacy data on HiDEX was used in the model as a proxy for conventional chemotherapy
Type of economic evaluation	Cost effectiveness analysis	Yes	
Perspective on costs	NHS and PSS	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	Time horizon is 15 years (lifetime), median OS ranges from 3 to 10 months.[68, 69, 76-78]
Synthesis of evidence in outcomes	Systematic review	Yes	Meta-analysis was not used, since there is no connected evidence network. Other methods were used like MAIC and covariate adjustments
Measure of health effects	QALYs Life-years	Yes	
Source of data for measurement HRQL	Reported directly by patients and/or carers	Yes (for POM + LoDEX)	A utility regression model is used, which was based on the EQ-5D data from the MM-003 trial, which is reported by the patients.
Source of preference data for valuation of changes in HRQL	Sample of public	Yes	UK tariff was applied to the data from the EQ-5D data.
Discount rate	Annual rate of 3.5% on costs and health effects	Yes	
Equity weighting	No special weighting	Yes	
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Besides the PSA, a range of sensitivity analysis was performed.

CS, company submission; EQ-5D, EuroQoL five dimensions; HRQL, health-related quality of life; LoDEX, low-dose dexamethasone; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; POM, pomalidomide; PSA, probabilistic sensitivity analysis; PSS, personal social services; QALY, quality-adjusted life year

5.2.2 Model structure

In this submission, rather than building a *de novo* model, the model submitted within the original submission to NICE for TA338 was adapted. This model was developed in Microsoft® Excel 2010 using a semi-Markov partitioned survival structure. The model comprises four health states: a pre-progressive state (split into on treatment and off treatment), a post-progression state (progressive disease), and death. Health states were defined in relation to disease progression based on the International Myeloma Working Group (IWMG, 2013) uniform response criteria assessed by investigator review. IMWG was used within the primary endpoints across the POM+LoDEX trials and in the CS, as it was mentioned that little difference was seen between IMWG and European Society for Blood and Marrow Transplantation (EBMT) assessments in MM-002 and MM-003 trials. Furthermore, in the CS, it was discussed that investigator assessment was chosen as the central review data was not available for the most recent data cut in the MM-003 and MM-010 trials. The CS stated that little difference was seen between central review and investigator review data in MM-003 (earlier data cut) and MM-010 trials. The model structure is shown in Figure 5.1 below. Patients in pre-progression (on and off treatment) and in progressive disease states can go to the death state.

Figure 5.1: Model Diagram



These four model health states are designed to capture whether the patient is alive or not, whether the patient is pre-progression (responding to treatment or maintaining stable disease) or post-progression, whether the patient is receiving treatment or not, and the corresponding impact on quality of life and the costs of managing the disease. The cycle length was defined as one week and a half cycle correction was applied.

ERG comment: the structure of the model is in line with previous model structures in other NICE STAs for metastatic cancer drugs and is appropriate in the view of the ERG.

The ERG identified a programming error in the implementation of the half cycle corrections. For the half cycle correction, instead of the average of first and second cycles, the average of first cycle, and the cell above was calculated, which gave inconsistent results, as the cell above the first cycle included text and not a number. This error was corrected in the model used for ERG exploratory analyses.

5.2.3 Population and baseline characteristics

Baseline patient characteristics are presented in Table 5.4. Most of the baseline patient characteristics were obtained from two studies considering the real world outcomes of POM across a number of UK

centres.[46, 47] Where real world data were unavailable, available estimates from MM-003, MM-002 and MM-010 trials relevant to each comparator were considered. Patient characteristics were used in the model to inform the covariate values of the utility regression equations and to adjust OS and PFS (see ERG comments below).

Table 5.4: Baseline characteristics

Patient characteristic	POM+LoDEX vs. BTD	POM+LoDEX vs. PANO+BOR+DEX	POM+LoDEX vs. CTD	Source
Mean age	67.6			Maciocia et al. 2015[46] and Miles and Wells 2015[47]
Proportion male	54.87%[a]	56.88%[b]	59.93%[c]	[a]MM-002 [b]Weighted average across MM-003, MM-002 and MM-010 [c]MM-003 [d]Weighted average across MM-003 and MM-002 (not reported in MM-010) [e]Weighted average across MM-003 and MM-010 (not reported in MM-002) [f]MM-003 (not reported in MM-002 or MM-010)
Mean patient height (cm)	167.13[a]	167.32[b]	168.67[c]	
Mean patient weight (kg)	79.36[a]	73.58[b]	74.89[c]	
Baseline ECOG status: 0	28.32%[a]	40.02%[b]	37.09%[c]	
Baseline ECOG status: 1	59.29%[a]	47.77%[b]	45.70%[c]	
Baseline ECOG status: 2/3	12.39%[a]	12.22%[b]	17.22%[c]	
Baseline Durie Salmon stage: 1	7.08%[a]	6.99%[d]	6.95%[c]	
Baseline Durie Salmon stage: 2	25.66%[a]	29.64%[d]	31.13%[c]	
Baseline Durie Salmon stage: 3	67.26%[a]	63.37%[d]	61.92%[c]	
Baseline ISS stage: 1	23.07%[e]		26.82%[c]	
Baseline ISS stage: 2	39.02%[e]		38.41%[c]	
Baseline ISS stage: 3	37.91%[e]		34.77%[c]	
Proportion of patients refractory to lenalidomide	77.88%[a]	93.71%[b]	94.70%[c]	
RBC level (10^12/L)	3.1[f]			
Proportion of patients having received prior thalidomide	84%			Maciocia et al. 2015[46]
Mean prior treatment lines (range)	3.7 (1.6-7.7)			Maciocia et al. 2015[46] and Miles and Wells 2015[47]

Patient characteristic	POM+LoDEX vs. BTD	POM+LoDEX vs. PANO+BOR+DEX	POM+LoDEX vs. CTD	Source
Proportion European	100%			NICE Reference Case[79]

BOR, bortezomib; BTD, bendamustine + thalidomide + dexamethasone; CTD, cyclophosphamide + thalidomide + dexamethasone; DEX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; LoDEX, low-dose dexamethasone; NICE, National Institute for Health and Care Excellence; PANO, panobinostat; POM, pomalidomide; RBC, red blood cell

ERG comment: In the economic model, proportion of lenadilomide refractory patients, proportion of patients that received thalidomide and previous number of therapy lines are used in OS/PFS calculations. In the base case, the weighted average of the proportion of patients that were refractory to lenalidomide was around 89% for the POM+LoDEX vs. PANO+BOR+DEX comparison and it was around 56% for the POM+LoDEX vs. BTD comparison. Similarly, the weighted average of the proportion of patients that had previously received thalidomide was 59% for the POM+LoDEX vs. PANO+BOR+DEX comparison and it was around 68% for the POM+LoDEX vs. BTD comparison. Finally, while the number of prior lines of therapy was around 4.95 for the POM+LoDEX vs. PANO+BOR+DEX comparison, it was 6.5 for the POM+LoDEX vs. BTD comparison. These figures used in the model differ from the ones given in the CS, as shown in Table 5.4 above. The values in Table 5.4 for number of prior lines of therapy, percentage of lenalidomide refractoriness, and percentage for the receipt of thalidomide were used, but only in one of the scenario analyses.

As will be discussed in Section 5.2.8, the number of prior lines of therapy is also one of the covariates in the utility regression function. For utility calculations, the value in Table 5.4 was used in the base-case and in all scenarios. This led to inconsistencies in the base-case (i.e. in the base-case, for OS/PFS 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).

5.2.4 Interventions and comparators

The intervention in the current submission consisted of pomalidomide (POM) (4 mg taken orally, once daily, on days 1-21 of repeated 28-day cycles) in combination with low-dose dexamethasone (LoDEX) (40 mg for patients younger than 75 years and 20 mg for patients older than 75 years; taken orally, once daily, on days 1, 8, 15 and 22 of each 28-day treatment cycle).

The model considers the following comparators: BTD, PANO+BOR+DEX and conventional chemotherapy. The dosage of these comparators is discussed in Section 5.2.8.

ERG comment: In the scope of the current appraisal[30] NICE requested the following comparisons to be made:

- At third line: POM+LoDEX versus PANO+BOR+DEX
- At fourth line onwards versus all comparators (BTD, PANO+BOR+DEX and CC)

In the CS, the cost effectiveness analyses were not stratified into third line (POM+LoDEX versus PANO+BOR+DEX) and fourth and later lines (POM+LoDEX vs. BTD, vs. PANO+BOR+DEX and vs. CC). The ERG considers this acceptable, as data would be lacking for such stratification.

5.2.5 Perspective, time horizon and discounting

The perspective considers all health effects on individuals and costs for NHS and Personal Social Services. A 15-year time horizon (which in practice means lifetime horizon, given the short life expectancy of these patients) is adopted and a discount rate of 3.5% for costs and effects is used.

5.2.6 Treatment effectiveness and extrapolation

In the previous NICE review (TA338), the ERG stated that the main limitation of the evidence submitted was the lack of clinical effectiveness data for the comparators listed in the scope.[80] In the CS it was mentioned that based on this feedback, real world data were collected and the previous systematic review has been refined and updated to ensure that all relevant clinical data are included. However, the collected real world data were deemed not suitable to be utilised within the model due to the heterogeneity between the real world data and the clinical trial data, and confounding of key outcomes. In the CS, it was also mentioned that more data were used due to the incorporation of additional trials as well as more recent datasets.

Data used for POM+LoDEX

Key model inputs related to POM+LoDEX have been obtained from MM-003[59], MM-002[32] and MM-010[33] trials. The latest available data cut has been used for each of the trials: the September 2013 data cut from MM-003, June 2014 data cut from MM-002 and May 2015 data cut from MM-010.

- For the comparison of POM+LoDEX with BTD, clinical data for POM+LoDEX were sourced from the MM-002 trial.
- For the comparison of POM+LoDEX with PANO+BOR+DEX, clinical data for POM+LoDEX were obtained from pooled estimates across MM-003, MM-002 and MM-010 trials.
- For the comparison of POM+LoDEX with conventional chemotherapy, clinical data for POM+LoDEX were sourced from the MM-003 trial.

Data used for BTD

In addition to the data used in the previous submission (KM data from Gooding 2015[68] and median estimates from the observational study described in Tarant 2013[69]), the clinical SLR identified a UK trial, MUK-One, for which patient level data were available.[67] These studies are all specific to UK practice and contain data for the relevant patient population (all patients with RRMM having received both previous LEN and BOR). The comparison was undertaken using patient level data for both POM and BTD.

Data used for PANO+BOR+DEX

Since no direct comparison was present between POM+LoDEX and PANO+BOR+DEX, a matched adjusted indirect (MAIC) was conducted to inform the efficacy inputs within the model.[81] The MAIC matched using reported baseline summary statistics across MM-003, MM-002 and MM-010 and the PANORAMA-2 trial.[70] In order to match the POM+LoDEX patients to the PANORAMA-2 trial, only patients in MM-003, MM-002 and MM-010 that were refractory to prior BOR and were not primary refractory (third or later lines) were included in the Cox regression analysis. Full details of the MAIC conducted and rationale for study selection are provided in Section 4.10 of the CS.[3]

Data used for conventional chemotherapy

In the CS, it was mentioned that no sources of data considering treatment of RRMM with conventional chemotherapy (CC) within the relevant patient population were identified in the clinical SLR. Therefore, in the CS, HiDEX data have been used as a proxy for all CC regimens.

In line with the previous submission to NICE (TA338), data for HiDEX from MM-003 trial[59] have been included within the model using the two-stage method to adjust for crossover to POM+LoDEX post progression based upon the results of the published crossover analysis.[82]

In using HiDEX as a proxy, it was assumed that the efficacy and safety results observed in the MM-003 study for POM+LoDEX versus HiDEX were equivalent for all conventional chemotherapies. For

costing purposes, the cost of cyclophosphamide + thalidomide + dexamethasone (CTD) was included within the model as this was thought to be representative of the type of chemotherapy received by frail patients and it was cheaper than melphalan +prednisone+thalidomide (MPT), which is the other frequently used regimen.

Covariate adjustment

As stated in Section 5.2.3 above, in the previous NICE submission (TA338), the ERG concluded that differences in patient characteristics meant that the populations included across the clinical data were not comparable.[80] Therefore, the company chose to use the methods described in Section 4.4 of this report to estimate survival, controlling for differences between the characteritics of the patients in the data sources for POM+LoDEX, BTD and PANO+BOR+DEX. In the model, the propoprtion surviving in each cycle has to be predicted from the estimated survival functions, e.g. exponential (see Survival analysis summary below). This requires that each covariate from the survival function be multiplied by the value of the covariate. For example, as shown in the Excel model, the covariate for age for the exponential survival function for OS is 0.0065 and this needs to be multiplied by a value for age in order to predict the actual probability of surviving. Given that the predicted value applies to not only one individual patient, but a cohort, mean age can be used and similarly, the mean for all covariate values including prior lines of therapy etc. (see Table 5.5). However, the company chose to use another method, the corrected group prognosis (CGP) method for the base-case analysis, and the 'mean of covariates' method was used in a scenario analysis.[83] The sources of data and covariates included in the base-case economic model are presented in Table 5.5 below.

Table 5.5: Base-case analyses: source and covariate data

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

Notes: [a]ISS stage at baseline was not included due to data limitations in the MM-002 and Gooding et al. data, other covariates considered potentially prognostic (including refractory to BOR) could not be included due to data limitations in the evidence for BEN; [b]Refractoriness to LEN and ISS stage were not included due to data limitations in the PANORAMA-2 and MM-002 trials. Refractory to BOR is not a covariate because 100% of the PANORAMA-2 population is refractory to BOR and the subset of POM data that was refractory to BOR was used.

BOR, bortezomib; BTD, bendamustine, thalidomide and dexamethasone; DEX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; LEN, lenalidomide; LoDEX, low-dose dexamethasone; PANO, panobinostat; POM, pomalidomide; THAL, thalidomide

Survival analysis summary

In the CS, it was stated that the applicability of a single parametric model or a Cox proportional hazards model was determined using visual inspection of the KM curves, the log cumulative hazard plots (LCHP) and the Q-Q curves, in line with NICE Decision Support Unit (DSU) guidance.[62] In the CS, it was mentioned that the LCHPs were assessed to determine the suitability of using a single parametric

model for the two treatment arms in terms of the underlying hazard and in assessing the suitability of projecting using exponential, Weibull and Gompertz curves. Q-Q plots were assessed to determine the suitability of the use of accelerated failure time (AFT) models.

In the CS, for each clinical outcome (OS, PFS and TTF), six parametric distributions (exponential, log-normal, log-logistic, Gompertz, gamma and Weibull) were examined and the fit of each parametric model to the covariate adjusted survival data was explored using visual inspection, LCHPs, Q-Q plots, Akaike information criterion (AIC) and Bayesian information criterion (BIC) goodness of fit statistics and clinical plausibility.

The impact on model results of selecting different parametric curves for OS/PFS was tested in scenario analyses. Additionally, to characterise uncertainty in model inputs a probabilistic sensitivity analysis (PSA) was conducted, which selects the choice of OS curve by sampling from the probability that each parametric model is the best of the fitted parametric models using the AIC estimates.[84]

The individual AIC values are first transformed

$$\Delta_i = AIC_i - AIC_{min}$$

where AIC_{min} is the minimum across the AIC values from six parametric curves. According to the CS, due this transformation, Δ_i represents the information loss experienced if the model uses an alternative parametric model rather than the best fitted parametric model. The model likelihoods can then be estimated and normalised to provide the probability of each parametric model being the best fitted parametric model. The PSA selects the type of OS / PFS curve based upon sampling from a categorical distribution, which represents the probability that each parametric model is the best fitted parametric model, and therefore incorporates uncertainty around the choice of parametric curve.

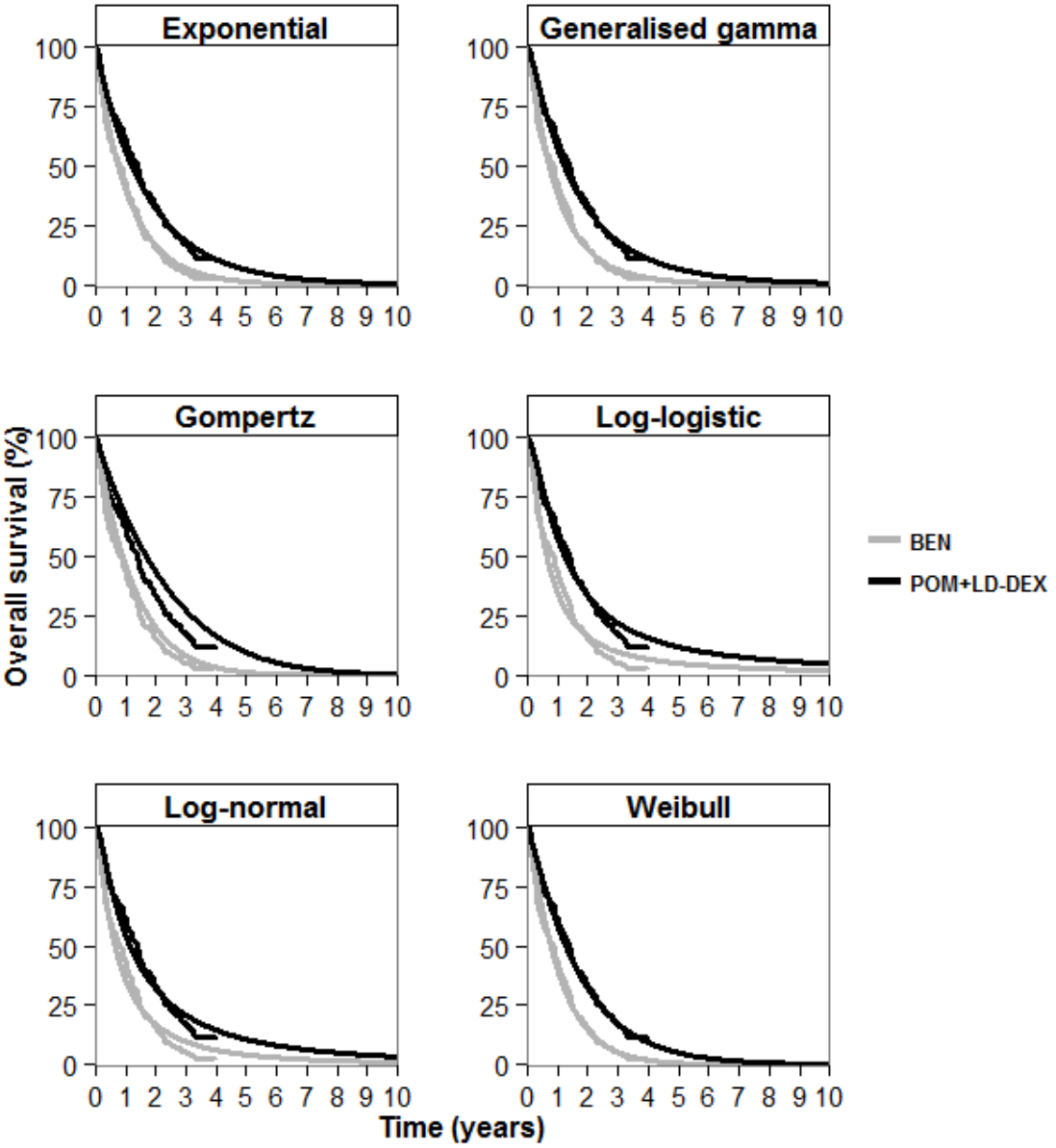
POM+LoDEX vs. BTD, results of the survival analyses for PFS, OS and TTF (base case)
Recall that in the base-case, for the POM+LoDEX vs. BTD comparison, the pooled dataset from MM-002[32], Gooding 2015[68], Tarant 2013[69]) and MUK-One[67] trials were used.

For OS, model fit results can be found in Appendix 18 of the CS[37] (LCHP in Figure 17, Q-Q plot in Figure 18, visual fit of parametric curves to the adjusted KM in Figure 19 and AIC/BIC statistics in Table 48 of the Appendices).

Similarly, for PFS, corresponding results can be found in Appendix 19 of the CS[37] (LCHP in Figure 28, Q-Q plot in Figure 29, visual fit of parametric curves to the adjusted KM in Figure 30 and AIC/BIC statistics in Table 51 of the Appendices).

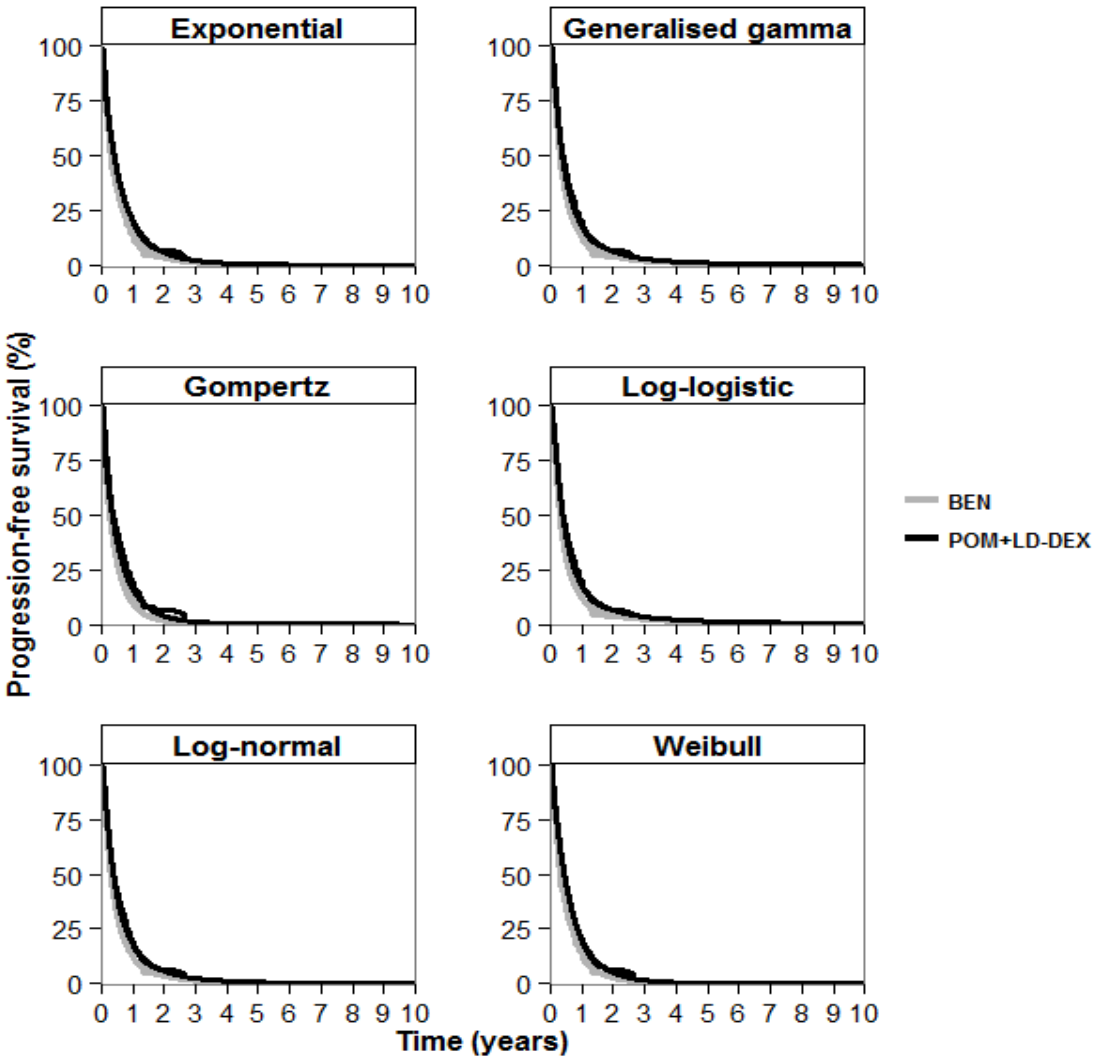
For the reader's convenience, the visual fit inspection results of the six explored parametric functions compared to the adjusted KM are presented in Figures 5.2 and 5.3 for OS and PFS, respectively.

Figure 5.2: OS parametric curve fits adjusting for covariates using the CGP method: POM+LoDEX vs. BTD (including MM-002 only)



BEN, bendamustine; BTD, bendamustine, thalidomide and dexamethasone; CGP, corrected group prognosis; POM, pomalidomide; LD-DEX/LoDEX, low-dose dexamethasone; MM, multiple myeloma; OS, overall survival.

Figure 5.3: PFS parametric curve fits adjusting for covariates using the CGP method: POM+LoDEX vs. BTD (MM-002 only)

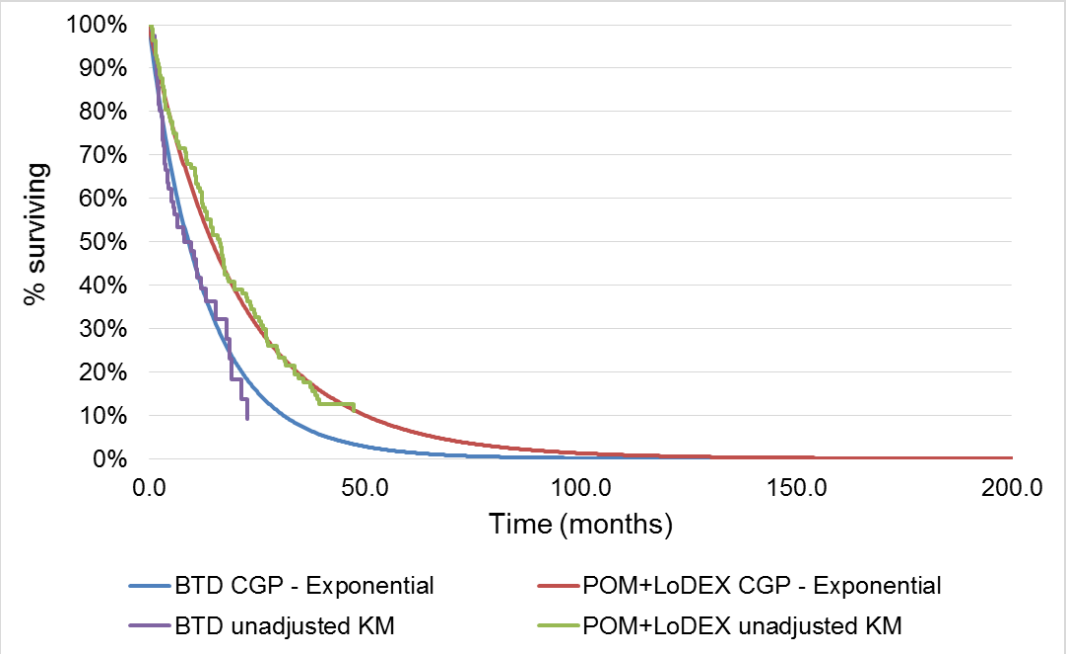


BEN, bendamustine; BTD, bendamustine, thalidomide and dexamethasone; CGP, corrected group prognosis; LD-DEX/LoDEX, low-dose dexamethasone; MM, multiple myeloma; PFS, progression-free survival; POM, pomalidomide.

In the CS[3], based on these Q-Q plots (Figure 18 for OS and Figure 29 for PFS from the Appendices), it was discussed that the AFT assumption does not hold neither for the PFS nor for the OS curves of POM+LoDEX and BTD arms. Similarly, based on LCHPs (Figure 17 for OS and Figure 28 for PFS from the Appendices), it was discussed that log cumulative hazards seemed to be parallel and proportional hazard assumption was considered plausible for both OS and PFS. Based on AIC/BIC statistics (Table 48 for OS and Table 51 for PFS from the Appendices) and visual fit of parametric functions to the adjusted KM (Figure 19 for OS and Figure 30 for PFS from the Appendices), the exponential function was selected as the best parametric distribution for modelling the OS curves, and the generalised gamma function was selected as the best parametric distribution for modelling the PFS curves related to the POM+LoDEX and BTD arms.

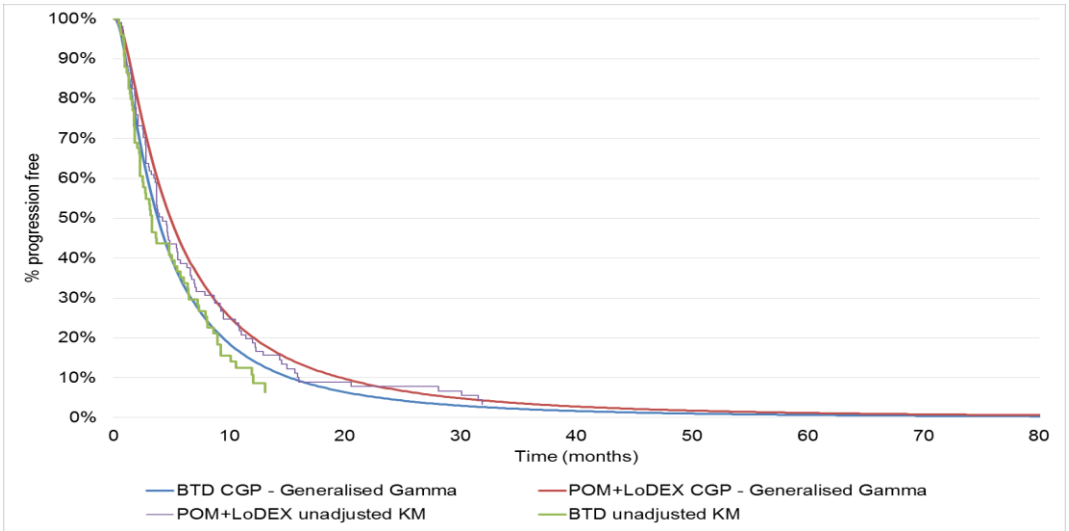
These selected parametric curves (exponential for OS and generalised gamma for PFS) in comparison to the corresponding unadjusted KM curves from the dataset are provided in Figures 5.4 and 5.5 below.

Figure 5.4: Comparison of fitted OS curves (exponential) with unadjusted KM curves for POM+LoDEX and BTD



BTD, bendamustine, thalidomide and dexamethasone; CGP, corrected group prognosis; LoDEX, low-dose dexamethasone; KM, Kaplan-Meier; OS, overall survival; POM, pomalidomide.

Figure 5.5: Comparison of fitted PFS curves (generalised gamma) with unadjusted KM curves for POM+LoDEX and BTD



BTD, bendamustine, thalidomide and dexamethasone; CGP, corrected group prognosis; LoDEX, low-dose dexamethasone; KM, Kaplan-Meier; OS, overall survival; POM, pomalidomide

For time to treatment failure, complete data were only available for POM+LoDEX treatment. The company argued that using standard parametric functions to model the TTF data led to inconsistent TTF estimations that were greater than PFS. Therefore, in the CS, a common treatment effect approach was proposed, in which the unstratified PFS and TTF parametric survival curves were produced for each of the six relevant explored functions, specifying treatment arm 1 as the PFS and treatment arm 2 as the TTF for each individual POM+LoDEX patient in the MM-002 trial. From each of the produced parametric survival curves of PFS and TTF, the treatment effect for TTF relative to PFS was estimated. The estimated treatment effect for TTF relative to PFS was then applied to the corresponding PFS curve

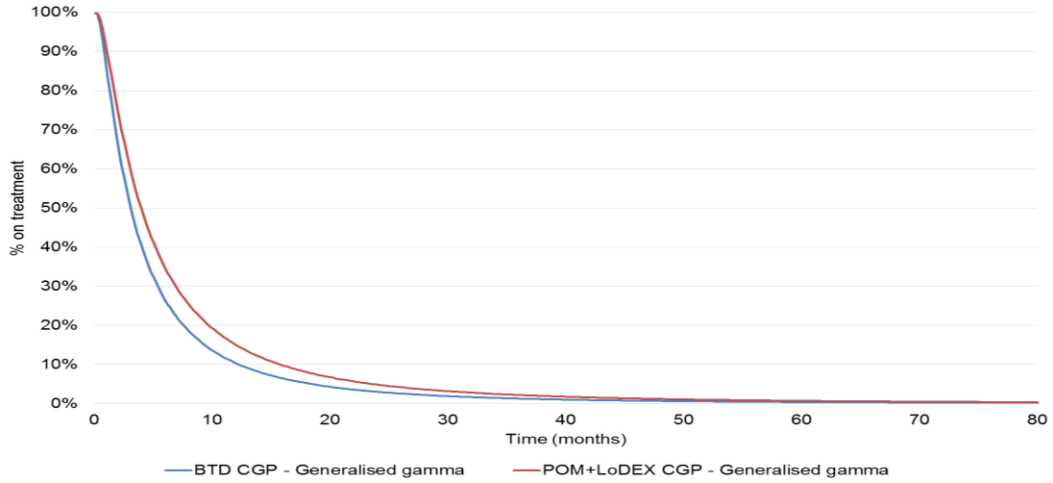
based on the distribution used to model PFS (e.g. generalised gamma curve in the base case) for both POM-LoDEX and BTD arms within the economic model to estimate TTF. The common treatment effects for TTF (relative to PFS) and the resulting TTF curves applied in the base case are given in Table 5.6 and Figure 5.6, respectively.

Table 5.6: Estimated treatment effects for TTF relative to PFS for each parametric model: MM-002 only

Parametric model	Effect
Exponential	0.2074
Weibull	0.0392
Log-normal	0.4382
Log-logistic	0.2853
Gompertz	-0.2037
Generalised gamma	0.2507

BTD, bendamustine, thalidomide and dexamethasone; LoDEX, low-dose dexamethasone; PFS, progression-free survival; POM, pomalidomide; TTF, time to treatment failure

Figure 5.6: Base case TTF curves for POM+LoDEX vs. BTD



BTD, bendamustine, thalidomide and dexamethasone; CGP, corrected group prognosis; LoDEX, low-dose dexamethasone; POM, pomalidomide; TTF, time to treatment failure

POM+LoDEX vs. BTD, results of the survival analyses for PFS, OS and TTF (scenario analysis using POM+LoDEX data from MM-002, MM-003 and MM-010)

For this comparison, the pooled dataset from MM-002[32], MM-003[59], MM-010[33], Gooding[68], Tarant[69]) and MUK-One[67] trials were used.

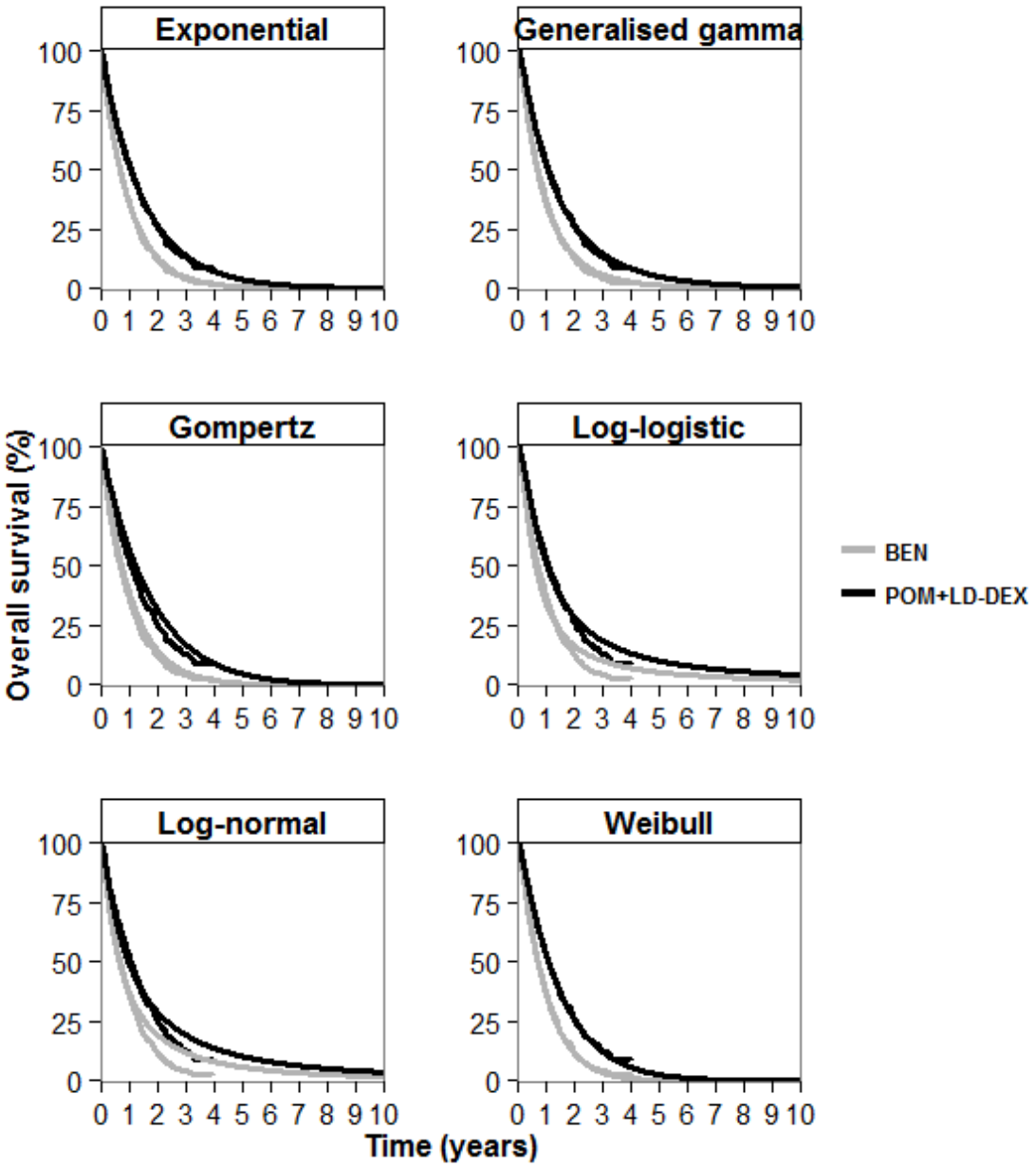
The corresponding OS model fit results can be found in Appendix 18 of the CS[37] (LCHP in Figure 20, Q-Q plot in Figure 21, visual fit of parametric curves using CGP and mean covariate methods to the adjusted KM in Figure 22 and Figure 23, and AIC/BIC statistics in Table 49 of the Appendices[37]).

Similarly, for the PFS, the corresponding results can be found in Appendix 19 of the CS[37] (LCHP in Figure 31, Q-Q plot in Figure 32, visual fit of parametric curves using CGP and mean covariate methods to the adjusted KM in Figure 33 and Figure 34, and AIC/BIC statistics in Table 52 of the Appendices[37]).

For the reader's convenience, the visual fit inspection results of the six explored parametric functions compared to the adjusted KM are presented below (for OS: CGP and mean covariate methods for

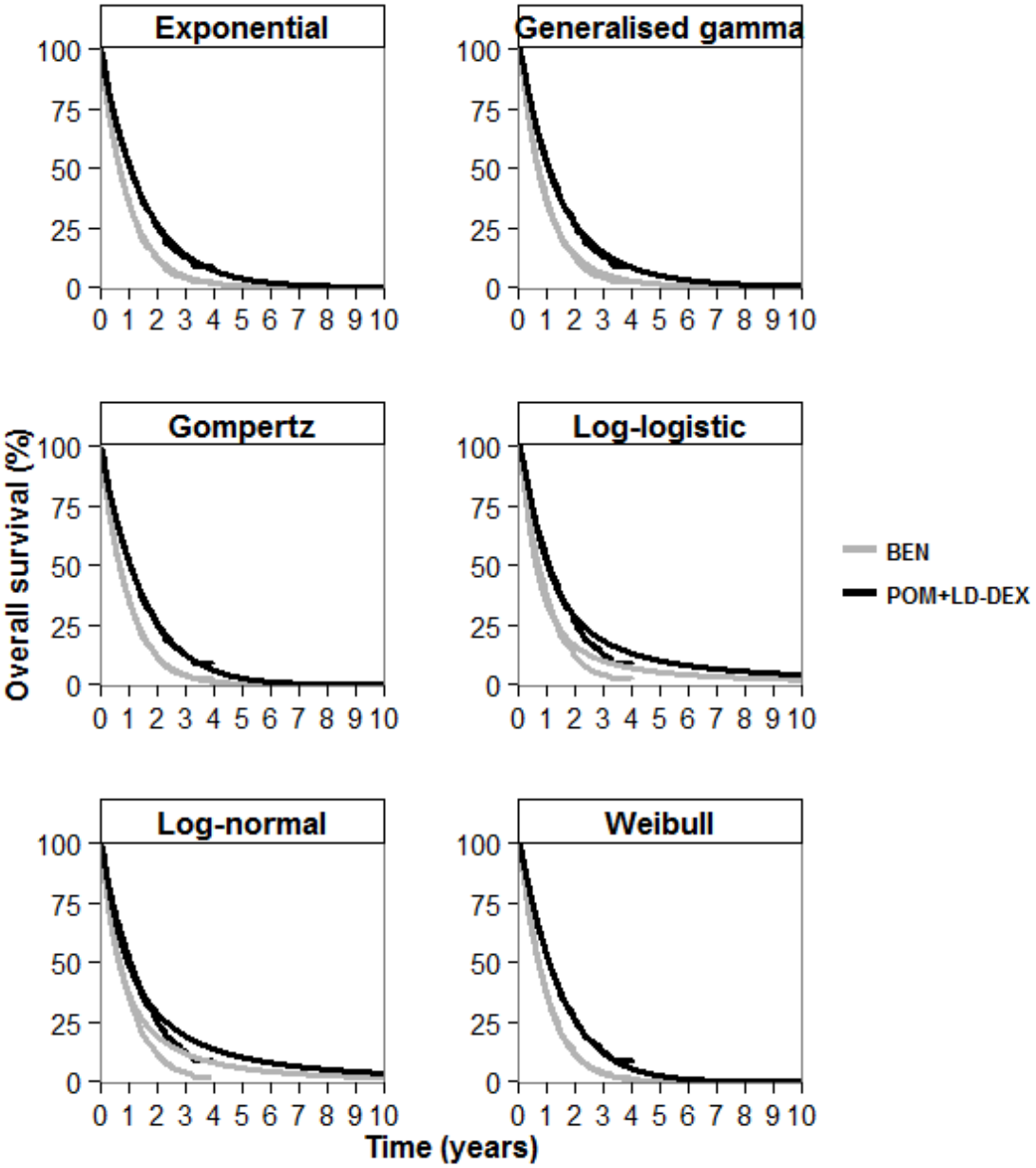
covariate adjustments in Figures 5.7-5.8 and for PFS: CGP and mean covariate methods for covariate adjustments in Figures 5.9-5.10).

Figure 5.7: OS parametric curve fits adjusting for covariates using the CGP method: POM+LoDEX vs. BTD (including MM-003, MM-002 and MM-010)



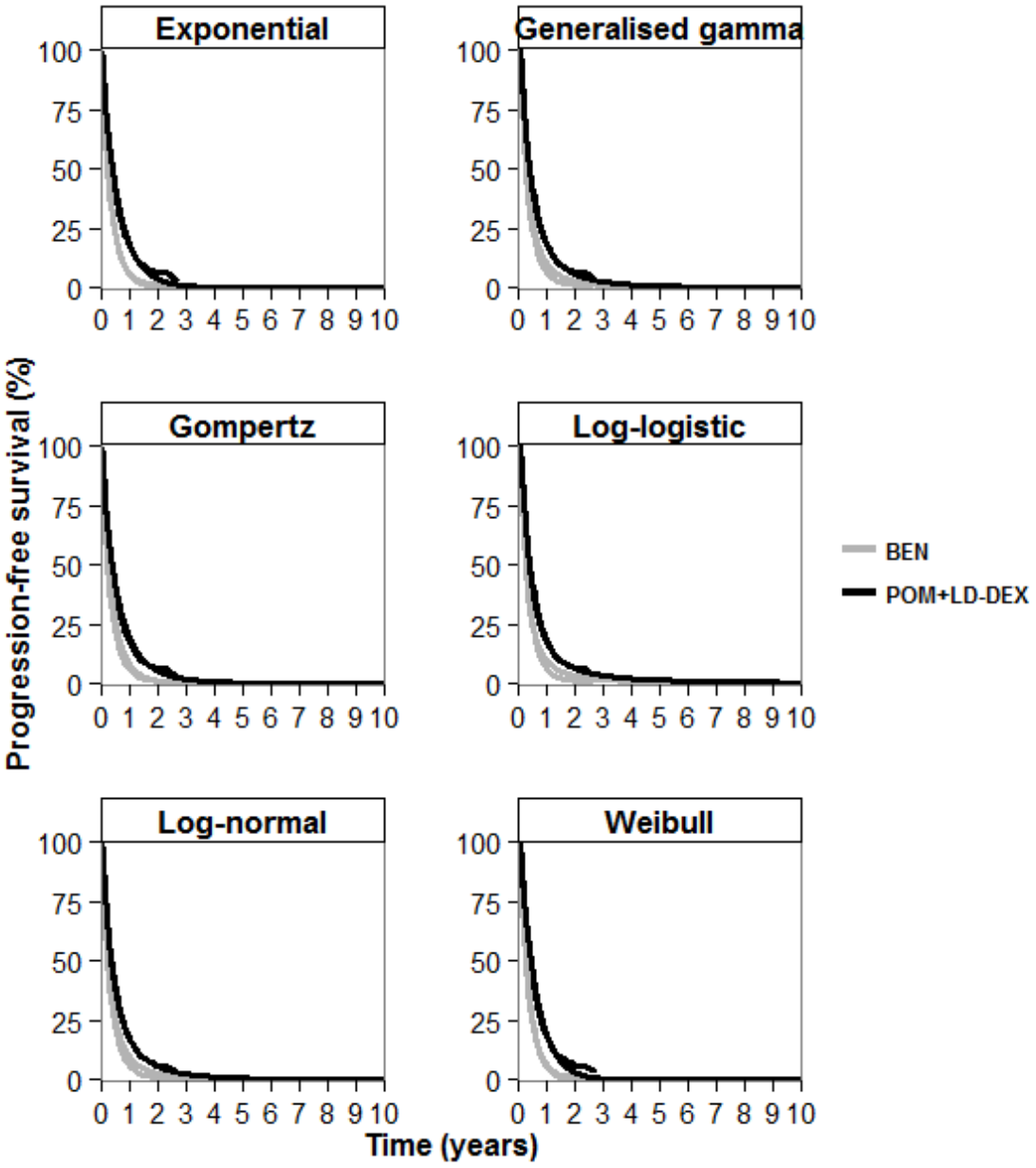
BEN, bendamustine; BTD, bendamustine, thalidomide and dexamethasone; CGP, corrected group prognosis; POM, pomalidomide; LD-DEX/LoDEX, low-dose dexamethasone; MM, multiple myeloma; OS, overall survival

Figure 5.8: OS parametric curve fits adjusting for covariates using the mean covariate method: POM+LoDEX vs. BTD (including MM-003, MM-002 and MM-010)



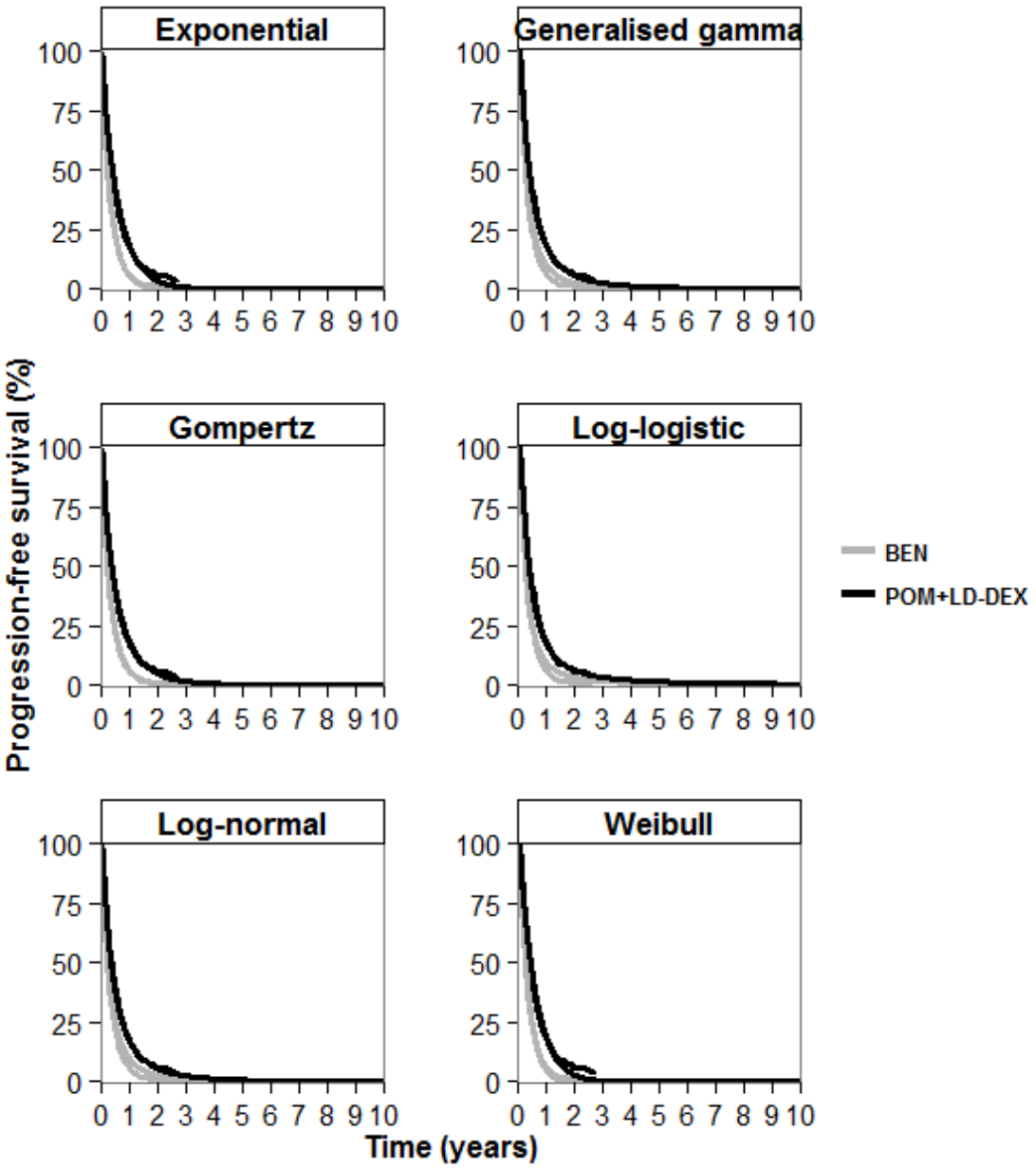
BEN, bendamustine; BTD, bendamustine, thalidomide and dexamethasone; LD-DEX/LoDEX, low-dose dexamethasone; MM, multiple myeloma; OS, overall survival; POM, pomalidomide.

Figure 5.9: PFS parametric curve fits adjusting for covariates using the CGP method: POM+LoDEX vs. BTD (including MM-003, MM-002 and MM-010)



BEN, bendamustine; BTD, bendamustine, thalidomide and dexamethasone; CGP, corrected group prognosis; DEX, dexamethasone; LD-DEX/LoDEX, low-dose dexamethasone; MM, multiple myeloma; PFS, progression-free survival; POM, pomalidomide

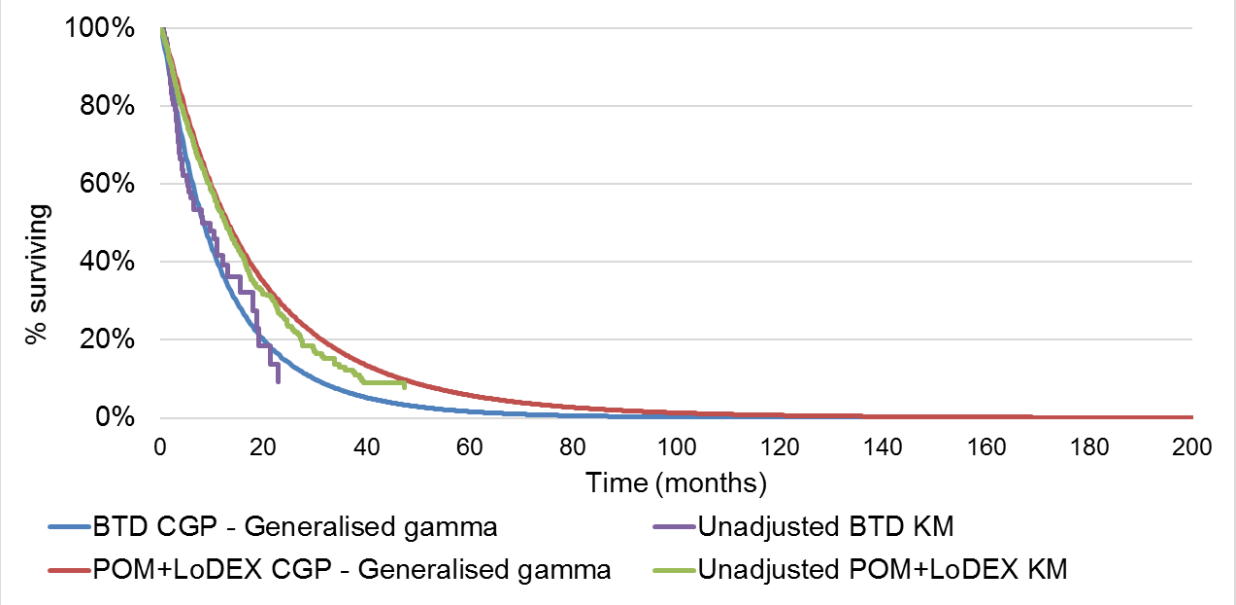
Figure 5.10: PFS parametric curve fits adjusting for covariates using the mean of covariates method: POM+LoDEX vs. BTD (including MM-003, MM-002 and MM-010)



BEN, bendamustine; BTD, bendamustine, thalidomide and dexamethasone; LD-DEX/LoDEX, low-dose dexamethasone; MM, multiple myeloma; PFS, progression-free survival; POM, pomalidomide

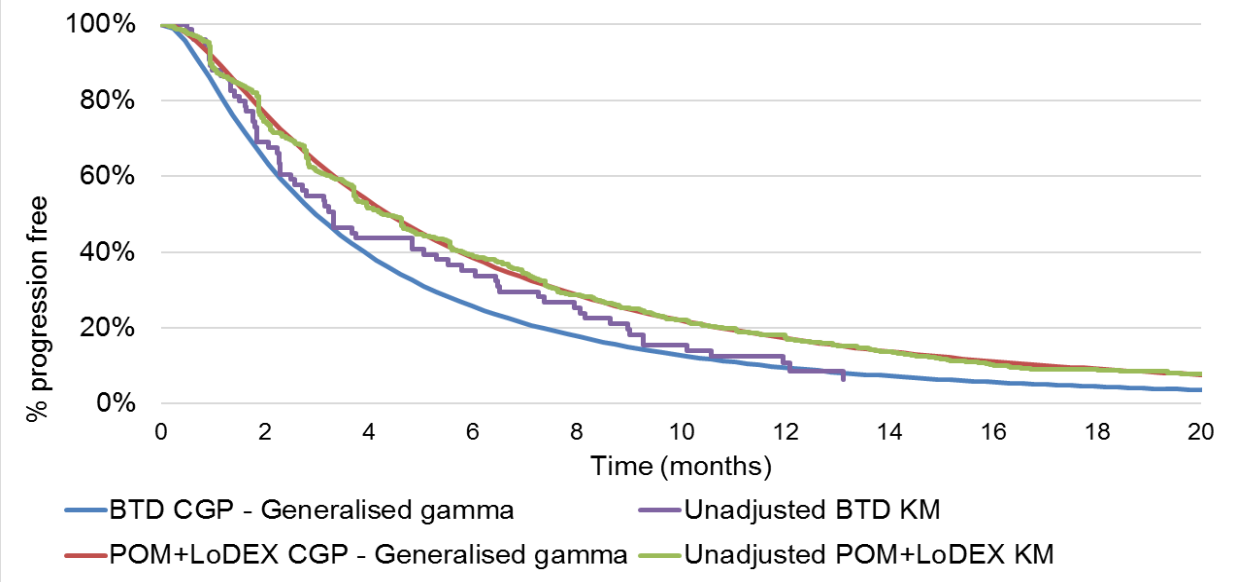
Based on the Q-Q plots (Figure 21 for OS and Figure 32 for PFS from the Appendices[72]), it was discussed that the AFT assumption does not hold neither for the PFS nor for the OS curves of POM+LoDEX and BTD arms. Based on LCHPs (Figure 20 for OS and Figure 31 for PFS from the Appendices), it was argued that that log cumulative hazards seemed to be parallel and proportional hazard assumption was considered plausible for both OS and PFS. Based on AIC/BIC statistics (Table 49 for OS and Table 52 for PFS from the Appendices) and visual fit of parametric curves with adjusted KM, the generalised gamma function was selected as the best parametric function for modelling both OS and PFS curves related to the POM+LoDEX and BTD arms. These selected parametric curves (generalised gamma for both OS and PFS) in comparison to the corresponding unadjusted KM curves from the dataset are provided in Figures 5.11-5.12 below.

Figure 5.11: Comparison of fitted OS curves (exponential) with unadjusted KM curves for POM+LoDEX and BTD (MM-002, MM-003 and MM-010 trials)



BTD, bendamustine, thalidomide and dexamethasone; CGP, corrected group prognosis; LoDEX, low-dose dexamethasone; KM, Kaplan-Meier; OS, overall survival; POM, pomalidomide

Figure 5.12: Comparison of fitted PFS curves (exponential) with unadjusted KM curves for POM+LoDEX and BTD (MM-002, MM-003 and MM-010 trials)



BTD, bendamustine, thalidomide and dexamethasone; CGP, corrected group prognosis; LoDEX, low-dose dexamethasone; KM, Kaplan-Meier; OS, overall survival; POM, pomalidomide

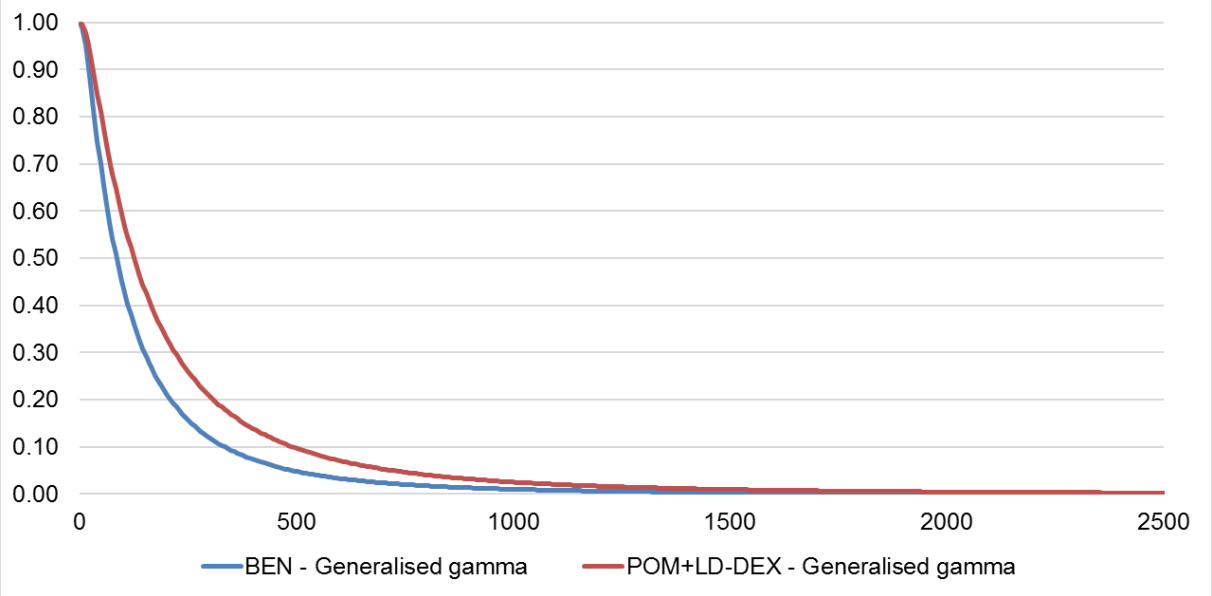
For modelling time to treatment failure, complete data was only available for POM+LoDEX, and the same approach (common treatment effect) was followed for this dataset, as well. The common treatment effects for TTF (relative to PFS) obtained from the extended dataset (MM-002, MM-003 and MM-010) and the resulting TTF curves applied in the base case are given in Table 5.7 and Figure 5.13, respectively.

Table 5.7: Estimated treatment effects for TTF relative to PFS: pooled dataset MM-003, MM-010 and MM-002

	Effect
Exponential	0.0415
Weibull	0.0392
Log-normal	0.1029
Log-logistic	0.0434
Gompertz	0.0420
Generalised gamma	-0.0575

BOR, bortezomib; DEX, dexamethasone; LoDEX, low-dose dexamethasone; PFS, progression-free survival; POM, pomalidomide; TTF, time to treatment failure.

Figure 5.13: TTF curves for POM+LoDEX vs. BTD (based on data from MM-002, MM-003 and MM-010 trials)



BEN, bendamustine; LD-DEX, low-dose dexamethasone; POM, pomalidomide; TTF, time to treatment failure

POM+LoDEX vs. PANO+BOR+DEX, results of the survival analyses for PFS, OS and TTF

For the POM+LoDEX vs. PANO+BOR+DEX comparison, OS and PFS data from MM-002, MM-003, MM-010 and PANORAMA-2 trials were used.

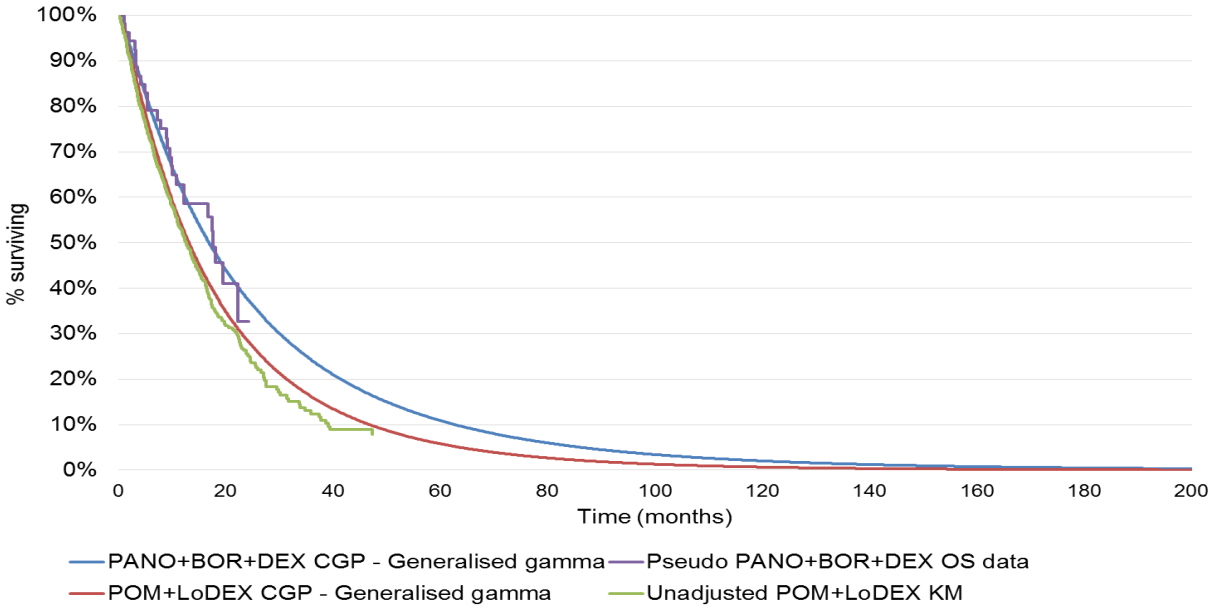
To determine the appropriateness of fitting a Cox regression model to the POM+LoDEX and PANO+BOR+DEX data, first, patient level data for the subgroup of patients who were refractory to BOR but were not primary refractory (number of prior lines>1) were obtained from MM-003, MM-002 and MM-010 trials and afterwards they were compared with the pseudo patient level data (estimated from the published survical curve) from PANORAMA-2 trials. Propensity weights were calculated for the POM+LoDEX data based on the summary table of the observed baseline characteristics in PANORAMA-2 trial with respect to age, prior lines of therapy, receipt of prior THAL and ECOG.

The weighted patient level-data for POM+LoDEX and pseudo patient-level data for PANO+BOR+DEX were included in a Cox proportional hazards model to calculate a MAIC OS and PFS HRs between PANO+BOR+DEX and POM+LoDEX. The details of the calculations were given in the Section 4.10 of CS.[3]

The Cox proportional hazards models estimated a HR of 0.778 [95% CI: 0.555 – 1.090] for OS and a HR of 1.178 [95% CI: 0.893 – 1.555] for PFS of the PANO+BOR+DEX compared with the matched POM+LoDEX population. These HRs was applied to the parametric functions fitted to the OS/PFS data taken from the full POM+LoDEX trial datasets (MM-003, MM-002 and MM-010).

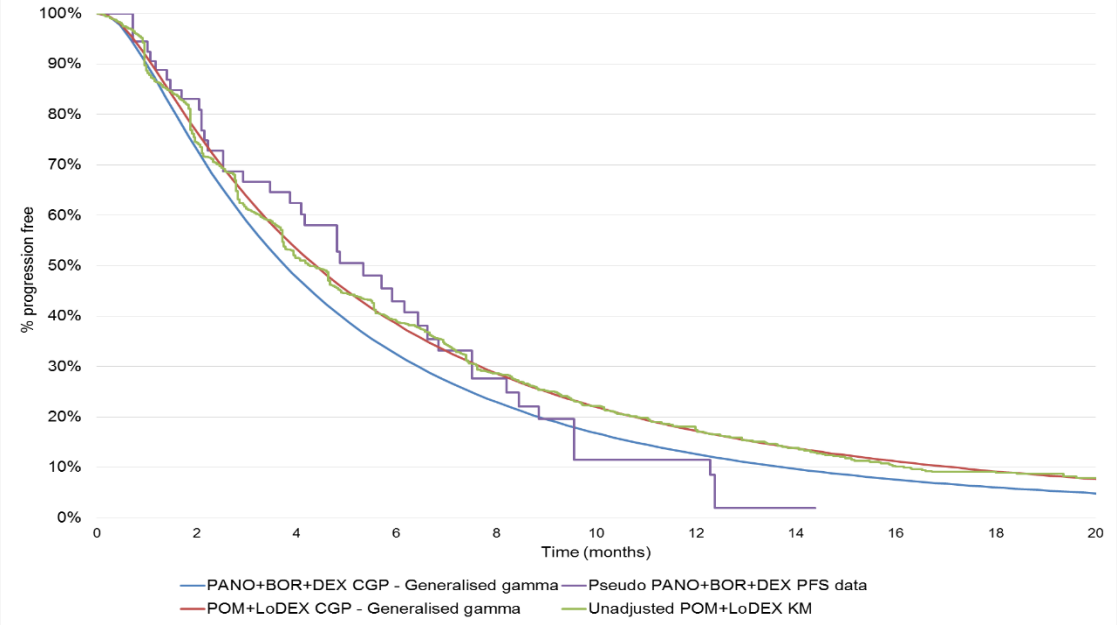
A comparison of the modelled POM+LoDEX and PANO+BOR+DEX curves (generalized gamma) compared with the unadjusted POM+LoDEX KM data from the pooled dataset (including MM-002, MM-003 and MM-010 trials) and pseudo patient level PANO+BOR+DEX KM data from PANORAMA-2 trial can be seen in Figures 5.14 and 5.15 for OS and PFS, respectively.

Figure 5.14: Comparison of fitted curves (generalised gamma) for OS with unadjusted POM+LoDEX KM data (including MM-003, MM-002 and MM-010) and pseudo patient level data for PANO+BOR+DEX



BOR, bortezomib; CGP, corrected group prognosis; DEX, dexamethasone; KM, Kaplan-Meier; LoDEX, low-dose dexamethasone; OS, overall survival; PANO, panobinostat; POM, pomalidomide

Figure 5.15: Comparison of fitted curves (generalised gamma) for PFS with unadjusted POM+LoDEX KM data (including MM-003, MM-002 and MM-010) and pseudo patient level data for PANO+BOR+DEX



BOR, bortezomib; CGP, corrected group prognosis; DEX, dexamethasone; KM, Kaplan-Meier; LoDEX, low-dose dexamethasone; OS, overall survival; PANO, panobinostat; POM, pomalidomide

To assess the appropriateness of the proportional hazards assumption, the LCHP and the Q-Q plots for the POM+LoDEX vs. PANO+BOR+DEX comparison were given in Figures 24 and 25 for the OS, and in Figures 35 and 36 for the PFS in the Appendices of the CS.[3]

The LCHPs and the Q-Q plots for the OS curves (Figures 24 and 25 in the Appendices) for POM+LoDEX vs. PANO+BOR+DEX comparison indicated towards the appropriateness of the proportional hazards assumption, whereas for PFS, the LCHPs (Figure 35 in Appendices) depict the lack of a parallel trend, conflicting with the proportional hazard assumption in the fitting the Cox proportional hazards model.[37] Nevertheless, the company applied the Cox proportional hazard model both for OS and PFS.

For TTF of the POM+LoDEX arm, the same approach that had been followed while calculating the TTF curves for the POM+LoDEX vs. BTD analysis was used (based on pooled data from MM-002, MM-003 and MM-010 trials).

PANO+BOR+DEX is a fixed dose regimen, and therefore treatment does not exceed 42 weekly cycles within the model (14 treatment cycles of 21 days each). In the model, it was assumed that all patients are treated until the first of either progression or end of the fixed dose, therefore no TTF curve was applied.

POM+LoDEX vs. CC, results of the survival analyses for PFS, OS and TTF

The POM+LoDEX vs. CC comparison was a within trial comparison based on data from the MM-003 trial, where POM+LoDEX and HiDEX were compared and the latter was used as a proxy for conventional care. In the original NICE (TA 338) submission[85], the OS estimates for the exponential, log-normal, log-logistic and Weibull curves for the HiDEX data were provided. In order to account for treatment switching within the MM-003 trial, two methods were used: the two-stage method and the rank preserving structure failure time model (RPSFTM) approach. Parametric functions for PFS and

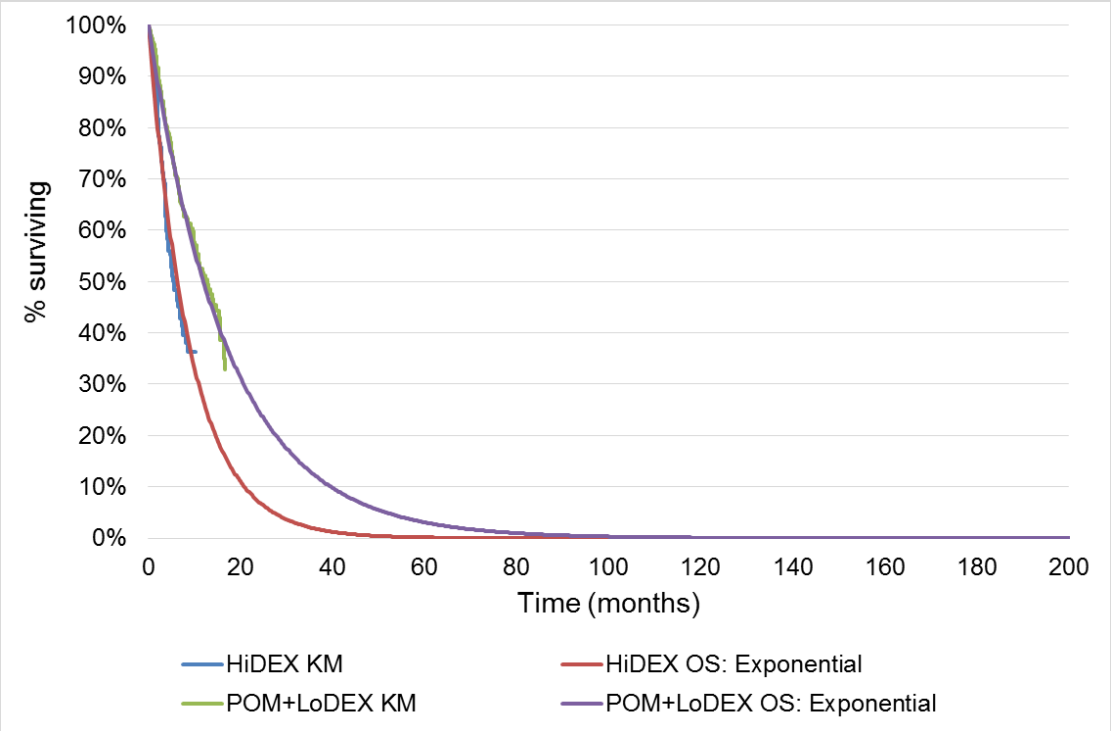
TTF were also fitted using the Kaplan Meier data from the trial. For PFS and TTF, additionally, the extreme value curve was also considered.

In this resubmission[3], in addition to the parametric functions in the previous technology appraisal[85], the generalised gamma and Gompertz parametric curves were also fitted, using both the two-stage and RPSFTM methods.

The final choice of parametric distribution to model OS, PFS and TTF curves was based on the Q-Q plots, AIC/BIC statistics and visual fits. The results of these methods can be found in Appendices 18 and 19 from the CS[37], as well as in the previous submission (TA 338) of POM+LoDEX[85].

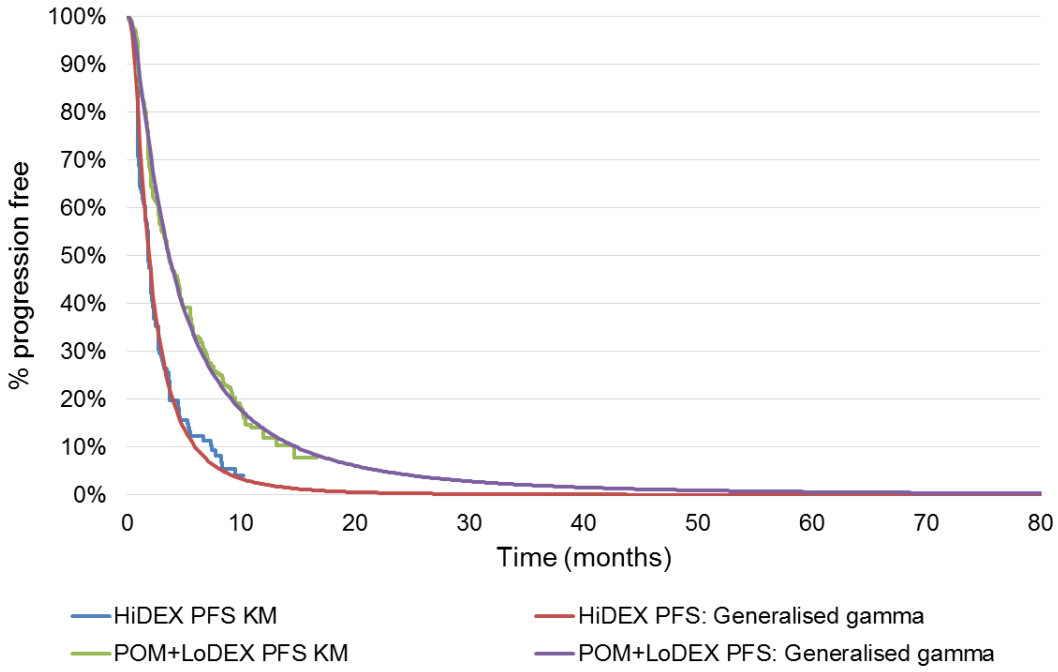
Based on these methods, in the CS[3], it was mentioned that the exponential adjusted curve, using the two stage Weibull approach had provided the best fit for the OS data. The generalised gamma curve was selected as the base case for the parametric distribution for modeling the PFS data and the extreme value distribution was selected as the base case for the parametric distribution for modeling the TTF data. The comparison of fitted curves with the OS, PFS and TTF KM data can be seen in Figures 5.16-5.18 below.

Figure 5.16: Comparison of fitted curves (exponential) for OS with POM+LoDEX and HiDEX KM data



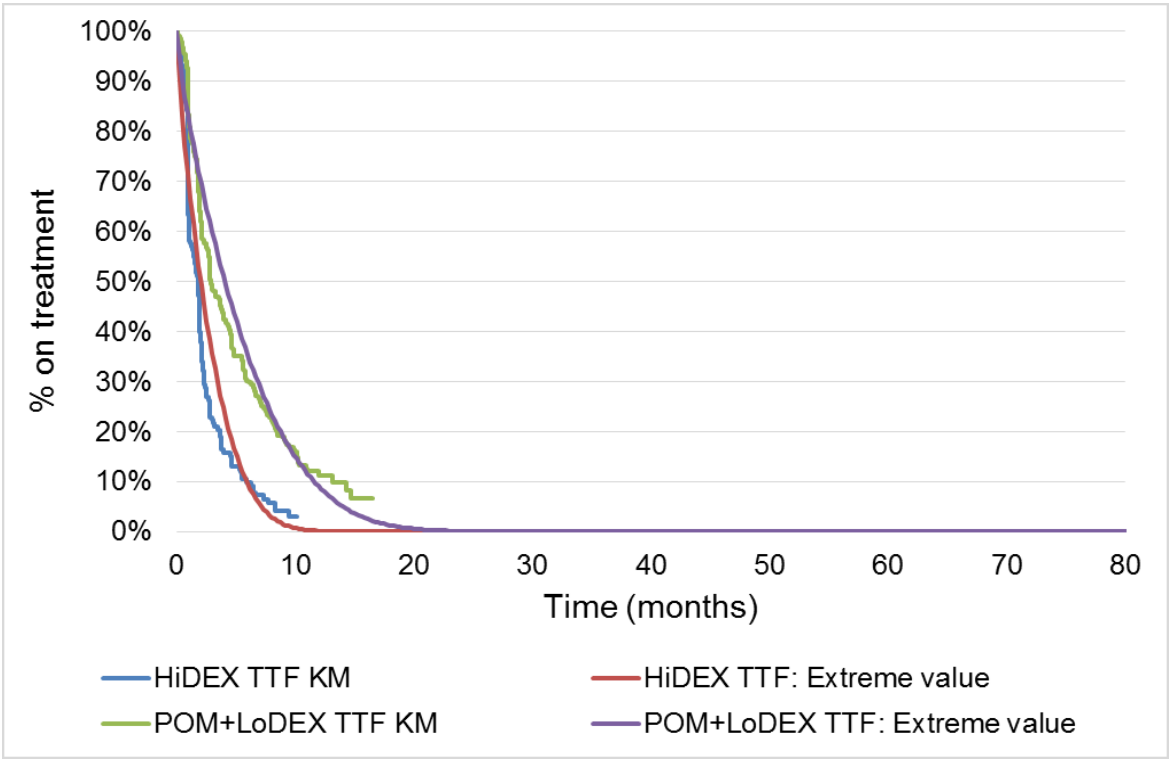
HiDEX, high-dose dexamethasone; KM, Kaplan-Meier; LoDEX, low-dose dexamethasone; OS, overall survival; POM, pomalidomide

Figure 5.17: Comparison of fitted curves (generalised gamma) for PFS with POM+LoDEX and HiDEX KM data



HiDEX, high-dose dexamethasone; KM, Kaplan-Meier; LoDEX, low-dose dexamethasone; PFS, progression-free survival; POM, pomalidomide

Figure 5.18: Comparison of fitted curves (generalised gamma) for PFS with POM+LoDEX and HiDEX KM data



HiDEX, high-dose dexamethasone; KM, Kaplan-Meier; LoDEX, low-dose dexamethasone; POM, pomalidomide; TTF, time to treatment failure

ERG comment: The main issues and critique given in Section 4.4 apply for this section, as well. The results should be interpreted with caution, because even though some of the baseline covariates were adjusted, there can be still some unmeasured confounders or other factors that add uncertainty to the treatment effectiveness results of the CS (e.g. the fact that refractoriness to BOR was not in the dataset, the representativeness of the HiDEX efficacy for the conventional care, etc.).[3]

In the CS[3], a different dataset is used for each of the three comparisons (bendamustine trials and MM-002 only for POM+LoDEX vs BTD, PANORAMA-02 and MM-002, MM-003 and MM-010 and for POM+LoDEX vs PANO+BOR+DEX and MM-003 trial for POM+LoDEX vs CC). The ERG considers that this pairwise approach is not that informative, because the decision for POM+LoDEX should be based on a fully incremental analysis. Furthermore, the pairwise approach is more prone to bias, for instance due to differences in baseline characteristics of the three datasets used, different cost and QALY outcomes were estimated for the same treatment (POM+LoDEX), in the three different comparisons. It might be reasonable to have three different estimates if they related to three different populations. However, the ERG considers that the differences between the baseline characteristics of the datasets cannot be directly generalised to UK clinical practice, i.e. it is not possible to define an exact subgroup for whom only POM+LoDEX vs BTD is relevant as opposed to any of the other comparators. Moreover, there is no convincing reason *why* different relevant patient populations should be considered for different comparisons, e.g. for POM+LoDEX vs BTD and for POM+LoDEX vs PANO+BOR+DEX.

Therefore, the ERG requested the company to provide a full incremental analysis using a single source of data for POM+LoDEX and applying any treatment effect between POM+LoDEX and the other compactors as required. The company did this using pooled data from all POM+LoDEX (MM-002, MM-003 and MM-010) and all BTD trials. After the OS and PFS of POM+LoDEX and BTD are obtained, the OS and PFS of both PANO+BOR+DEX and CC were estimated using proportional hazards assumption, by applying the corresponding treatment effects (HR) for OS/PFS on the POM+LoDEX OS/PFS. This approach enables a full incremental analysis between comparisons.

For the effect of treatment on survival, to adjust for selection bias, with PANO+BOR+DEX, the 'MAIC' based on aggregate trial data method was used and for BTD, regression analysis based on individual patient data (IPD) was used. Matching and regression analysis based on IPD are given as options in the NICE Decision Support Unit Document 17 on the use of observational data and, as such, appear to be reasonable approaches.[86] For implementing these adjustments in the model, only two methods (CGP and mean covariate adjustment) were discussed. Another method might have been individual patient simulation given its availability for POM+LoDEX and BTD and that the curve for PANO+BOR+DEX was calculated by applying a HR to the curve for POM+LoDEX. Therefore, the selection of these methods seemed arbitrary, as no explanation was given in the CS for the selection of either of these methods and why the CGP method was selected in the base-case analysis rather than the mean covariate method.

Moroever, prediction can also be used to incorporate real world data on baseline characteritics. In Ghali et al. 2001, which is the main reference that the company cited for the definition of CGP and mean covariate adjustment methods, it was mentioned that for the latter method, the mean value of the covariates (derived from the dataset analysed) should be inserted into the survival function.[83] However, in the model, the company did not insert the mean covariate values from the dataset to the survival function, but instead used real world data obtained from a number of UK centres.[46, 47] Technically it is not wrong to use real world data for the baseline characteristics (it is actually preferable), but then the difference between CGP and mean covariate methods in the CS is not only due to the difference in methods, but the combined effect of difference in methods and baseline assumptions.

The ERG identified some errors in the implementation of the CGP method that was causing inconsistent survival outcomes (e.g. greater than 100%). After the ERG had notified the company, these errors were corrected in the model submitted after the clarification letter.[38] In addition, the ERG obtained different OS/PFS results than the OS/PFS results used in the model, after following the steps for CGP method implementation provided in the response to clarification letter.[38] In the exploratory analyses conducted by the ERG, the OS/PFS results that were obtained are those after following these steps.

The ERG finds the "common treatment effect" assumption between TTF and PFS questionable, because with this approach, the underlying assumption is that the TTF (or the number of patients on treatment) is always less than PFS (or number of patients in pre-progression), whereas in clinical practice TTF can be the same as PFS. Moreover, the ERG also thinks that the "common treatment effect" derived from POM+LoDEX may not hold true for BTD, since these are two different type of drugs with different ways of administration. Lastly, the ERG does not agree with the company about the model assumption that treatment discontinuation only occurs with progression for PANO+BOR+DEX patients. This assumption is explored by the ERG in Section 5.3.

During the parametric survival function selection procedure, especially during the visual assessment fit step, it was not clear to the ERG what sort of data (unadjusted vs. adjusted) was used in the graphs where visual fit between the parametric model function and KM data from the trial were assessed. Upon the ERG's request, the company stated that the unadjusted raw data from the trials were compared with the covariate adjusted fitted survival functions. However, the ERG is unclear whether the covariate adjustment methods applied for the parametric model selection assume each time a common baseline for both arms. The ERG considers that, for the assessment of the visual fit of the parametric survival functions, if the KM data of the comparators come from separate trials, it might be more plausible to assume arm specific baselines instead of assuming a common baseline derived from pooled dataset for different arms. Unfortunately, within the STA timeline, the ERG was unable to undertake additional OS/PFS analysis, and assess visual fit between raw KM data from trials with covariate adjusted parametric functions using arm-specific baseline characteristics.

5.2.7 Adverse events

In the CS, it was mentioned that treatment emergent adverse events (TEAEs) grades 3 and 4 were included in the economic analysis if they occurred in at least 2% of POM+LoDEX patients in the MM-003 trial dataset. The MM-002 and MM-010 trials were not taken into the consideration, since they were lacking the necessary level of detail for adverse events. Furthermore, no separate treatment emergent adverse event rate data for the comparator treatments were found in the literature.

Therefore, in the CS, two approaches were followed in order to estimate the impact of AEs on patients under differing treatments:

1. Use of the proportion of patients that discontinued treatment due to a TEAE under a comparator treatment relative to the proportion of patients discontinuing in the POM+LoDEX arm of the MM-003 trial. This approach provides relative changes in the proportion of TEAEs occurring in at least 2% of patients. This relative increase or decrease is then applied to each of the included adverse events in the model.
2. Use of relative safety estimates provided by the advisory board (March 2016).[87]

In the base-case, the first approach was followed. In both of the approaches, the adverse event rates were not adjusted based on covariates due to limited data availability on the toxicity data.

In the first approach, the TEAE related treatment discontinuation proportions (relative to the TEAE discontinuations MM-003) were calculated based on the data given in Table 5.8 below.

Table 5.8: Percentage change in AEs derived from treatment discontinuations due to AEs for different treatments sourced from different trials

Treatment	Trial name	No discontinued due to AE	Total No	% discontinued due to AEs	% change relative to MM-003 - discontinuation due to AEs
POM+LoDEX	MM-003	26	302	8.61%	100.00%
	MM-002	8	113	7.08%	82.23%
	MM-010	34	682	5.00%	58.08%
BTD	MUK-ONE	11	66	16.67%	193.59%
PBD	PANORAMA-2	10	55	18.18%	211.19%
Hi-DEX	MM-003	16	153	10.46%	121.47%

AE, adverse event; BTD, bendamustine + thalidomide + dexamethasone; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; PBD, panobinostat; POM, pomalidomide

This method estimates a relative decrease in TEAEs for the POM+LoDEX arms in all POM+LoDEX trials (27.89% decrease), and a relative increase in TEAEs for CC, BTD and PANO+BOR+DEX (21.47%, 93.59% and 111.19% increase, respectively). These relative changes in discontinuation proportions in Table 5.8 were applied to the TEAE rates derived from the MM-003 trial occurring in at least 2% of patients. The final AE rates resulting from this approach that were used in the model can be found in Appendix 21 of the CS.

In the second approach, TEAE rates were estimated by applying the relative safety scores provided by clinicians during an advisory board to the POM+LoDEX data sourced from MM-003 trial. The safety scores for the treatments given by the clinic experts during the advisory board[87] and these scores were translated to the corresponding relative changes in the TEAEs as in Table 5.9 below.

Table 5.9: Percentage change in AEs derived from safety scoring in advisory board

	Average score out of 10	% change relative to MM-003 - clinician tolerability scores
POM+LoDEX	7.40	100.00%
BTD	4.70	63.51%
PBD	3.90	52.70%
HiDEX	4.30	58.11%

AE, adverse event; BTD, bendamustine + thalidomide + dexamethasone; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; PBD, panobinostat; POM, pomalidomide

This method estimates a relative decrease in TEAEs compared with POM+LoDEX for BTD, PANO+BOR+DEX and conventional chemotherapy; 36.5%, 47.3% and 41.9%, respectively. These relative changes in Table 5.9 were applied to the TEAE rates derived from the MM-003 trial (TEAEs occurring in at least 2% of patients). The final AE rates for each treatment obtained from this approach can be found in Appendix 21.[37]

As an additional analysis, in the CS, the AE rates that were based on AEs (for both POM+LoDEX and HiDEX) occurred in the MM-003 trial after three weeks were compared to each other.[3] This analysis was conducted to assess the long-term safety profile of POM+LoDEX. From this analysis, the company discussed that the AE rates applied in the model would be an overestimate, given that their findings from this analysis suggested that a greater proportion of patients on the POM+LoDEX arm remain AE

free after the initial three treatment cycles. The details of this additional analysis can be found in Appendix 22 in the CS.[37]

ERG comment: In the CS[3], it was mentioned that an AE was included if an AE had occurred in at least 2% of POM+LoDEX patients in the MM-003 trial dataset the initial three treatment cycles. However, the ERG had identified a potential reporting error, because in the electronic model, it appears as if an AE was included if an AE had occurred in at least 2% of both HiDEX and POM+LoDEX arms in the MM-003 trial dataset. Similar to the issue raised by the previous TA338 submission[73], the 2% threshold seems to be chosen arbitrarily, though is not uncommon in company submissions to NICE.

For the POM+LoDEX AE disutilities, the overall AE rate is used in the utility regression, whereas for the costs, a unique cost and rate for each of the AE type were taken into account. For the comparators of POM+LoDEX, in the base case, the proportion of TEAE discontinuation probabilities (compared to POM+LoDEX) was multiplied with the POM+LoDEX specific AE rates for each comparator.

The ERG has concerns on the approach discussed above. Firstly, the TEAE discontinuation probabilities for each comparator were derived from disconnected parallel trials without any adjustments for baseline characteristic differences. Secondly, the approach above would mirror the frequency order of the AEs of POM+LoDEX (MM-003 trial) for each of the comparators, in the same magnitude. For instance, if neutropenia is the most common AE for POM+LoDEX, it will be also the most common AE for BTD and PANO+BOR+DEX. The ERG considers this assumption not to be plausible, because each drug has different working mechanisms and different safety profiles, and it is unlikely that the AE frequency order would be mirrored for other comparators, in the same magnitude.

Finally, the ERG suspects that in the scenario analysis in which the clinician estimates for tolerability scores were used, the scores were misinterpreted, because in the electronic model, it appears as if a higher tolerability score leads to more AEs, and this scenario analysis gives contradictory results with the base case. As this approach is not used in the base case, the ERG did not want to correct it before company's confirmation, in the new model used in the exploratory analyses.

5.2.8 Health-related quality of life

Health-related quality of life data from the MM-003

In section 5.4 of the CS the measurement and valuation of health effects is described.[3] Within the model's base-case data from the MM-003 trial were used (no data about HRQL was collected in the MM-002 or MM-010 trial). In the MM-003 study, HRQL was measured using the EQ-5D-3L, the EORTC QLQ-C30 and the EORTC QLQ-MY20 on the first day of every cycle, and at study discontinuation and treatment phase discontinuation visits. EQ-5D utilities were derived by combining the answers to the EQ-5D-3L with the EQ-5D UK tariff.[88]

To determine the most important predictors of HRQL (using the EQ-5D) over all time points, the company conducted a multivariate analysis using a mixed effect model. Potential explanatory variables of HRQL were determined in consultation with UK clinicians.[89] A separate analysis was run by converting the EORTC QLQ-C30 to utilities using the EORTC-8D algorithm by Rowen et al.[90] Table 5.10 shows the explanatory variables and their coefficients to predict utilities (based on the EQ-5D and EORTC-8D). Stepwise and backward selection provided identical results. The results of a forward selection procedure were discarded. The regression model derived from EQ-5D data was used in the base-case to estimate utilities, in accordance with the NICE reference case. However, the results of residual diagnostic tests (Appendix R of CS TA338) suggest a statistical preference for the model based upon EORTC-8D values, since the data better satisfy the underlying multivariate model

assumption of normality of the outcome variable (utility). Therefore, the company explored the use of the disease-specific EORTC-8D model is explored in a scenario analysis.

Table 5.10: Regression coefficients to predict utilities, obtained using EQ-5D and EORTC-8D from the MM-003 trial

Item	Stepwise and backward selection	
	EQ-5D	EORTC-8D
Intercept	0.727	0.703
Disease progression	-0.037	-0.035
BORR: Stable Disease (relative to response)	-0.095	-
BORR: Progressive Disease (relative to response)	-0.139	-
Age (decades)	-	-
Age^2	-	-
Hospitalisation	-0.138	-0.080
Adverse event(s)	-0.076	-0.035
Gender: male	0.074	0.027
Baseline ECOG = 1 (relative to 0)	-0.134	-0.066
Baseline ECOG = 2 or 3 (relative to 0)	-0.332	-0.118
Baseline Durie Salmon stage = 1 (relative to 3)	0.030	-
Baseline Durie Salmon stage = 2 (relative to 3)	0.071	-
Log(Prior lines of treatment)	-	-
RBC level (10^{12}/l)	0.049	0.033
European	-0.069	-

BORR, best overall response rate; ECOG, European Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; EORTC-8D, EORTC eight dimension questionnaire; RBC, red blood cell.

The regression coefficients were combined with estimates of the explanatory variables. These estimates were based on data from various sources. The estimates for disease progression, best overall response, hospitalisations and adverse events differ between POM+LoDEX and its comparators. These are provided in Table 5.11, except for disease progression as the proportions of patients with disease progression were derived from the PFS analyses. All other explanatory variables were kept the same across treatments within a comparison (but not across comparisons). The estimates were derived from real-world evidence or data from the MM-002, MM-003 and/or MM-010 trial (depending on the comparison).

Table 5.11: Estimates of explanatory variables to inform the regression models

Explanatory variable	POM+LoDEX			BTD[91]	PANO + BOR+ DEX[70]	Conventional chemo-therapy[d59]
	MM-003, MM-002, MM-010	MM-002	MM-003			
BORR: Response to therapy	33.09%[a]	33.00%	31.10%	40.91%	34.50%	10.37%
BORR: Stable Disease	48.22%[b]	37.00%	50.70%	23.62%	36.40%	59.26%
BORR: Progressive Disease	18.69%[c]	30.00%	18.20%	35.47%	29.10%	30.37%
Hospitalisation			5.5%	6.4%[e]	6.4%[e]	6.4%
Adverse event(s)	3.7%	4.2%	5.1%	9.6%	10.5%	6.2%

Notes: a, Weighted proportion across MM-003, MM-002 and MM-010; b, Weighted proportion across MM-003 and MM-002 (stable disease not presented for MM-010); c, normalised using data only from MM-003; d, due to lack of data for conventional chemotherapies HiDEX is used as a proxy; e, due to lack of data assumed to be the same as for conventional chemotherapies (i.e. HiDEX used as proxy).
BOR, bortezomib; BORR, best overall response rate; BTD, bendamustine + thalidomide + dexamethasone; DEX, dexamethasone; LoDEX, low-dose dexamethasone; PANO, panobinostat; POM, pomalidomide

Best overall response rates (BORRs) were derived from the literature, and the associated utility decrements were applied in the model from week 12 onwards (until death). The model assumes that before 12 weeks all patients achieve a BORR of stable disease, relative to response; after these 12 weeks the values of Table 5.11 are used. In a scenario-analysis, BORRs are assumed equal between POM+LoDEX and the comparators after treatment discontinuation to account for the suggestion that the impact of BORR on HRQL cannot be extrapolated over the full time horizon of the model.

The proportions of patients who require a hospitalisation were derived from the MM-003 trial in which hospitalisations up to 28 days following treatment discontinuation were collected. Weekly cycle rates of hospitalisations were 0.055 for POM+LoDEX and 0.064 for HiDEX, where the hospitalization rate for HiDEX was assumed to apply to the comparators. This assumption is deemed plausible by the company, as the study by Gooding et al [ref CS37] showed a weekly hospitalisation rate for BTD of 0.061. The latter value is used in a scenario analysis. Similar to BORRs, it is assumed that hospitalisation and the associated utility decrement can be extrapolated and held constant for the remaining time (until death).

In the regression analysis a single coefficient for adverse events was estimated. The derivation of TEAEs is discussed in Section 5.2.7. The resulting cycle rates are 3.7%, 9.6%, 10.5% and 6.2% for POM+LoDEX, BTD, PANO+BOR+DEX and conventional chemotherapy, respectively. These were multiplied by the percentage of patients on therapy. In a scenario-analysis, utility decrements associated with adverse events were derived from the literature for each adverse event separately, and weighted for the duration of these events. These duration-weighted decrements were then multiplied by the adverse event rates per year for each event and treatment to provide overall adverse event related utility decrements per year per treatment.

Lastly, the company included a utility decrement of 0.025 in the base-case for patients receiving IV or SC therapy. This is based on the premise that the use of an oral agent such as POM reduces the treatment burden on both patients and carers, relative to IV and SC treatments. The utility decrement was derived from two previous NICE appraisals in small cell lung cancer,[92, 93] as no multiple myeloma specific information was available.

Health-related quality of life data from literature

The company updated the SLR from the previous NICE submission (TA338). In addition to the six studies identified as part of the original SLR, four additional (unique) studies reporting utilities (or presenting data that could be mapped to derive utilities) of RRMM patients were identified.[94-97] The populations in these studies were less refractory and less heavily pre-treated than the population as described in the final scope. As a consequence, the utilities as found in these studies are not representative for the utilities of patients with RRMM who have had at least two prior treatment regimens (including both lenalidomide and bortezomib). Nevertheless, the utilities as reported by Quin et al. were used in a scenario-analysis, as this study is the only study that reported utilities in RRMM patients by health state[96]: 0.733 before progression and 0.710 post-progression. In this phase III clinical trial, elotuzumab plus lenalidomide and dexamethasone was compared with lenalidomide and dexamethasone in patients with RRMM. Utilities were based on the EORTC QLQ-C30 and the EORTC QLQ-MY20 (combined with a mapping algorithm developed by Proskorovsky et al.).[98]

ERG comment: The approach taken by the company to include HRQL is largely the same as the approach used for TA338. For example, the regression model applied is the same, as are some estimates for the exploratory variables. Also, some changes have been made in the company base case. This is for example the case for the utility decrement for adverse events; in the current submission the base case includes a single coefficient for adverse events in the regression model, while this was a scenario in the previous submission.

In line with the conclusion of the previous ERG report, the use of a regression model is still deemed appropriate. An advantage of this approach is that all EQ-5D data from the MM-003 trial were used, wherein utilities are measured within the population of interest (in contrast to the studies that are identified within the SLR) according to the NICE reference case. Thus, the ERG did not encounter any major issues with the approach used to include quality of life in the model.

Many of the covariates in the regression model are not used to find differences in the utilities across treatments. Therefore, the ERG requested in the clarification letter that the company explores the impact on the ICERs of using a limited regression model that only included disease progression, best overall response, hospitalisations and adverse events as independent variables (Q B9). In their response, the company showed that the incremental QALYs, and thus the ICERs, would remain more of less the same.[38] The company also showed the results of the formal test to show that the fit of the regression model used in the CS was significantly better than the fit of more parsimonious models.

However, there are some smaller limitations regarding the parameters needed to inform the regression model and predict utilities, for example, it is unknown if BORRs (i.e. the proportion of patients with stable disease or progressive disease) are measured similarly across studies and within similar patient populations. BORR is not only influenced by treatment, but also by baseline patient and disease characteristics. Since the study populations differ across the studies used in this cost effectiveness analysis, BORRs across studies might not be comparable.

Also, the ERG found some inconsistencies within the categorisation of BORR; whereas patients with a minimal response (12%) due to treatment with POM+LoDEX within the MM-002 trial were included in the group ‘progressive disease’, patients with a minimal response (8%) within the MM-003 trial were

included in the group 'stable disease'. Additionally, patients with a minimal response (18%) due to treatment with PANO+BOR+DEX were included in the group 'progressive disease'. The ERG was unable to verify BORR associated with treatment with BTD.

As no data about the proportion of patients requiring hospitalisation were available for PANO+BOR+DEX and conventional chemotherapies, data from patients treated with HiDEX in the MM-003 trial were used as a proxy for all comparators. However, it is unknown if these data provide a correct representation of hospitalisations related to treatment with PANO+BOR+DEX and conventional chemotherapies.

In the regression analysis, a single coefficient for adverse events was estimated based on the MM-003 trial. When applying the regression equation to the comparators, an implicit assumption is made that the mix of adverse events is comparable across treatments, which might not be the case.

As is clear from the above, the data about BORR, hospitalisation and adverse events has its limitations which might cause bias in the estimation of utilities. Therefore, the ERG will explore (see Section 5.3) a scenario-analysis in which only disease progression varies across treatments in the estimation of utilities (equal BORR, adverse event rate and hospitalisation rate).

In the previous NICE review (TA338), the ERG described the limitations of the derivation of the utility decrement associated with intravenous or subcutaneous treatment.[80] They considered the estimated utility decrement uncertain, given the fact that it was derived from EQ-5D VAS scores given to descriptions of various health states. Moreover, the health state descriptions relate to relapsed lung cancer, and thus it is not clear to what extend this estimate can be applied to the current population. Therefore, the ERG will explore, as in the previous assessment, a scenario in which no utility decrement is assumed for IV treatments.

5.2.9 Resources and costs

In Section 5.5 of the CS the identification, measurement and valuation of costs and healthcare resource use is described.[3] The following cost components were included in the analysis: drug acquisition costs (including administration costs), costs of monitoring and tests (including transfusions), concomitant medications and adverse events, costs of subsequent therapies and terminal care costs.

Drug acquisition costs

Table 5.12 provides information about the dosing of POM+LoDEX and its comparators. Drug acquisition costs per treatment cycle are provided in Table 5.15. Note that these costs do not take into account dose interruptions. To calculate drug acquisition costs, the number of full pack(s) of either POM, THAL, PANO or CYC needed per treatment cycle were calculated. These numbers were multiplied by the costs of a full pack.

To calculate the mean number of vials of BEN and BOR per administration, the method of moments technique was used[99] combined with data on weight and height from the MM-003, MM-002 and MM-010 trials. To calculate the costs of BEN and BOR, the number of vials needed per treatment cycle was calculated.

For simplicity, the costs of DEX were calculated by multiplying the total dose per treatment cycle by the price per milligram (in POM+LoDEX, the dose of DEX was based on a weighted average dose per cycle from trials MM-010, MM-002 and MM-003 [MM-002 only for the comparison with BTD]).

Weekly costs were multiplied by the proportion of patients on therapy. The calculation of the number of patients on therapy is discussed in Section 5.2.6.

Table 5.12: Dosing of POM+LoDEX and its comparators within the economic model

POM+LoDEX		
POM	Oral	4 mg on days 1-21 of 28-day cycle
LoDEX	Oral	observed weighted average dose per cycle
BTD[a]		
BEN	IV	60mg/m2 BSA on days 1 and 2
THAL	Oral	100mg thalidomide daily for 21 days in each 28 day cycle
DEX	Oral	20mg dexamethasone 4 times per 28 days
PANO+BOR+DEX[b]		
PANO (first 8 cycles)	Oral	20mg three times a week for 2 weeks in a 21 day cycle for 8 cycles
PANO (subsequent 6 cycles)	Oral	20mg three times a week for 2 weeks in a 21 day cycle for 6 cycles
BOR + DEX (first 8 cycle)	IV/Oral	1.3 mg/m2 twice weekly for 2 weeks in a 21 day cycle with 20mg dexamethasone 8 days per 21 days
BOR + DEX (subsequent 6 cycles)	IV/Oral	1.3 mg/m2 once weekly for 2 weeks in a 21 day cycle with 20mg dexamethasone 2 days per 21 days
CTD		
CYC	Oral	500mg once weekly
THAL	Oral	100mg daily increasing to 200mg daily (average of 167mg used in the model)
DEX	Oral	DEX dose of 160mg or 320 mg total per cycle (average of 240mg used in the model)

Notes: a The dosing regimen of BTD was based on the MUK-One trial, as this trial included most patients treated with BTD in comparison with the studies by Gooding et al.[68] and Tarant et al.[69]; b The dosing regimen of PANO+BOR+DEX was informed by the PANORAMA-2 trial

BEN, bendamustine; BOR, bortezomib; BTD, bendamustine + thalidomide + dexamethasone; CYC, cyclophosphamide; DEX, dexamethasone; LoDEX, low-dose dexamethasone; PANO, panobinostat; POM, pomalidomide; THAL, thalidomide

Cost savings due to dose interruptions of POM that last longer than 28 days were included in the base-case, as it is assumed that these interruptions will save a full pack of POM to the NHS. Data from the MM trials indicated that 4.06%, 3.59% and 3.56% of packs would not be distributed to the patients in the comparison with BTD, PANO+BOR+DEX and conventional chemotherapy, respectively. To take into account dose interruptions of PANO, the relative dose intensity of PANO, relative to the dose intensity of POM was used, which provided a relative increase in the proportion of whole packs saved. The proportion of whole packs PANO saved was estimated to be 4.43%.

Administration costs for treatments administered intravenously or subcutaneously amounted to £222.15 for the first visit and £312.87 for subsequent visits, in line with the BOR first line appraisal (TA311). However, in their response to the clarification letter the company indicated that more recent cost estimates were available now, i.e. £239.12 (SB12Z) and £362, respectively. These new cost estimates were included in the revised model that was provided. In a scenario analysis the company addressed the impact of lower administration costs, by replacing these administration costs with the costs of an outpatient visit to a hematologist (£154.05). In addition to the administration costs, the costs of a full blood count were taken into account for BOR and BEN.

Table 5.13: Drug acquisition costs of POM+LoDEX and its comparators per treatment cycle

	Cost per treatment cycle	Cost is applied every
POM+LoDEX		
POM	[redacted]	4 weeks
LoDEX	£5.07 to £8.83[a]	4 weeks
BTD[a]		
BEN	£691	4 weeks
THAL	£597	4 weeks
DEX	£20	4 weeks
PANO+BOR+DEX		
PANO	£4,656	3 weeks
BOR (first 8 cycle)	£3,050[b]	3 weeks
BOR (subsequent cycles)	£1,525[c]	3 weeks
DEX (first 8 cycle)	£40	3 weeks
DEX (subsequent cycles)	£10	3 weeks
CTD		
CYC	£139	4 weeks
THAL	£1,1194	4 weeks
DEX	£61	4 weeks

Notes: [a] In POM+LoDEX, the dose of DEX was based on a weighted average dose per cycle from trials MM-010, MM-002 and MM-003 [MM-002 only for the comparison with BTD].[b] The model submitted by Company used £4,574 here, in the response to the CL this was corrected; [c] The model submitted by Company used £3,050 here, in the response to the CL this was corrected.
BEN, bendamustine; BOR, bortezomib; BTD, bendamustine + thalidomide + dexamethasone; CYC, cyclophosphamide; DEX, dexamethasone; LoDEX, low-dose dexamethasone; PANO, panobinostat; POM, pomalidomide; THAL, thalidomide

Costs of monitoring and tests, concomitant medications and adverse events

As the cost and resource use SLR did not identify any treatment-specific resource use, a questionnaire was sent out to clinical experts to collect data about resource use associated with the treatment of patients with RRMM in the UK. The questionnaire consisted of questions related to current treatment practice (including dosing schedules), (treatment-specific) routine follow-up care, subsequent treatment use and resource use associated with adverse events.

Six clinical experts completed the questionnaire. Average annual resource use associated with POM+LoDEX, BTD, PANO+BOR+DEX, off active treatment (pre-progression) and off active treatment (post-progression) was derived from the questionnaire, and implemented in the economic model. Resource use related to conventional chemotherapy was assumed equal to the resource use related to BTD. Resource use was combined with unit costs derived from either the TA228 NICE review[19] or NHS reference costs[100].

The costs of monitoring and tests per cycle are presented in Table 5.14, just as the costs of concomitant medications and adverse events. With respect to concomitant medications, only costs associated with granulocyte-colony stimulating factor (G-CSF) were taken into account, as it is assumed that no differences exist in the use of other concomitant medications across treatments or between pre- and post-progression.

For the adverse events, the resource use questionnaire provided data about the percentage of patients that did not require any treatment, the percentage of patients requiring outpatient care and the percentage of patients requiring a hospital admission. Unit costs of adverse events were primarily based on NHS reference costs.[100]

Table 5.14: Costs of monitoring and tests, concomitant medications and adverse events per cycle

	POM+Lo-DEX	BTD	PANO+BOR+DEX	Conv. chemo-therapy	Pre-progression off treatment	Post-progression off treatment
Monitoring and tests[a] (cost per cycle)	£63.80 (£141.35)	£150.36 (£168.27)	£185.30 (£220.26)	£150.36 (£168.27)	£101.09 (£109.06)	£142.23 (£159.42)
Concomitant medications[a] (cost per cycle)	£71.43 (£92.82)	£83.50 (£115)	£80.08 (£108.43)	£83.50 (£115)	£5.16 (£5.26)	£21.45 (£23)
Adverse events[b] (cost per cycle)	£21.76	£51.22	£55.88	£32.14		

Notes: [a] The values between brackets represent the values after correcting an error in the CS, see ERG comments; [b] These numbers are based on a correction made by the company in response to question B18
BOR, bortezomib; BTD, bendamustine + thalidomide + dexamethasone; DEX, dexamethasone; LoDEX, low-dose dexamethasone; PANO, panobinostat; POM, pomalidomide

Costs of subsequent therapies

Because of the uncertainty about the use of subsequent therapies, the costs of subsequent therapies were not taken into account in the base-case. Nevertheless, these costs were included in two scenario-analyses. The distributions of subsequent therapies used within those two scenarios are provided in Table 5.15. In one scenario, the use of fifth line therapies was derived from the haematological malignancy research network (HMRN) registry.[101] The HMRN registry did not provide data about the use of subsequent therapies stratified by treatment. Costs of subsequent therapies were therefore estimated to be £20.74 per week for POM+LoDEX and all its comparators.

In a second scenario, the use of fifth-line therapies was derived from the resource use questionnaire. The resource use questionnaire did provide information about the use of subsequent therapies for all treatments separately. Within this scenario, costs were estimated to be £1,188, £1,171, £95 and £1,171 per week for patients discontinuing POM+LoDEX, BTD, PANO+BOR+DEX and conventional chemotherapy, respectively. Note that the costs of subsequent therapies for patients discontinuing conventional chemotherapy were assumed similar to the costs of subsequent therapies for patients discontinuing BTD.

In both scenarios, it is assumed that subsequent therapy only lasts for a maximum of 17 weeks (based on data from the registry).[101]

Table 5.15: Distribution of subsequent therapies, as used in two scenario analyses

	Regardless of treatment	POM+LoDEX	BTD	PANO+BOR+DEX
Scenario-analysis based on HMRN registry				
MP	5.9%			
THAL+DEX	17.6%			
No active treatment	76.5%			
Scenario-analysis based on resource use questionnaire				
BTD		21.7%	N/A	28.3%
PANO+BOR+DEX		33.3%	35.0%	N/A
THAL-based		1.7%	0%	1.7%
CYC/steroids		3.3%	6.7%	5.0%
No active treatment		40.0%	58.3%	65.0%

BOR, bortezomib; BTD, bendamustine + thalidomide + dexamethasone; CYC, cyclophosphamide; DEX, dexamethasone; HMRN, haematological malignancy research network; LoDEX, low-dose dexamethasone; MP, melphalan + prednisone; PANO, panobinostat; POM, pomalidomide; THAL, thalidomide

Terminal care costs

Terminal care costs (£5,363) are implemented in the base-case as a one-off cost to account for the costs of the last eight weeks prior to death, based on Kings Fund's estimate.[102] In a scenario analysis terminal care costs (£867) are based on the distribution of patients receiving care in a hospital setting or hospice, or patients using home services during the last week prior to death, based on estimates derived during the advisory board.

ERG comment: The current submission has re-estimated various types of resource use compared to TA338. For example, monitoring costs are now based on an extensive questionnaire filled in by six clinical experts, whereas TA338[80] used values from TA228[19]. Also, a new estimate of terminal care costs is now used, based on retrospective data on 40 cancer patients in the UK.[102]

An important error was found in the electronic model submitted by the company. The resource use estimates for monitoring were based on the questionnaires filled in by six clinical experts and in this questionnaire resource use was asked on a yearly basis. In the model, these yearly numbers are transformed into weekly numbers. This is done through an exponential function, which suggests that the number per year is interpreted as a rate, and is then transformed into a weekly probability. This is incorrect; the number of visits or tests per year should simply be divided by 52. As a result, in the CS the monitoring costs are underestimated, for all treatments, and since the extent of the underestimation varies by treatment the ICERs in the CS are also incorrect. The impact of correcting this error will be shown in Section 5.3.

Another important issue according to the ERG is the approach to estimating the treatment costs. In the CS, it is assumed that only whole packages of the oral medications POM, PANO, CYC, and THAL can be dispensed by a pharmacist each cycle. However, pharmacists can and should deliver the exact number of tablets prescribed by the specialist. Thus, the ERG considers the costs per week for both BTD and PANO+BOR+DEX incorrect. Since POM and PANO require exactly one package per cycle, the issue of rounding upwards to the next integer only causes an overestimation of the costs for CYC (1 instead of 0.4 per cycle) and THAL(4 instead of 3.3 and 2 instead of 1.5). In the exploratory analyses in section 5.3 it can be seen how this influences the outcomes.

The model allows for a decrease in treatment costs based on treatment interruptions lasting longer than 28 days. The pertinent data was available for POM-LoDEX, and this was used to also estimate the cost decrease for panobinostat. However, dose interruptions of BOR (within PANO+BOR+DEX), BTD and conventional chemotherapies were not taken into account at all, creating a potential inconsistency. To assess the impact of this, the company altered the model, in response to the clarification letter (question B14), so that a scenario can be run where the costs of BOR, BTD and conventional chemotherapies are decreased at the same rate as panobinostat.

The approach to estimating resource use is well documented in the CS. However, the questionnaire is quite long and detailed and thus might be difficult to fill in. Additionally, only six clinical experts completed the questionnaire. As a consequence, input parameters derived from this questionnaire should be considered with care. It is therefore unfortunate that the one-way sensitivity analysis is based on inexplicable lower and upper boundaries. Despite the fact that these yearly resource use estimates vary between 0 (for bone densitometry) and 36.22 (biochemistry) per year, the lower limit is set to 2 and the upper limit to 9 for all types of resource use for all treatments. Thus, for many types of resource use the estimate of the mean falls outside the range between 2 and 9, rendering the results of the one-way sensitivity analyses less informative. The PSA on the other hand reflects the uncertainty around these estimates appropriately.

With respect to concomitant medications, the CS only took costs associated with G-CSF into account, as it was assumed that no differences exist in the use of other concomitant medications across treatments or between pre- and post-progression. However, when one treatment leads to an increased life span compared to another, more concomitant medication will be used, increasing the total costs per patient for that treatment. Thus, exclusion of these costs creates a bias in the outcomes.

Regarding the costs of subsequent treatment, the ERG does not agree with the base case choice to not include these costs. As stated in the CS, the effects of these subsequent treatments are implicitly incorporated in the OS results, and thus it would be rational to also include the costs required to achieve those effects. However, the two estimates of these costs provided in the CS for scenario analyses differ greatly and which should be preferred is difficult to determine based on the information provided in the CS.

It is unclear to the ERG to what extent the annual adverse event rates of the comparators of POM-LoDEX used in the model are representative of the actual adverse event rates associated to these treatments, as explained in section 5.2.7. The mix of adverse events probably varies across treatments, which would lead to different AE costs.

5.2.10 Cost effectiveness results

Base case incremental cost effectiveness analysis results

In the CS, for the base case cost effectiveness analyses, the comparisons of POM+LoDEX vs. BTD, POM+LoDEX vs. PANO+BOR+DEX and POM+LoDEX vs. CC were presented separately. Since each comparison was based on a different dataset, resulting in different outcomes for POM+LoDEX, a full incremental analysis was not performed.

During the clarification procedure, the ERG had identified several programming errors. These errors were corrected in the post-clarification model. Based on this model, the corrected base case results are given in Tables 5.16-5.18 below for POM+LoDEX vs. BTD, POM+LoDEX vs. PANO+BOR+DEX and POM+LoDEX vs. CC comparisons.

For the comparison with BTD, POM+LoDEX is associated with a gain of 0.67 incremental life years and [redacted] incremental QALYs per patient, and an increase in overall costs of [redacted] per patient, which resulted in an ICER of £39,665 per QALY gained.

For the comparison with CC, POM+LoDEX is associated with a gain of 0.68 incremental life years and [redacted] incremental QALYs per patient, and an increase in overall costs of [redacted] per patient, which resulted in an ICER of £45,164 per QALY gained.

For the comparison with PANO+BOR+DEX, POM+LoDEX is associated with a reduction of 0.53 incremental life years and a reduction of [redacted] incremental QALYs per patient, and a decrease in overall costs of [redacted] per patient, which resulted in an ICER of £141,793 per QALY gained (in the southwest quadrant of the cost effectiveness plane, i.e. reduced cost and reduced effectiveness).

Table 5.16: Base-case results – vs. BTD

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
BTD	[redacted]	1.14	[redacted]	[redacted]	-	-	-
POM+ LoDEX	[redacted]	1.81	[redacted]	[redacted]	0.67	[redacted]	£39,665

BTD, bendamustine, thalidomide and dexamethasone; ICER, incremental cost effectiveness ratio; LoDEX, low-dose dexamethasone; POM, pomalidomide; QALYs, quality-adjusted life years

Table 5.17: Base-case results – vs. PANO+BOR+DEX

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
PANO+BOR+DEX	[redacted]	2.25	[redacted]	[redacted]	-	-	-
POM+ LoDEX	[redacted]	1.71	[redacted]	[redacted]	-0.53	[redacted]	£141,793 (SW)

BOR, bortezomib; DEX, dexamethasone; ; ICER, incremental cost effectiveness ratio; LoDEX, low-dose dexamethasone; NMB, net monetary benefit; PANO, panobinostat; POM, pomalidomide; QALYs, quality-adjusted life years

Table 5.18: Base-case results – vs. conventional chemotherapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Conventional chemotherapy	[redacted]	0.78	[redacted]	-	-	-	-

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
POM+ LoDEX	[redacted]	1.45	[redacted]	[redacted]	0.68	[redacted]	£44,811
ICER, incremental cost effectiveness ratio; LoDEX, low-dose dexamethasone; POM, pomalidomide; QALYs, quality-adjusted life years							

Clinical outcomes from the model

Table 5.19 displays the clinical outcomes from the trials and the model outcomes for the three main outcome measures; OS, PFS and TTF. Clinical outcomes are presented for all base case comparisons assuming the base case parametric curve functions and adjusting for baseline covariates using the CGP method (as discussed in Section 5.2.6).

The company found the median OS, PFS and TTF results were comparable and consistent with the respective observed clinical outcomes reported in the trial datasets and in the literature.

ERG comment: The ERG holds the opinion that there are some remarkable differences between trial outcomes and model outcomes, especially in the PFS results of BTD and PANO+BOR+DEX. However, it should also be noted that the model estimates of PANO+BOR+DEX PFS, were based on the baseline covariate adjustments according to a dataset that consists of POM+LoDEX (MM-002, MM-003 and MM-010) and BTD trials. For a better reflection, it would have been more informative if the trial results were compared with the model results which were based on covariate adjustments according to the baseline characteristics of that trial.

Table 5.19: Comparison of the clinical outcomes from the trial datasets with the base case model outcomes

Clinical outcome (values in years)	POM+LoDEX (MM-002)		POM+LoDEX (MM-003, MM-002 and MM-010)		POM+LoDEX (MM-003)	
	Observed (95% CI)	**Modelled medians**	**Observed (95% CI)**	**Modelled medians**	**Observed (95% CI)**	**Modelled medians**
Median OS (months)	16.5	14.26	13.1 (MM-003) 16.5 (MM-002) 11.9 (MM-010)	13.11	13.1	11.73
Median PFS (months)	4.2	4.83	4.0 (MM-003) 4.2 (MM-002) 4.6 (MM-010)	4.37	4.0	3.68
Median TTF (months)	4.5	3.91	2.9 (MM-003) 4.5 (MM-002)	3.91	2.9	3.91
Clinical outcome (values in years)	**BTD (base case: Gooding et al., Tarant et al. and MUK-One)**		**PANO+BOR+DEX (base case: PANORAMA-2)**		**Conventional chemotherapies (assumed same as the HiDEX arm in MM-003)**	
	Observed (95% CI)	**Modelled medians**	**Observed (95% CI)**	**Modelled medians**	**Observed (95% CI)**	**Modelled medians**
Median OS (months)	8.2 (MUK-One)	8.97	17.5 (10.8-25.2)	16.79	5.7	6.21
Median PFS (months)	3.3 (MUK-One)	3.68	5.4 (3.5-6.7)	3.68	1.9	1.84
Median TTF (months)	Not reported	2.99	Not reported	Not modelled	1.8	1.84
Adverse Events	Rates taken from trial and relevant literature.					

BOR bortezomib; BTD, bendamustine, thalidomide and dexamethasone; CI, confidence interval; DEX dexamethasone; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; PANO, panobinostat; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; TTF, time to failure.

Disaggregated results of the base case incremental cost effectiveness analysis

Corrected disaggregated results of the base case are given in Tables 5.20-5.31 below for POM+LoDEX vs. BTD, POM+LoDEX vs. PANO+BOR+DEX and POM+LoDEX vs. CC comparisons (based on the post-clarification model).

Tables 5.20-5.22 show the total life years gained by patients in each health state.

Table 5.20: Life years (undiscounted) – vs. BTD

Outcome	POM+LoDEX	BTD	Increment
Pre-progression: Life Years	0.76	0.60	0.17
Post-progression: Life Years	1.05	0.55	0.51
Life Years: On treatment	0.62	0.48	0.13
BTD, bendamustine, thalidomide and dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide			

Table 5.21: Life years (undiscounted) – vs. PANO+BOR+DEX

Outcome	POM+LoDEX	PANO+BOR+DEX	Increment
Pre-progression: Life Years	0.66	0.54	0.12
Post-progression: Life Years	1.05	1.71	-0.65
Life Years: On treatment	0.62	0.40	0.22
BOR, bortezomib; DEX, dexamethasone; PANO, panobinostat; LoDEX, low-dose dexamethasone; POM, pomalidomide			

Table 5.22: Life years (undiscounted) – vs. conventional chemotherapies

Outcome	POM+LoDEX	Conventional chemotherapies	Increment
Pre-progression: Life Years	0.58	0.26	0.32
Post-progression: Life Years	0.87	0.51	0.36
Life Years: On treatment	0.44	0.23	0.21
LoDEX, low-dose dexamethasone; POM, pomalidomide			

Similarly, Tables 5.23-5.25 show the total QALYs gained by patients in each health state.

Table 5.23: QALYs (discounted) – vs. BTD

Outcome	POM+LoDEX	BTD	Increment
Pre-progression: QALYs	[redacted]	[redacted]	[redacted]
Post-progression: QALYs	[redacted]	[redacted]	[redacted]
BTD, bendamustine, thalidomide and dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide; QALYs, quality-adjusted life years.			

Table 5.24: QALYs (discounted) – vs. PANO+BOR+DEX

Outcome	POM+LoDEX	PANO+BOR+DEX	Increment
Pre-progression: QALYs	[redacted]	[redacted]	[redacted]
Post-progression: QALYs	[redacted]	[redacted]	[redacted]

Outcome	POM+LoDEX	PANO+BOR+DEX	Increment
BOR, bortezomib; DEX, dexamethasone; PANO, panobinostat; LoDEX, low-dose dexamethasone; POM, pomalidomide; QALYs, quality-adjusted life years			

Table 5.25: QALYs (discounted) – vs. conventional chemotherapies

Outcome	POM+LoDEX	Conventional chemotherapies	Increment
Pre-progression: QALYs	[redacted]	[redacted]	[redacted]
Post-progression: QALYs	[redacted]	[redacted]	[redacted]
LoDEX, low-dose dexamethasone; POM, pomalidomide; QALYs, quality-adjusted life years			

Tables 5.26, Table 5.28 and Table 5.30 show the total discounted costs per patient by health state for POM+LoDEX vs. BTD, POM+LoDEX vs. PANO+BOR+DEX and POM+LoDEX vs. CC comparisons. Table 5.27, Table 5.29 and Table 5.31 show the costs by category for all comparisons. The majority of costs incurred by RRMM patients occur pre-progression because of the therapy costs within this state (costs of subsequent therapies were excluded from the base-case), except for the patients treated with conventional chemotherapy.

Table 5.26: Total costs (discounted) – vs. BTD

Outcome	POM+LoDEX	BTD	Increment
Pre-progression: Total costs	[redacted]	[redacted]	[redacted]
Post-progression: Total costs	[redacted]	[redacted]	[redacted]
BTD, bendamustine, thalidomide and dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide			

Table 5.27: Costs by category (discounted) – vs. BTD

Outcome	POM+LoDEX	BTD	Increment
Therapy Cost	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Resource use, on treatment: pre progression	[redacted]	[redacted]	[redacted]
Resource use, off treatment: pre progression	[redacted]	[redacted]	[redacted]
Resource use, off treatment: post progression	[redacted]	[redacted]	[redacted]
Terminal Care	[redacted]	[redacted]	[redacted]
Subsequent Therapy	[redacted]	[redacted]	[redacted]
Adverse Events	[redacted]	[redacted]	[redacted]
Concomitant Medication	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Outcome	POM+LoDEX	BTD	Increment
BTD, bendamustine, thalidomide and dexamethasone; LoDEX, low-dose dexamethasone; POM, pomalidomide			

Table 5.28: Total costs (discounted) – vs. PANO+BOR+DEX

Outcome	POM+LoDEX	PANO+BOR+DEX	Increment
Pre-progression: Total costs	[redacted]	[redacted]	[redacted]
Post-progression: Total costs	[redacted]	[redacted]	[redacted]
BOR, bortezomib; DEX, dexamethasone; PANO, panobinostat; LoDEX, low-dose dexamethasone; POM, pomalidomide			

Table 5.29: Costs by category (discounted) – vs. PANO+BOR+DEX

Outcome	POM+LoDEX	PANO+BOR+DEX	Increment
Therapy Cost	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Resource use, on treatment: pre progression	[redacted]	[redacted]	[redacted]
Resource use, off treatment: pre progression	[redacted]	[redacted]	[redacted]
Resource use, off treatment: post progression	[redacted]	[redacted]	[redacted]
Terminal Care	[redacted]	[redacted]	[redacted]
Subsequent Therapy	[redacted]	[redacted]	[redacted]
Adverse Events	[redacted]	[redacted]	[redacted]
Concomitant Medication	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
BOR, bortezomib; DEX, dexamethasone; PANO, panobinostat; LoDEX, low-dose dexamethasone; POM, pomalidomide			

Table 5.30: Total costs (discounted) – vs. conventional chemotherapies

Outcome	POM+LoDEX	Conventional chemotherapies	Increment
Pre-progression: Total costs	[redacted]	[redacted]	[redacted]
Post-progression: Total costs	[redacted]	[redacted]	[redacted]
LoDEX, low-dose dexamethasone; POM, pomalidomide			

Table 5.31: Costs by category (discounted) – vs. conventional chemotherapies

Outcome	POM+LoDEX	Conventional chemotherapies	Increment
Therapy Cost	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Resource use, on treatment: pre progression	[redacted]	[redacted]	[redacted]
Resource use, off treatment: pre progression	[redacted]	[redacted]	[redacted]
Resource use, off treatment: post progression	[redacted]	[redacted]	[redacted]
Terminal Care	[redacted]	[redacted]	[redacted]
Subsequent Therapy	[redacted]	[redacted]	[redacted]
Adverse Events	[redacted]	[redacted]	[redacted]
Concomitant Medication	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

LoDEX, low-dose dexamethasone; POM, pomalidomide

5.2.11 Sensitivity analyses

Probabilistic sensitivity analyses

To examine the impact of the joint uncertainty across all model inputs probabilistic sensitivity analyses were conducted for POM+LoDEX vs. BTD, POM+LoDEX vs. PANO+BOR+DEX and POM+LoDEX vs. CC. In these analyses, all inputs vary simultaneously, based upon their distributional information. The PSA also included the uncertainty around the choice of parametric OS, PFS and TTF curves (see Section 5.2.6).

The results of 1,000 PSA iterations are shown in the figures below. Cost effectiveness planes show the incremental QALYs and costs of POM+LoDEX relative to the relevant comparators (Figures 5.19, 5.21 and 5.23). Additionally, cost effectiveness acceptability curves (CEACs) are presented, showing the likelihood of POM+LoDEX cost effectiveness at different willingness-to-pay thresholds (Figures 5.20, 5.22 and 5.24).

POM+LoDEX vs. BTD

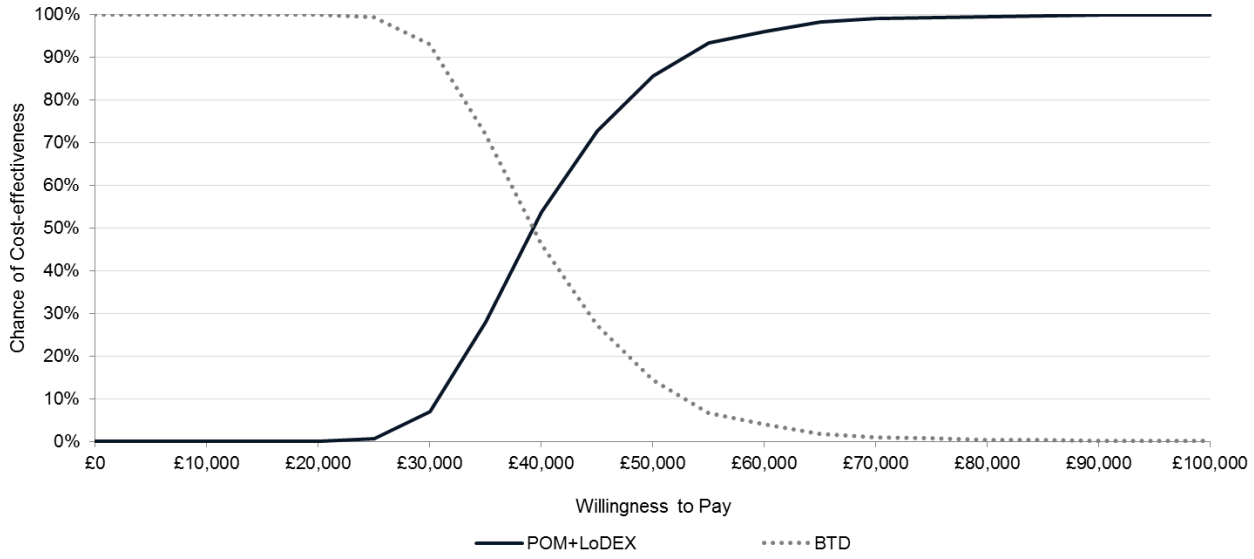
Mean incremental QALYs from POM+LoDEX were [redacted] (SD: 0.08; 95% CI: [redacted]). Mean incremental costs were [redacted] (SD: £1,198; 95% CI: [redacted]). The resulting probabilistic ICER from 1,000 iterations was £39,317 (comparable to the deterministic, base-case ICER of £39,665).

The CEAC in Figure 5.20 suggests that there is an 8% likelihood of POM+LoDEX cost effectiveness at a willingness-to-pay threshold of £30,000/QALY and a 85% likelihood of POM+LoDEX cost effectiveness at a willingness-to-pay threshold of £50,000/QALY.

Figure 5.19: Cost effectiveness plane – vs. BTD

[redacted]

Figure 5.20: Cost effectiveness acceptability curve – vs. BTD



POM+LoDEX vs. PANO+BOR+DEX

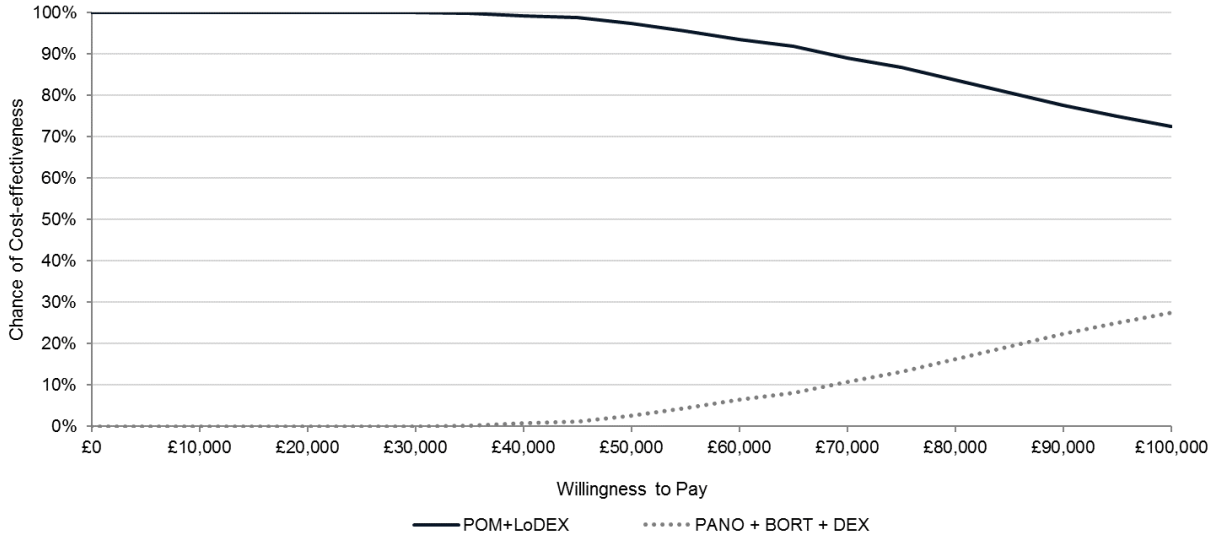
Mean incremental QALYs from POM+LoDEX were [redacted] (SD: 0.27; 95% CI: [redacted]). Mean incremental costs were [redacted] (SD: £5,967; 95% CI: [redacted]). The resulting probabilistic ICER from 1,000 iterations was £134,379 (comparable to the deterministic, base-case ICER of £141,793); NMB of £31,953.

The CEAC in Figure 5.22 suggests that there is a n almost 100% likelihood of POM+LoDEX cost effectiveness at a willingness-to-pay threshold of £30,000/QALY and a 97% likelihood of POM+LoDEX cost effectiveness at a willingness-to-pay threshold of £50,000/QALY.

Figure 5.21: Cost effectiveness plane – vs. PANO+BOR+DEX

[redacted]

Figure 5.22: Cost effectiveness acceptability curve – vs. PANO+BOR+DEX



POM+LoDEX vs. conventional chemotherapies

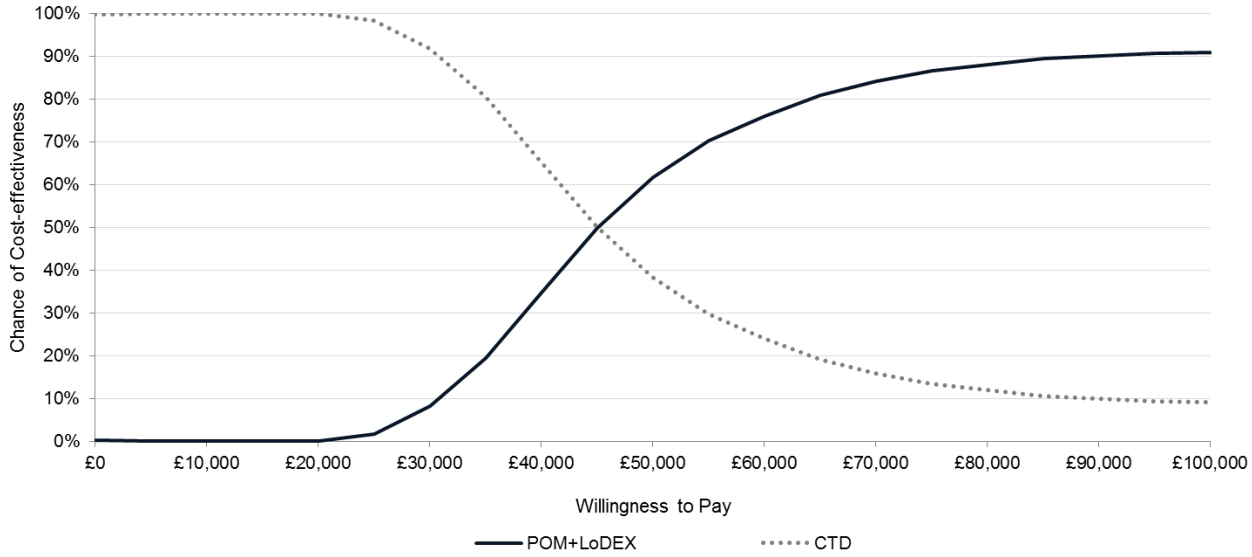
Mean incremental QALYs from POM+LoDEX were [redacted] (SD: 0.32; 95% CI: [redacted]). Mean incremental costs were [redacted] (SD: £4,880; 95% CI: [redacted]). The resulting probabilistic ICER from 1,000 iterations was £45,831 (comparable to the deterministic, base-case ICER of £44,811).

The CEAC in Figure 5.24 suggests that there is an 8% likelihood of POM+LoDEX cost effectiveness at a willingness-to-pay threshold of £30,000/QALY and a 60% likelihood of POM+LoDEX cost effectiveness at a willingness-to-pay threshold of £50,000/QALY.

Figure 5.23: Cost effectiveness plane – vs. conventional chemotherapies

[redacted]

Figure 5.24: Cost effectiveness acceptability curve – vs. conventional chemotherapies



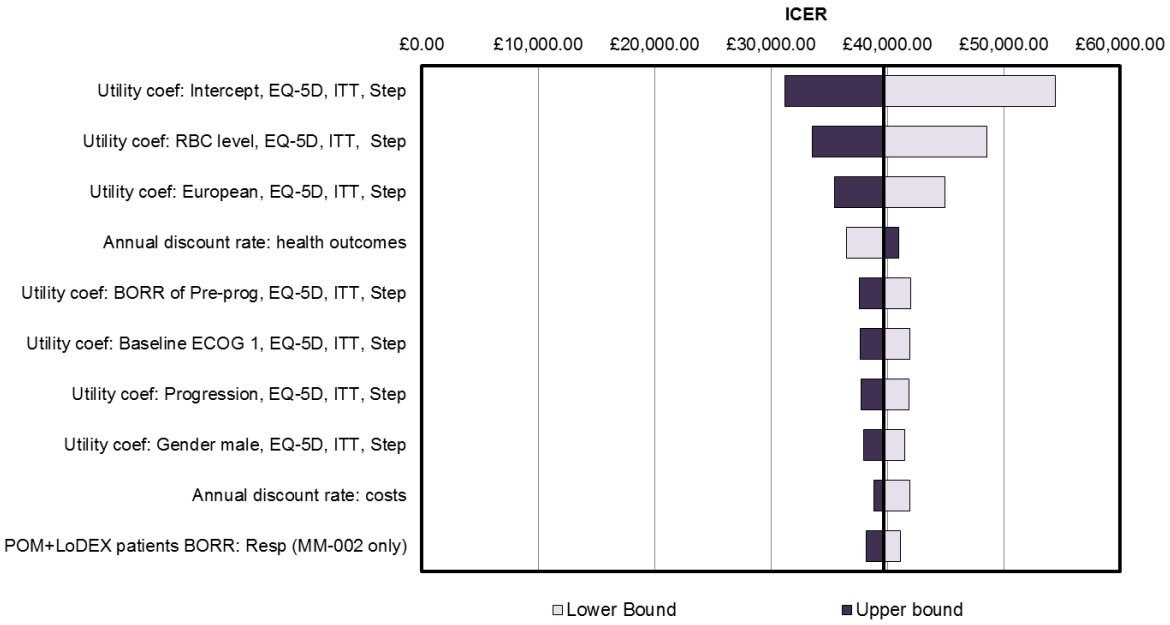
Deterministic sensitivity analyses

The sensitivity of the model ICER to critical model parameters is assessed by a series of one-way sensitivity analyses. These analyses consist of making individual parameters vary between a lower and upper bounds, while holding every other input constant. The distribution information for each parameter is presented in Appendix 28 of the CS. Model results for recorded ICERs are presented in the form of tornado diagrams for each of the comparators, with parameters shown in descending order of ICER sensitivity.

POM+LoDEX vs. BTD

Figure 5.25 presents the tornado diagram for the POM+LoDEX vs. BTD comparison. The parameters that showed the greatest impact on the ICER were the coefficients used within the regression analysis for utilities. Besides those parameters, the model showed relatively insensitivity to others inputs assessed in the OWSA.

Figure 5.25: Results of the one-way sensitivity analysis – BTD

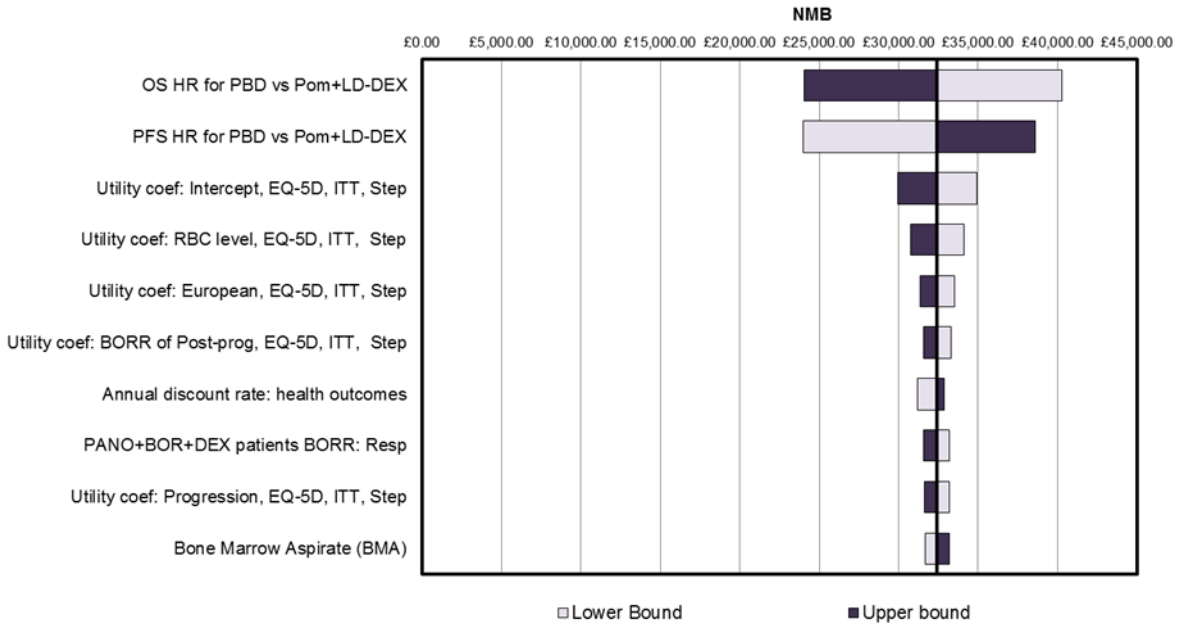


Note: as the corrected group prognosis method was used to estimate survival it was not feasible to include covariates used within the survival analysis in the OWSA
BORR; best overall response rate; BTD, bendamustine, thalidomide and dexamethasone; coef, coefficient; ECOG, Eastern Cooperative Oncology Group; EQ-5D, EuroQol five dimensions; ICER, incremental cost effectiveness ratio; ITT, intention to treat

POM+LoDEX vs. PANO+BOR+DEX

Figure 5.26 presents the tornado diagram for POM+LoDEX vs. PANO+BOR+DEX. The parameters showing the largest impact on the ICER were the HRs used to model comparative effectiveness. It should be mentioned that for every analysed input the NMB remained positive at a WTP threshold of £30,000 per QALY.

Figure 5.26: Results of the one-way sensitivity analysis - PANO+BOR+DEX

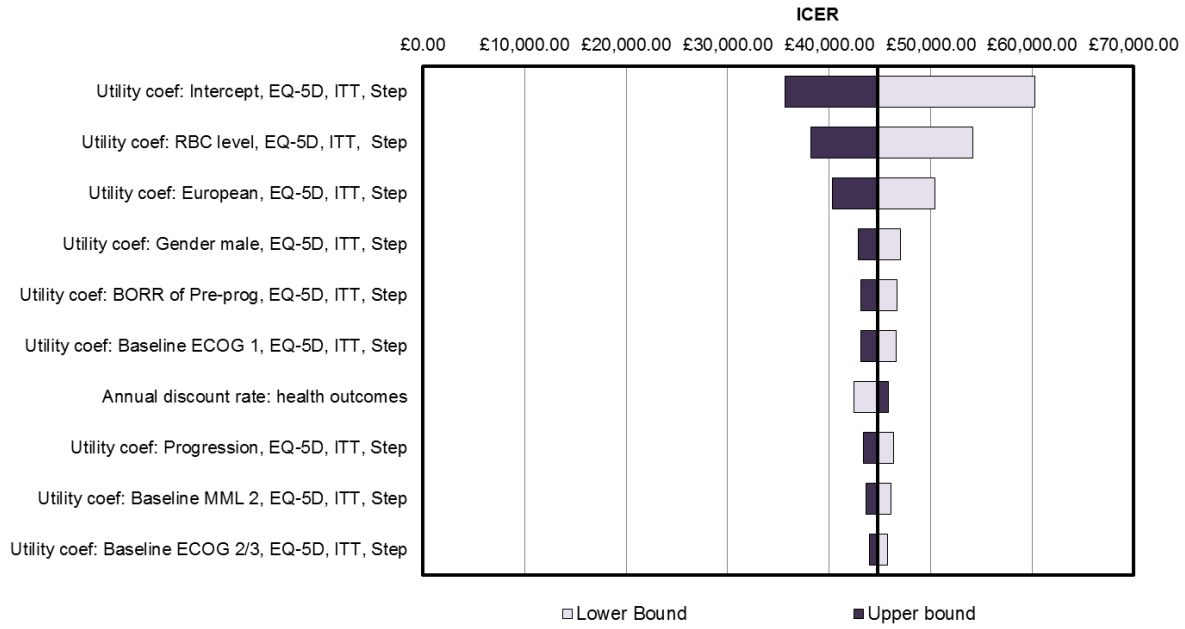


Note: as the corrected group prognosis method was used to estimate survival it was not feasible to include covariates used within the survival analysis in the OWSA
BORR; best overall response rate; BTD, bendamustine, thalidomide and dexamethasone; coef, coefficient; ECOG, Eastern Cooperative Oncology Group; EQ-5D, EuroQol five dimensions; ICER, incremental cost effectiveness ratio; ITT, intention to treat

POM+LoDEX vs. conventional chemotherapies

Figure 5.27 presents the tornado diagram for the comparison between POM+LoDEX and conventional chemotherapies. In this case, and similarly to the comparison vs. BTD, the parameters with greatest impact on the ICER were the coefficients used within the regression analysis for utilities. Likewise, the model showed relatively insensitivity to the remaining inputs assessed in the OWSA.

Figure 5.27: Results of the one-way sensitivity analysis - conventional chemotherapies



Note: as the corrected group prognosis method was used to estimate survival it was not feasible to include covariates used within the survival analysis in the OWSA
BORR; best overall response rate; BTD, bendamustine, thalidomide and dexamethasone; coef, coefficient; ECOG, Eastern Cooperative Oncology Group; EQ-5D, EuroQol five dimensions; ICER, incremental cost effectiveness ratio; ITT, intention to treat

Scenario analyses

Scenario analyses are used for assessing the uncertainty resulting from the various structural assumptions of the model. In effect, the structural assumptions in the base case and the corresponding scenarios which are used as alternatives to the base case are presented in the Table 74 of the CS.[3] Similar to what happens with the deterministic sensitivity analyses, the scenario analyses are run for each of the pairwise comparisons included in the model. The results of the scenario analyses are presented in Table 5.32 for POM+LoDEX vs. BTD, Table 5.33 for POM+LoDEX vs. PANO+BOR+DEX, and Table 5.34 for POM+LoDEX vs. BTD.

Table 5.32: Scenario analyses POM+LoDEX vs. BTD

Scenario	Incremental Costs	Incremental QALYs	ICER	Difference from baseline ICER
POM+LoDEX data for the BTD comparison using all trial data	[redacted]	[redacted]	£46,206	32.94%
OS curve choices				
Exponential	[redacted]	[redacted]	£39,273	28.00%
Log-normal	[redacted]	[redacted]	£35,059	24.99%
Log-logistic	[redacted]	[redacted]	£32,368	23.08%
Weibull	[redacted]	[redacted]	£38,524	27.46%

Scenario	Incremental Costs	Incremental QALYs	ICER	Difference from baseline ICER
Gompertz	[redacted]	[redacted]	£39,709	28.31%
Generalised gamma	[redacted]	[redacted]	£37,131	26.47%
PFS curve choices				
Exponential	[redacted]	[redacted]	£41,306	29.45%
Log-normal	[redacted]	[redacted]	£34,560	24.64%
Log-logistic	[redacted]	[redacted]	£40,499	28.87%
Weibull	[redacted]	[redacted]	£14,568	10.39%
Gompertz	[redacted]	[redacted]	£42,177	30.07%
Generalised gamma	[redacted]	[redacted]	£39,273	28.00%
Administration costs of IV/SC treatments from NHS reference costs	[redacted]	[redacted]	£44,200	31.51%
Equal BORRs after discontinuation	[redacted]	[redacted]	£35,706	25.45%
Mean covariate method used	[redacted]	[redacted]	£37,229	26.54%
EORTC-8D values used in regression (instead of EQ-5D)	[redacted]	[redacted]	£34,609	24.67%
Utility values sourced from Quinn et al. 2015[96]	[redacted]	[redacted]	£35,676	25.43%
Utility associated with AEs from the literature (base case from the regression)	[redacted]	[redacted]	£38,941	27.76%
The utility decrement associated with IV/SC administration = 0.076	[redacted]	[redacted]	£38,087	27.15%
Cost of subsequent therapy included using HMRN data	[redacted]	[redacted]	£39,342	28.05%
Cost of subsequent therapy included using resource use questionnaires	[redacted]	[redacted]	£44,451	31.69%
5 year time horizon	[redacted]	[redacted]	£41,605	29.66%
10 year time horizon	[redacted]	[redacted]	£39,332	28.04%
20 year time horizon	[redacted]	[redacted]	£39,309	28.02%
Hospitalisation rate reported in Gooding et al. 2015[68]	[redacted]	[redacted]	£39,285	28.01%
AEs based on relative tolerability profiles	[redacted]	[redacted]	£43,585	31.07%
BORRs applied from cycle 0	[redacted]	[redacted]	£39,260	27.99%

Scenario	Incremental Costs	Incremental QALYs	ICER	Difference from baseline ICER
Terminal care costs: National Audit Office	[redacted]	[redacted]	£39,502	28.16%

AE, adverse event; BORR, best overall response rate; BTD, bendamustine + thalidomide + dexamethasone; EORTC-8D, European Organisation for Research and Treatment of Cancer eight dimensions; EQ-5D, EuroQoL five dimensions; HMRN, haematological malignancy research network; ICER, incremental cost effectiveness ratio; IV, intravenous; LoDEX, low-dose dexamethasone; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; QALY, quality-adjusted life year; QoL, quality of life; SC, subcutaneous

Table 5.33: Scenario analyses - PANO+BOR+DEX

Scenario	Incremental Costs	Incremental QALYs	ICER	NMB (at £30,000)	%baseline ICER
OS curve choices					
Exponential	[redacted]	[redacted]	£158,863	£31,885	115.44%
Log-normal	[redacted]	[redacted]	£98,761	£29,098	71.76%
Log-logistic	[redacted]	[redacted]	£97,411	£28,977	70.78%
Weibull	[redacted]	[redacted]	£178,883	£32,378	129.98%
Gompertz	[redacted]	[redacted]	£176,308	£32,336	128.11%
Generalised gamma	[redacted]	[redacted]	£137,619	£31,222	100.00%
PFS curve choices					
Exponential	[redacted]	[redacted]	£146,139	£33,809	106.19%
Log-normal	[redacted]	[redacted]	£140,521	£32,052	102.11%
Log-logistic	[redacted]	[redacted]	£127,894	£28,304	92.93%
Weibull	[redacted]	[redacted]	£152,051	£35,513	110.49%
Gompertz	[redacted]	[redacted]	£136,702	£31,021	99.33%
Generalised gamma	[redacted]	[redacted]	£137,619	£31,222	100.00%
Administration costs of IV/SC treatments from NHS reference costs	[redacted]	[redacted]	£124,083	£27,295	90.16%
Equal BORRs after discontinuation	[redacted]	[redacted]	£113,526	£29,426	
Mean covariate method used	[redacted]	[redacted]	£152,848	£31,856	111.07%
EORTC-8D values used in regression (instead of EQ-5D)	[redacted]	[redacted]	£119,444	£29,898	86.79%
Utility values sourced from Quinn et al. 2015[96]	[redacted]	[redacted]	£123,111	£30,196	89.46%
Utility associated with AEs from the literature (base case from the regression)	[redacted]	[redacted]	£144,740	£31,650	105.17%
The utility decrement associated with IV/SC administration = 0.076	[redacted]	[redacted]	£144,130	£31,615	104.73%
Cost of subsequent therapy included using HMRN data	[redacted]	[redacted]	£137,844	£31,287	100.16%
Cost of subsequent therapy included using resource use questionnaires	[redacted]	[redacted]	£108,999	£22,919	79.20%

Scenario	Incremental Costs	Incremental QALYs	ICER	NMB (at £30,000)	%baseline ICER
5 year time horizon	[redacted]	[redacted]	£195,354	£32,846	141.95%
10 year time horizon	[redacted]	[redacted]	£145,273	£31,495	105.56%
20 year time horizon	[redacted]	[redacted]	£135,894	£31,156	98.75%
Hospitalisation rate reported in Gooding et al. 2015[68]	[redacted]	[redacted]	£137,504	£31,215	99.92%
Adverse events based on relative tolerability profiles	[redacted]	[redacted]	£132,940	£30,052	96.60%
BORRs applied from cycle 0	[redacted]	[redacted]	£137,934	£31,242	100.23%
Terminal care costs: National Audit Office	[redacted]	[redacted]	£137,901	£31,304	100.20%
Hazard ratio for PFS used to model OS for PANO+BOR+DEX comparison	[redacted]	[redacted]	Pom Dominates	£38,536	

AE, adverse event; BOR, bortezomib; BORR, best overall response rate; DEX, dexamethasone; EORTC-8D, European Organisation for Research and Treatment of Cancer eight dimensions; EQ-5D, EuroQoL five dimensions; HMRN, haematological malignancy research network; ICER, incremental cost effectiveness ratio; IV, intravenous; LoDEX, low-dose dexamethasone; NHS, National Health Service; NMB, net monetary benefit; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; POM, pomalidomide; QALY, quality-adjusted life year; QoL, quality of life; SC, subcutaneous

Table 5.34: Scenario analyses - conventional chemotherapies

Scenario	Incremental Costs	Incremental QALYs	ICER	Difference from baseline ICER
OS curve choices				
Exponential - TS Weibull	[redacted]	[redacted]	£44,811	100.00%
Log-normal - TS Weibull	[redacted]	[redacted]	£34,673	77.38%
Log-logistic - TS Weibull	[redacted]	[redacted]	£37,150	82.90%
Weibull - TS Weibull	[redacted]	[redacted]	£50,033	111.65%
Gompertz - TS Weibull	[redacted]	[redacted]	**£137,761**	**307.43%**
Generalised gamma - TS Weibull	[redacted]	[redacted]	£61,667	137.62%
Exponential – RPSFTM	[redacted]	[redacted]	£42,718	95.33%
Log-normal – RPSFTM	[redacted]	[redacted]	£36,789	82.10%
Log-logistic – RPSFTM	[redacted]	[redacted]	£39,170	87.41%
Weibull – RPSFTM	[redacted]	[redacted]	£49,446	110.34%
Gompertz – RPSFTM	[redacted]	[redacted]	**£90,588**	**202.16%**

Scenario	Incremental Costs	Incremental QALYs	ICER	Difference from baseline ICER
Generalised gamma – RPSFTM	[redacted]	[redacted]	£81,927	182.83%
PFS curve choices				
Extreme values	[redacted]	[redacted]	£46,518	103.81%
Log-normal	[redacted]	[redacted]	£45,108	100.66%
Log-logistic	[redacted]	[redacted]	£44,700	99.75%
Weibull	[redacted]	[redacted]	£46,365	103.47%
Gompertz	[redacted]	[redacted]	£46,062	102.79%
Generalised gamma	[redacted]	[redacted]	£44,811	100.00%
TTF curve choices				
Extreme values	[redacted]	[redacted]	£44,811	100.00%
Log-normal	[redacted]	[redacted]	£52,098	116.26%
Log-logistic	[redacted]	[redacted]	£53,550	119.50%
Weibull	[redacted]	[redacted]	£45,751	102.10%
Gompertz	[redacted]	[redacted]	£49,128	109.64%
Generalised gamma	[redacted]	[redacted]	£52,009	116.06%
Administration costs of IV/SC treatments from NHS reference costs	[redacted]	[redacted]	£44,811	100.00%
Equal BORRs after discontinuation	[redacted]	[redacted]	£42,540	94.93%
Mean covariate method used	[redacted]	[redacted]	£44,811	100.00%
EORTC-8D values used in regression (instead of EQ-5D)	[redacted]	[redacted]	£41,004	91.50%
Utility values sourced from Quinn et al. 2015[96]	[redacted]	[redacted]	£42,641	95.16%
Utility associated with AEs from the literature (base case from the regression)	[redacted]	[redacted]	£44,817	100.01%
The utility decrement associated with IV/SC administration = 0.076	[redacted]	[redacted]	£44,811	100.00%
Cost of subsequent therapy included using HMRN data	[redacted]	[redacted]	£44,796	99.97%
Cost of subsequent therapy included using resource use questionnaires	[redacted]	[redacted]	£45,993	102.64%
5 year time horizon	[redacted]	[redacted]	£46,302	103.33%
10 year time horizon	[redacted]	[redacted]	£44,854	100.10%

Scenario	Incremental Costs	Incremental QALYs	ICER	Difference from baseline ICER
20 year time horizon	[redacted]	[redacted]	£44,809	100.00%
Hospitalisation rate reported in Gooding et al. 2015[68]	[redacted]	[redacted]	£44,820	100.02%
Adverse events based on relative tolerability profiles	[redacted]	[redacted]	£45,295	101.08%
BORRs applied from cycle 0	[redacted]	[redacted]	£44,271	98.80%
Terminal care costs: National Audit Office	[redacted]	[redacted]	£45,020	100.47%

AE, adverse event; BORR, best overall response rate; BTD, bendamustine + thalidomide + dexamethasone; EORTC-8D, European Organisation for Research and Treatment of Cancer eight dimensions; EQ-5D, EuroQoL five dimensions; HMRN, haematological malignancy research network; ICER, incremental cost effectiveness ratio; IV, intravenous; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; QoL, quality of life; RPSFTM, rank preserving structure failure time model; SC, subcutaneous; TS, two-stage method

The scenario analyses reveal that the base case ICER is reasonably certain with regards to the structural assumptions of the base case model for all comparisons.

There are, however, noteworthy exceptions. For example, 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; using a time horizon of five years results in the following ICERs for POM+LoDEX vs. BTD, PANO+BOR+DEX and conventional chemotherapies, respectively: £41,605, £195,354 (SW quadrant), and £46,302. Since POM+LoDEX brings important survival benefits, this analysis shows that these benefits are unlikely to be captured using shorter time horizons.

Another potentially important structural uncertainty is related with the choice of parametric curve form to characterise OS, PFS and TTF. Changing the distribution of the parametric curves can lead to both upward and downward changes in the ICER. Namely, using a Weibull distribution for PFS when comparing to BTD leads to a dramatic decrease in the ICER, whilst using a generalised gamma and the RPSFTM method for the comparison with conventional chemotherapies significantly increases the ICER, raising it above the £50,000 threshold. However, the company claims that neither of these curves provide optimal fits to the data. This argument is supported by comparably higher AIC and BIC values and poor visually assessed fit to the KM curves.

ERG comment: Some of the parameters in the model delivered after clarification were not included in the sensitivity analyses (e.g. PFS/ OS and TTF HRs for CC, which were derived from MM-003) or the administration costs of the IV chemotherapy drugs. The ERG thinks that not incorporating these variables in the probabilistic sensitivity analysis will lead to an underrepresentation of the uncertainty in the model.

As already mentioned in Section 5.2.9, the one-way sensitivity analyses were based on inexplicable lower and upper boundaries for the resource use for monitoring. Despite the fact that these yearly resource use estimates vary between 0 (for bone densitometry) and 36.22 (biochemistry) per year, the lower limit is set to 2 and the upper limit to 9 for all types of resource use for all treatments. Thus, for many types of resource use the estimate of the mean falls outside the range between 2 and 9, rendering the results of the one-way sensitivity analyses less informative.

The ERG finds the approach of incorporating structural model uncertainty due to parametric model choice plausible.

5.2.12 Model validation and face validity check

The company presented the conducted validation efforts in the CS[3], which were categorized as internal and external validation, which are summarised below.

Internal validation

In the CS, it was mentioned that the model was quality-assured by external economists who were not involved in the model adaptation reviewed the model for coding errors, inconsistencies and the plausibility of inputs. Afterwards, it was stated that the model had been put through a checklist of known modelling errors, and questioning of the assumptions based upon the Phillips checklist.[103]

External validation

An advisory board was conducted in the UK to validate the clinical inputs informing the cost effectiveness model. The clinicians were asked to provide their opinion on the relative efficacy of each treatment based on their experience in UK clinical practice. In the CS, it was stated that on the average, POM+LoDEX was considered the most efficacious, followed by BTD, PANO+BOR+DEX then conventional chemotherapies.[87]

Estimated life years and QALYs of the model were compared to those from the two previous NICE submissions (TA 338 and TA380), for the same indication. The comparisons are given in Table 5.35 below.

Table 5.35: Comparison of life years and QALYs across NICE submissions for patients who have received at least two prior lines of therapy in RRMM

	Life years	QALYs
POM+LoDEX (MM-002 only)	1.81	1.13
POM+LoDEX (all trials)	1.71	1.10
POM+LoDEX (MM-003)	1.45	0.93
BTD	1.14	0.72
PANO+BOR+DEX using PANORAMA-2	2.25	1.39
Conventional chemotherapy using HiDEX (MM-003)	0.78	0.49
POM+LoDEX – previous NICE submission (TA338)	2.23	1.29
Comparator – previous NICE submission (TA338)	1.17	0.68
PANO+BOR+DEX – NICE submission (TA380)	2.29	1.52
BOR+DEX – NICE submission (TA380)	2.25	1.48

BOR, bortezomib; BTD, bendamustine, thalidomide and dexamethasone; DEX, dexamethasone; HiDEX, high-dose dexamethasone; LoDEX, low-dose dexamethasone; NICE, National Institute for Health and Care Excellence; PANO, panobinostat; POM, pomalidomide; QALYs, quality-adjusted life years

In addition to comparing the model outcomes with previous submissions, in the CS[3], the resource use outcomes of the model were compared with the real world health care costs from Gooding 2015[68], which estimated that patients had incurred £8,448 in medical resource use costs based on a mean time on treatment of 15.5 weeks during fourth line anti-multiple myeloma therapy. The model estimates that over 15.5 weeks, patients incur £9,480 and £9,147 in medical resource use costs when treated with BTD and conventional chemotherapies respectively. The company stated that the cost estimates of BTD and conventional therapies over 15.5 weeks were very similar to the Gooding estimate, and argued that this validated the way the resource use costs were modelled.

ERG comment: In the CS, the details of the internal validation procedure were not provided clearly. Therefore, the ERG has conducted an in-house technical verification protocol (TECH-VER Protocol) to verify whether the model was correctly implemented and whether the report (description of the model as well as the results) and the model (calculations and results) were consistent or not. The protocol and cell by cell checking of the model helped ERG identifying a number of programming errors, which will be corrected in ERG exploratory analyses.

The visual fit of the adjusted parametric survival curves with the raw Kaplan Meier curves from the POM+LoDEX, BTD and PANO+BOR+DEX trials could also have been considered here as a sort of a validation, however, as discussed in Section 5.2.6, the adjustment here should be made in accordance with the baseline characteristics of treatment arms, e.g. the covariate adjustments for POM+LoDEX should consider only the baseline characteristics of the POM+LoDEX patients. This way, it can be visually assessed how good the parametric survival function estimates can predict the OS and PFS of the patients given the same baseline characteristics, under the same treatment.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

5.3.1 Correction of the additional programming errors

After the clarification letter was send to the company, additional programming errors were found. The list of errors are presented below:

1. Half cycle correction was wrongly implemented as discussed in Section 5.2.5

2. As described in Section 5.2.6, the model did not use the CGP results that were obtained from the provided VBA macro, as described in the response to the clarification letter document.[38]
3. As described in Section 5.2.9, 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 this ERG-corrected model. Based on this model, the corrected base case results are given in Tables 5.36-5.38 below for POM+LoDEX vs. BTD, POM+LoDEX vs. PANO+BOR+DEX and POM+LoDEX vs. CC comparisons.

For the comparison with BTD, POM+LoDEX is associated with a gain of 0.67 incremental undiscounted life years and [redacted] incremental QALYs per patient, and an increase in overall costs of [redacted] per patient, which resulted in an ICER of £45,082 per QALY gained.

For the comparison with CC, POM+LoDEX is associated with a gain of 0.68 incremental life years and [redacted] incremental QALYs per patient, and an increase in overall costs of [redacted] per patient, which resulted in an ICER of £49,235 per QALY gained.

For the comparison with PANO+BOR+DEX, POM+LoDEX is associated with a reduction of 0.49 incremental life years and a reduction of [redacted] incremental QALYs per patient, and a decrease in overall costs of [redacted] per patient, which resulted in an ICER of £139,954 per QALY gained (in the southwest quarter of the plane).

Table 5.36: Base-case results – 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

BTD, bendamustine, thalidomide and dexamethasone; ICER, incremental cost effectiveness ratio; LoDEX, low-dose dexamethasone; POM, pomalidomide; QALYs, quality-adjusted life years

Table 5.37: Base-case results – 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)

BOR, bortezomib; DEX, dexamethasone; PANO, panobinostat; ICER, incremental cost effectiveness ratio; LoDEX, low-dose dexamethasone; NMB, net monetary benefit; POM, pomalidomide; QALYs, quality-adjusted life years

Table 5.38: Base-case results – vs. conventional chemotherapy

Technologies	Total costs (£)	Total LYG (undiscounted)	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£) versus baseline (QALYs)
Conventional chemotherapy	[redacted]	0.76	[redacted]	[redacted]	-	-	-
POM+ LoDEX	[redacted]	1.43	[redacted]	[redacted]	0.68	[redacted]	£48,673

ICER, incremental cost effectiveness ratio; LoDEX, low-dose dexamethasone; POM, pomalidomide; QALYs, quality-adjusted life years

5.3.2 Full incremental cost effectiveness analysis

In this section, a full incremental analysis is conducted, including all comparators by the corrected post-clarification model. For this purpose, the pooled dataset including MM-002, MM-003 and MM-010 trials and all BTD trials were used. From this pooled dataset, BTD and POM+LoDEX OS, PFS and TTF parametric curves were estimated using the covariate adjustment methods (CGP).

As in the CS, for PANO+BOR+DEX, the HRs obtained from MAIC were applied on the POM+LoDEX OS, PFS and TTF curves. However, for CC, the HRs obtained from the ITT (as opposed to the two-stage) analysis of the MM-003 trial (POM+LoDEX vs HiDEX) were applied on the POM+LoDEX OS, PFS and TTF curves. The full incremental results can be seen in Table 5.39 below. The ICER of POM+LoDEX vs CC is £81,209 per QALY gained, and BTD is dominated by CC. The ICER of PANO+BOR+DEX vs POM+LoDEX is £142,930 per QALY.

Note that in this analysis, ITT HR (POM+LoDEX vs HiDEX) from the MM-003 trial was used. In the next exploratory analysis, the effect of using HR from a two stage adjusted analysis, as used in the CS, will be used.

Note that in this analysis, ITT HR (POM+LoDEX vs. HiDEX) from the MM-003 trial was used. In the next exploratory analysis, the effect of using HR from a two stage adjusted analysis will be used.

Table 5.39: Full incremental analysis (based on pooled MM-002, MM-003 and MM-010 dataset, using ITT HRs from MM-003 for CC OS/PFS and TTF curves and CGP is used for covariate adjustments)

	Total Costs	Total LYs	Total QALYs	Incr Costs	Incr QALYs	ICER
PANO+BOR+DEX	[redacted]	2.05	[redacted]	[redacted]	[redacted]	£142,930
POM+LoDEX	[redacted]	1.55	[redacted]	[redacted]	[redacted]	£81,209
BTD	[redacted]	0.99	[redacted]	[redacted]	[redacted]	Dominated by CC
CC	[redacted]	1.09	[redacted]	[redacted]	[redacted]	-

BOR, bortezomib; BTD, bendamustine + thalidomide + dexamethasone; CC, conventional chemotherapy; CPG, corrected group prognosis; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost effectiveness ratio; ITT, intention to treat, LoDEX, low-dose dexamethasone; LY, life year; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; POM, pomalidomide; QALY, quality-adjusted life year; TTF, time to treatment failure

5.3.3 Full incremental cost effectiveness analysis with two stage HR from MM-003 trial

In this section, a full incremental analysis is conducted, including all comparators by the corrected post-clarification model. Different from the previous analysis, for the OS, not the ITT (0.72) HR but the two stage HR (0.52) was applied. The 2-stage method is one of the methods used for treatment switching adjustments and in MM-003 trial, treatment switching was allowed for HiDEX patients who had progressed.

The full incremental analyses can be seen in Table 5.40 below. As can be seen the ICER of POM+LoDEX vs. CC is now £57,288 per QALY gained, and BTD is extendedly dominated by POM+LoDEX. The ICER of PANO+BOR+DEX vs. POM+LoDEX is £142,930 per QALY.

Table 5.40: Full incremental analysis (based on pooled MM-002, MM-003 and MM-010 dataset, using two stage HRs from MM-003 for CC OS/PFS and TTF curves and CGP is used for covariate adjustments)

	Total Costs	Total LYs	Total QALYs	Incr Costs	Incr QALYs	ICER
PANO+BOR+DEX	[redacted]	2.05	[redacted]	[redacted]	[redacted]	£142,930
POM+LoDEX	[redacted]	1.55	[redacted]	[redacted]	[redacted]	£57,288
BTD	[redacted]	0.99	[redacted]	[redacted]	[redacted]	Extendedly dominated by POM+LoDEX
CC	[redacted]	0.78	[redacted]	[redacted]	[redacted]	-

BOR, bortezomib; BTD, bendamustine + thalidomide + dexamethasone; CC, conventional chemotherapy; CPG, corrected group prognosis; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost effectiveness ratio; ITT, intention to treat, LoDEX, low-dose dexamethasone; LY, life year; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; POM, pomalidomide; QALY, quality-adjusted life year; TTF, time to treatment failure

5.3.4 Full incremental cost effectiveness analysis with mean covariate adjustment method

In this section, a full incremental analysis is conducted, including all comparators by the corrected post-clarification model. Different from the previous analysis in Section 5.3.2, for the covariate adjustment, not CGP but mean covariate adjustment method was used. The baseline covariates were adjusted based on real world data from UK as discussed in Section 5.2.3.

The full incremental analyses can be seen in Table 5.41 below. Now the ICER of POM+LoDEX vs. CC is £84,091 per QALY gained, and BTD is dominated by CC. The ICER of PANO+BOR+DEX vs. POM+LoDEX is £146,307 per QALY.

Table 5.41: Full incremental analysis (based on pooled MM-002, MM-003 and MM-010 dataset, using ITT HRs from MM-003 for CC OS/PFS and TTF curves and mean covariate adjustment method is used for covariate adjustments)

	Total Costs	Total LYs	Total QALYs	Incr Costs	Incr QALYs	ICER
PANO+BOR+DEX	[redacted]	1.96	[redacted]	[redacted]	[redacted]	£146,307
POM+LoDEX	[redacted]	1.49	[redacted]	[redacted]	[redacted]	£84,091
BTD	[redacted]	0.95	[redacted]	[redacted]	[redacted]	Dominated by CC
CC	[redacted]	1.05	[redacted]	[redacted]	[redacted]	-

BOR, bortezomib; BTD, bendamustine + thalidomide + dexamethasone; CC, conventional chemotherapy; CPG, corrected group prognosis; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost effectiveness ratio; ITT, intention to treat, LoDEX, low-dose dexamethasone; LY, life year; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; POM, pomalidomide; QALY, quality-adjusted life year; TTF, time to treatment failure

5.3.5 Full incremental cost effectiveness analysis with mean covariate adjustment method and 2-stage HR

In this section, again a full incremental analysis is conducted, including all comparators by the corrected post-clarification model. Different from the previous analysis in Section 5.3.2, both 2-stage HR is used instead of ITT HR from MM-003 for the CC OS. In addition, for the covariate adjustment, not CGP but mean covariate adjustment method was used, thus combining the analyses from Sections 5.3.3 and 5.3.4. The baseline covariates were adjusted based on real world data from UK as discussed in Section 5.2.3.

The full incremental analyses can be seen in Table 5.42 below. The ICER of POM+LoDEX vs. CC is £59,104 per QALY gained, and BTD is extendedly dominated by POM+LoDEX. The ICER of PANO+BOR+DEX vs. POM+LoDEX is £146,307 per QALY.

Table 5.42: Full incremental analysis (based on pooled MM-002, MM-003 and MM-010 dataset, using 2-stage HRs from MM-003 for CC OS/PFS and TTF curves and mean covariate adjustment method is used for covariate adjustments)

	Total Costs	Total LYs	Total QALYs	Incr Costs	Incr QALYs	ICER
PANO+BOR+DEX	[redacted]	1.96	[redacted]	[redacted]	[redacted]	£146,307
POM+LoDEX	[redacted]	1.49	[redacted]	[redacted]	[redacted]	£59,104
BTD	[redacted]	0.95	[redacted]	[redacted]	[redacted]	Extendedly dominated by POM+LoDEX
CC	[redacted]	0.75	[redacted]	[redacted]	[redacted]	-

BOR, bortezomib; BTD, bendamustine + thalidomide + dexamethasone; CC, conventional chemotherapy; CPG, corrected group prognosis; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost effectiveness ratio; ITT, intention to treat, LoDEX, low-dose dexamethasone; LY, life year; OS, overall survival; PANO, panobinostat; PFS, progression-free survival; POM, pomalidomide; QALY, quality-adjusted life year; TTF, time to treatment failure

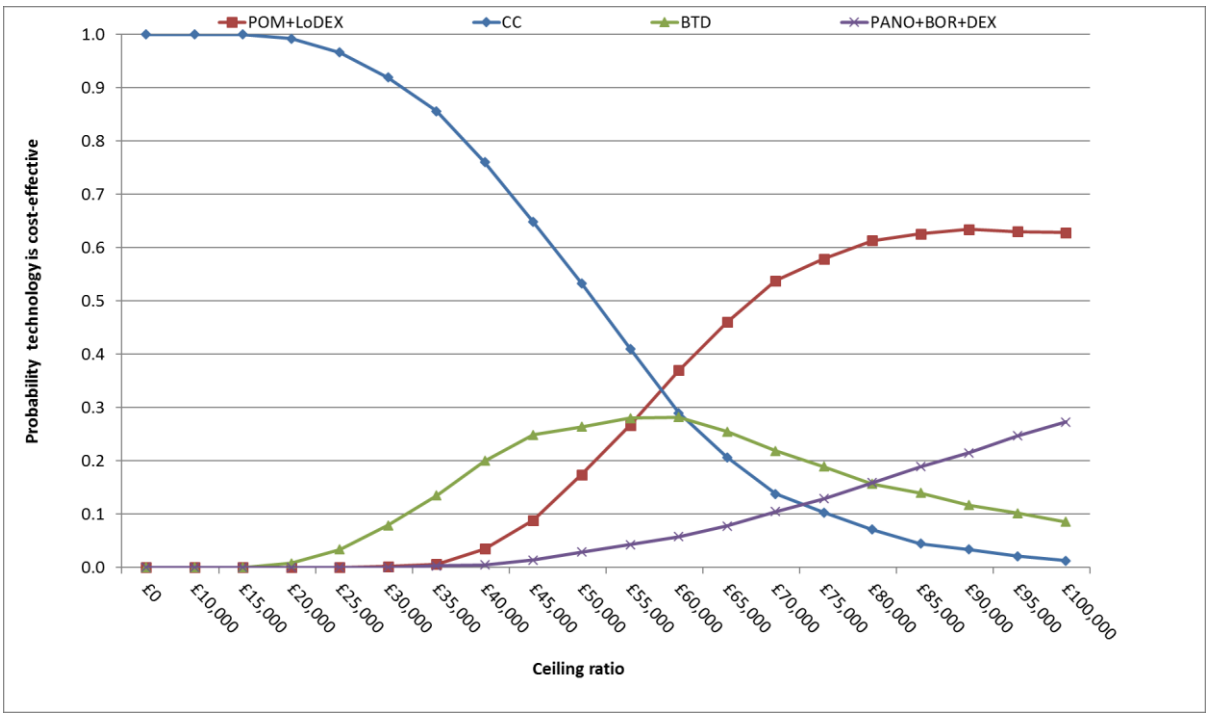
5.3.6 Additional analyses

Additional analyses were conducted on the model from 5.3.5, which is the ERG preferred model. Recall that the model in 5.3.5 was for a full incremental analysis, based on the pooled MM-002, MM-003, MM-010 and BTD trials, and including all comparators by the corrected post-clarification model. The model in 5.3.5 assumes a 2-stage HR to be used instead of ITT HR from MM-003 for the CC OS only.

Firstly, the PSA is run on the 5.3.5 model. The PSA give similar results as in 5.3.5. The scatter plot of the PSA and the CEAC curves are given in Figures 5.28 and 5.29, respectively.

Figure 5.28: Scatter plot of the PSA conducted on the 5.3.5 model

Figure 5.29: CEACs for POM+LoDEX, BTD, CC and PANO+BOR+DEX



It can be seen that the cost and QALYs from the PSA, especially for PANO+BOR+DEX are quite scattered. From the CEAC it can be seen that CC is the intervention having the highest probability of being cost-effective until a threshold of £60,000 per QALY. After that, POM+LoDEX becomes the most cost-effective intervention.

Next, some additional scenario analyses, conducted on the model in 5.3.5, are shown. A list of the scenarios are as follows:

1. Dose interruptions applied for all arms assuming equal proportion of packs are skipped among comparators
2. Including subsequent treatment cost using resource use questionnaire
3. Including subsequent treatment cost based on Hemateologic Cancer Research Center in York
4. No wastage of drugs
5. Equal BORR, AE discontinuation and hospitalization rates for all 4 treatments (all same as POM+ LoDEX) for estimating utilities

6. No disutility due to IV administration
7. AE rates of the comparators are the same as POM+LoDEX.
8. Utility weights are from Quinn et al

The results of these scenario analyses are provided in a pairwise manner (POM+LoDEX vs. a comparator) in Table 5.43 below. The results demonstrate that the ICER results do not change much and are more or less similar across the analyses.

Table 5.43: Additional scenario analyses conducted on model 5.3.5

	POM+LoDEX vs. BTD			POM+LoDEX vs. PANO+BOR+DEX			POM+LoDEX vs. CC		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER (SW)	Incr. Costs	Incr. QALYs	ICER
Model 5.3.5	[redacted]	[redacted]	£55,974	[redacted]	[redacted]	£146,307	[redacted]	[redacted]	£59,104
Scenario 1	[redacted]	[redacted]	£56,914	[redacted]	[redacted]	£143,274	[redacted]	[redacted]	£59,589
Scenario 2	[redacted]	[redacted]	£59,280	[redacted]	[redacted]	£116,924	[redacted]	[redacted]	£58,497
Scenario 3	[redacted]	[redacted]	£56,002	[redacted]	[redacted]	£146,586	[redacted]	[redacted]	£59,056
Scenario 4	[redacted]	[redacted]	£58,456	[redacted]	[redacted]	£146,307	[redacted]	[redacted]	£61,407
Scenario 5	[redacted]	[redacted]	£56,155	[redacted]	[redacted]	£142,380	[redacted]	[redacted]	£61,007
Scenario 6	[redacted]	[redacted]	£56,760	[redacted]	[redacted]	£143,073	[redacted]	[redacted]	£59,104
Scenario 7	[redacted]	[redacted]	£56,116	[redacted]	[redacted]	£145,622	[redacted]	[redacted]	£59,139
Scenario 8	[redacted]	[redacted]	£52,552	[redacted]	[redacted]	£130,928	[redacted]	[redacted]	£57,197

BOR, bortezomib; BTD, bendamustine + thalidomide + dexamethasone; CC, conventional chemotherapy; DEX, dexamethasone; ICER, incremental cost effectiveness ratio; LoDEX, low-dose dexamethasone; PANO, panobinostat; POM, pomalidomide; QALY, quality-adjusted life year

5.4 Conclusions of the cost effectiveness section

The economic model described in the CS is considered by the ERG to meet the NICE reference case and is largely in line with the decision problem specified in the scope. However, in the scope of the current appraisal[30] NICE requested that at third line POM+LoDEX versus PANO+BOR+DEX would be assessed and at fourth line onwards versus all comparators (BTD, PANO+BOR+DEX and CC). In the CS, the cost effectiveness analyses were not stratified into third line and fourth and later lines. The ERG considers this acceptable, as data would be lacking for such stratification.

The majority of the cost effectiveness searches in the CS were well documented and easily reproducible, and were carried out in line with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.[41] The ERG expressed concerns on the lack of relevant MeSH indexing terms on Embase.com, and the omission of specific searches for the identification of cost and healthcare resource use data.

The ERG assessment indicated that the model was generally well presented and reported. However, one of the major concerns of the ERG is that even though efforts were made to correct for differences in baseline covariates between data sets, there can be still some unmeasured confounders or other factors (e.g. the fact that refractoriness to BOR was not in the dataset, the representativeness of the HiDEX efficacy for the conventional care etc.) that add uncertainty to the treatment effectiveness results of the CS.[3] As a consequence, the results of the cost effectiveness analyses should be interpreted with caution.

Additionally, in the CS[3] a different dataset is used for each of the three comparisons. The ERG considers that this pairwise approach is not that informative, because it implies a slightly different population for each comparison, without being able to clearly define these sub populations. Thus, the decision for POM+LoDEX should be based on a fully incremental analysis. Therefore, the ERG requested the company to provide a full incremental analysis using a single source of data. This approach sustains the consistency among comparisons. It does mean that the data used for comparison with BTD might not be the most comparable to the BTD trials. However, there is adjustment for confounding by use of regression analysis and it strengthens the POM+LoDEX vs. BTD comparison insofar as it is based on a larger dataset (in the base case, this comparison used the MM-002 only and BTD trials dataset instead of pooled data from all POM+LoDEX [MM-002, MM-003 and MM-010] and all BTD trials).

The ERG also has some concerns related to the implementation of AEs. For the comparators of POM+LoDEX, in the base case, the proportion of TEAE discontinuation probabilities (compared to POM+LoDEX) was multiplied with the POM+LoDEX specific AE rates for each comparator. The TEAE discontinuation probabilities for each comparator were derived from disconnected parallel trials without any adjustments for baseline characteristic differences. Additionally, this approach would maintain the same frequency order of the AEs of POM+LoDEX (MM-003 trial) for each of the comparators. The ERG thinks that this assumption is not plausible, because each drug has different mechanisms and different safety profiles, and it is unlikely that the AE frequency order would be mirrored for other comparators, let alone the same relative frequency.

The approach taken by the company to include HRQL is largely the same as the approach used for TA338. In line with the conclusion of the previous ERG report, the use of a regression model is still deemed appropriate. Thus, the ERG did not encounter any major issues with the approach used to include quality of life in the model. Nevertheless, the data about the exploratory variables (i.e. BORR, hospitalization and adverse events) has its limitations which might cause bias in the estimation of utilities. Therefore, the ERG explored a scenario-analysis in which only disease progression varies across treatments in the estimation of utilities. Due to the uncertainty about the estimated utility decrement associated with intravenous or subcutaneous treatment, the ERG also explored a scenario in which no utility decrement is assumed for IV treatments.

The current submission has re-estimated various types of resource use compared to TA338. For example, monitoring costs are now based on an extensive questionnaire filled in by six clinical experts, whereas TA338[24] used values from TA228[19]. An important error was found in the electronic model submitted by the company in the transformation of yearly resource use for monitoring to weekly numbers. As a result, in the CS the monitoring costs are underestimated, for all treatments, and since the extent of the underestimation varies by treatment, the ICERs in the CS are also incorrect. The impact of correcting this error is shown in section 5.3. Moreover, input parameters derived from the resource use questionnaire should be considered with care, since the questionnaire is quite long and detailed and thus might have been difficult to fill in, and since only six clinical experts completed the questionnaire.

Another important issue is that the model allows for a decrease in treatment costs based on treatment interruptions lasting longer than 28 days. The pertinent data were available for POM-LoDEX, and used to also estimate the cost decrease for panobinostat. However, dose interruptions of BOR (within PANO+BOR+DEX), BTD and conventional chemotherapies were not taken into account at all, creating a potential inconsistency. To assess the impact of this, the company altered the model, in response to the clarification letter, so that a scenario could be run where the costs of BOR, BTD and conventional chemotherapies are decreased at the same rate as panobinostat.

Regarding the costs of subsequent treatment, the ERG does not agree with the base case choice to not include these costs. As stated in the CS, the effects of these subsequent treatments are implicitly incorporated in the OS results, and thus it would be rational to also include the costs required to achieve those effects. However, the two estimates of these costs provided in the CS for scenario analyses differ greatly and which should be preferred is difficult to determine based on the information provided in the CS. The impact of adding these costs was assessed in Section 5.3.6, and it was shown that including these costs have an impact on ICER.

Following the request for clarification, a new model was submitted by the company, in which the errors identified by the ERG were corrected. In that newly submitted model, the ERG identified additional errors. After these additional errors were corrected, the base case analyses of the company were repeated with the ERG-corrected model. The ICER results were around £45,000 per QALY gained vs. BTD, £143,000 per QALY 'lost' vs. PANO+BOR+DEX (SW quadrant) and £49,000 per QALY gained vs. CC.

After the base case analyses of the company were repeated, the ERG conducted a full incremental analysis, in which the effectiveness of BTD and POM+LoDEX treatments were based on the pooled dataset of MM-002, MM-003, MM-010 and all other BTD trials. CGP as covariate adjustment method was used. For PANO+BOR+DEX, the HR obtained from the MAIC is applied on top of POM+LoDEX curve; and similarly for CC, the HR of the OS data from MM-003 trial is applied on top of POM+LoDEX curve. However, unlike in the CS, the HR for CC was that based on the ITT analysis as opposed to using the 2-stage method for treatment switching adjustment.

In this full incremental analysis, CC was the cheapest treatment option, however BTD was the treatment that accumulated the lowest QALYs, hence it was dominated by CC. The ICER of POM+LoDEX vs. CC was around £81,000 per QALY gained and the ICER of PANO+BOR+DEX vs. POM+LoDEX was around £143,000 per QALY gained.

When the two stage HR was used instead of ITT HR, BTD was not dominated by CC anymore, but was extendedly dominated by POM+LoDEX. The ICER of POM+LoDEX vs. CC was around £55,000 per QALY gained, the ICER of PANO+BOR+DEX vs. POM+LoDEX was around £143,000 per QALY gained.

Finally, the ERG defined their preferred approach, i.e.with 2-stage corrected HR, when instead of CGP method the mean covariate adjustment method was selected, (using not trial data but real world data from UK centres). The ICERs slightly increased, but the main message stays the same as for the other approached. BTD was extendedly dominated by POM+LoDEX. The ICER of POM+LoDEX vs. CC was around £59,000 per QALY gained and the ICER of PANO+BOR+DEX vs. POM+LoDEX was around £146,000 per QALY gained.

Some additional scenario analyses were conducted on the last model, which represents the ERG preferred model (with 2-stage HR and mean covariate adjustment used to adjust for baseline differences). In these scenario analyses, the ICER of POM+LoDEX vs. BTD were between £52,000 and £59,000 per QALY gained; for POM+LoDEX vs. PANO+BOR+DEX, the ICER was in the range of £117,000 and £146,000 -in the SW quadrant- and for POM+LoDEX vs. CC, the ICER was between £57,000 and £61,000.

From the analyses, POM+LoDEX does not seem to be a cost-effective treatment option when common threshold values are assumed. However, the results should be interpreted cautiously as the effectiveness data was not dependent on a network of randomised trials, the PAS price of some of the comparators were not included and there were many uncertainties in the model.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The errors confirmed by the company were already corrected and a new model provided with the response to the clarification document.[38] Table 6.1 shows how each individual change of the ERG base case impacts the ICER plus the combined effect of all changes simultaneously.

Table 6.1: Revised base case cost effectiveness analysis, incorporating corrections and amendments identified by the ERG

	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
Base case from the CS sent with the response to the clarification letter[38]	[redacted]	[redacted]	£39,665	[redacted]	[redacted]	£141,793 (SW)	[redacted]	[redacted]	£44,811
Programming errors (5.3.1)	[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 (5.3.2)	[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 (5.3.3)	[redacted]	[redacted]	£54,428	[redacted]	[redacted]	£142,930 (SW)	[redacted]	[redacted]	£57,288
Using pooled data set (MM-002, MM-003 and MM-010), 2-stage HR from MM-003, Mean Covariate (5.3.5)	[redacted]	[redacted]	£55,974	[redacted]	[redacted]	£146,307 (SW)	[redacted]	[redacted]	£59,104

BOR, bortezomib; BTD, bendamustine + thalidomide + dexamethasone; CC, conventional chemotherapy; CS, company submission; DEX, dexamethasone; ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost effectiveness ratio; ITT, intention to treat, LoDEX, low-dose dexamethasone; PANO, panobinostat; PFS, progression-free survival; POM, pomalidomide; QALY, quality-adjusted life year

7. END OF LIFE

The NICE end of life criteria state that *'the treatment is indicated for patients with a short life expectancy, normally less than 24 months and there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.'*[104]

The company argued that POM+LoDEX is considered to meet the NICE end of life criteria in comparison to BEN and conventional chemotherapies:

'Median survival is 3-9 months across patients receiving current care in the UK.[CS REF 36-40] *Modelled mean survival is also < 14 months versus both BEN and conventional chemotherapy.*

The estimated survival benefit compared to BEN and conventional chemotherapy is > 5 months in all comparisons (covariate adjusted and unadjusted, crossover adjusted and unadjusted). Modelled mean survival increase is 7 – 8 months.'[3]

They further stated that *'evidence for end of life is less compelling in the comparison to PANO+BOR+DEX as no improvement was demonstrated in median outcomes for OS; difficulties in comparing to PANO+BOR+DEX are, however, considerable given the limited evidence available and lack of patient level data to correct for differences in patient population.'*[3]

ERG comment: The ERG agrees that the patient group, being at least at third line of treatment for RRMS, have a short life expectancy, normally less than 24 months. Hence the first criterion for end of life has been met.

The evidence reported by the company showed that the gain in median OS in the MM-003 study for POM + LoDEX compared to HiDEX was 4.4 months at the 01 March data cut and 5 months at the 01 September 2013 data cut (Table 4.8). The gain in median OS for POM + LoDEX compared to BTD was 6.1 months in the base case (MM-002 only) and 4.6 months in sensitivity analysis 1 (MM-002, MM-003 and MM-010), see Table 4.26. In the comparison of POM + LoDEX with PANO + BOR + DEX median OS was longer for patients receiving PANO + BOR + DEX. The median OS for patients treated with PANO + BOR + DEX was 17.5 months (95% CI 10.8 to 22.22) compared to 13.4 months (95% CI 11.4 to 15.6) for patients treated with POM + LoDEX, i.e. a reduction of 4.1 months (Table 4.27). POM + LoDEX meets the criteria for a gain of at least 3 months additional life compared to HiDEX or BTD. The evidence suggests that POM + LoDEX does not meet this criteria compared to PANO + BOR + DEX however the evidence for PANO + BOR + DEX is based on a small number of patients (n=55) and the analysis was limited by the lack of studies comparing these treatments. Given that the patient population for this appraisal represents a heavily pretreated population who have progressed on multiple previous lines of therapy and the limited alternatives available for this population the committee will need to decide whether or not this second criteria has been met.

From the model, the ERG sees that normal life expectancy depends on the treatment patients currently receive: for patients treated with BTD the mean survival is about 12 months, whereas for patients treated with conventional chemotherapy the mean survival is somewhat shorter at about 9 months. In contrast, the mean survival for patients receiving PANO+BOR+DEX is estimated at 24 months.

The estimated extension of life also depends on the comparator. Compared to BTD and CC, treatment with POM will lead to a mean increase in life expectancy of at least 3 months. However, POM+LoDEX will lead to a decrease in life expectancy of 6 months compared to PANO+BOR+DEX.

8. OVERALL CONCLUSIONS

8.1 Statement of principal findings

Based on the MM-003 trial, pomalidomide appears to extend overall survival by at least 4.6 months and progression-free survival in comparison with HiDEX in a heavily treated population who are refractory to bortezomib and lenalidomide. The adverse event profile appears to be manageable with appropriate dose reductions and interruptions. The ERG has drawn attention to those adverse events occurring more frequently in the pomalidomide arm, notably neutropaenia.

For the comparison with bendamustine the company used covariate adjusted Cox proportional hazards regression to adjust for the differences between studies in patient characteristics. The covariate adjusted results were very similar to the unadjusted results in terms of both PFS and OS indicating that the differences between studies in the selected covariates (patient characteristics) have relatively little impact on the outcomes observed. However the selection of different datasets for POM + LoDEX alters the results for OS. In the base case using only the MM-002 study the median OS in the covariate adjusted analysis was 16.6 months (95% CI 12.6 to 19.8) for patients receiving POM + LoDEX. In the sensitivity analysis based on data from MM-002, MM-003, MM-010 the median OS in the covariate adjusted analysis was 12.7 months (95% CI 11.9 to 13.9) for patients receiving POM + LoDEX. The corresponding results for patients treated with BTD were 3.3 months (95% CI 2.5 to 5.5) in the unadjusted analysis and 3.7 months (95% CI 2.8 to 5.6) in the adjusted analysis.

For the comparison with PANO + BOR + DEX the POM + LoDEX arms of the MM-002, MM-003 and MM-010 studies were compared with the PANO + BOR + DEX arm of the PANORAMA-2 study in a matching adjusted indirect comparison (MAIC). The application of the MAIC method resulted in a one month increase in median OS for patients receiving POM + LoDEX (13.4 months, 95% CI 11.4 to 15.6) compared to the unweighted analysis (12.4 months, 95% CI 11.1 to 13.4). In both cases the median OS was shorter than those patients receiving PANO + BOR + DEX (17.5 months, 95% CI 10.8 to 22.22). The hazard of death was reduced by a similar amount for patients receiving PANO + BOR + DEX compared to POM + LoDEX in both the unweighted analysis (HR=0.73, 95% CI 0.52 to 1.02) and in the MAIC (HR=0.78, 95% CI 0.56 to 1.09).

The economic model described in the CS is considered by the ERG to meet the NICE reference case to a reasonable extent and is in line with the decision problem specified in the scope.

The company provided pairwise comparisons with ICERs of POM+LoDEX versus each comparator as follows: £39,665 versus BTD; £141,793 (SW quadrant[2]) versus PANO+BOR+DEX and £44,811 versus CC. This submitted model included errors and the ERG corrected the model and conducted some exploratory analyses based on the pooled MM-002, MM-003, MM-010 and all BTD trial dataset. In these exploratory analyses, BTD was either dominated by CC or extendedly dominated by POM+LoDEX. The ICER of POM+LoDEX vs CC was around £55,000 or £82,000 per QALY gained, differing based on the OS HR chosen. The ICER of POM+LoDEX vs PANO+BOR+DEX is above £140,000 per QALY, where POM+LoDEX results in fewer QALYs, at lower costs.

If POM+LoDEX is compared to CC and BTD, it can be considered to satisfy the end of life criteria, but when it is compared to PANO+BOR+DEX, end of life criteria do not hold.

[2] ICERs in the south-west quadrant of the cost effectiveness plane (less effectiveness at lower costs) should be above the threshold in order to be deemed cost-effective

The various scenario analyses revealed that the ICER is relatively robust against changes in input values and assumptions.

8.2 Strengths and limitations of the assessment

The main evidence in the company submission came from the MM-003 trial which compares POM+LoDEX to HiDEX. Although this was a reasonably large, well conducted multi-centre trial, the main comparator is no longer optimal in current practice. Therefore the comparator can only be viewed as a proxy for conventional chemotherapy which might constitute an alternative. The trial was in a heavily treated population who had received a median of five therapies (range 2 to 17). Only 25 patients had received two prior therapies only, thus the trial is not representative of pomalidomide as a third line therapy. It could be assumed that pomalidomide might perform better at third line in a less treated population but this is an assumption. At third line patients can be offered panobinostat and there is no direct evidence comparing the two treatments.

There were limited data available to inform the comparison of POM + LoDEX with treatments other than HiDEX. There were no studies that directly compared POM + LoDEX with either BTD or PANO + BOR + DEX. In addition the available studies did not include a common comparator that would permit an indirect comparison or mixed treatment comparison (MTC). As a result the company presented evidence based on comparisons of observational data.

Although the evidence reported by the company is limited the ERG recognises that the lack of appropriate data excluded many of the standard alternatives. In the absence of any new direct head to head studies these results are likely to represent the best estimates of relative effectiveness that could be obtained given the limitations of the existing studies.

The model structure that was used in the model is a common model structure, used in other STAs as well, and was also used in TA338. The structural model uncertainty (in terms of choice of parametric functions for OS and PFS) was reflected in the probabilistic sensitivity analysis.

Even though there was no data based on direct randomised evidence, substantial effort was made to statistically estimate the comparative effectiveness input for the model. Also, a good regression model, based on EQ-5D measurements in the MM-003 trial, was used to estimate utilities for all health states per treatment. Compared to the previous TA, more effort was made to estimate the resource use associated with the treatments and the disease.

However, there are also various limitations and weaknesses regarding the cost effectiveness analysis. The trials used in the effectiveness data were not connected and even though adjustment techniques were used, it was not clear whether the data was appropriate to use for informing the effectiveness and cost effectiveness of POM+LoDEX.

The pairwise comparisons that were conducted in Company base case were giving inconsistent results, e.g. different outcomes for the same treatment (POM+LoDEX) in different comparisons, thus making it difficult to interpret these pairwise results. It might be reasonable to have three different estimates if they related to three different populations. However, in this situation it is not possible to define an exact subgroup for whom only POM+LoDEX vs BTD is relevant as opposed to any of the other comparators. Moreover, there is no convincing reason *why* different relevant patient populations should be considered for different comparisons, e.g. for POM+LoDEX vs BTD and for POM+LoDEX vs PANO+BOR+DEX

The model makes many assumptions surrounding adverse events. In essence, it is assumed that the frequency order of the adverse events for POM+LoDEX is mirrored in other comparators, which may bias both the estimates of costs and disutility associated with AE.

The CS did not report on the model validation efforts and many modelling errors were found, some with a clear impact on the results.

The model assumed that all oral drugs would only be dispensed per full package per cycle, thus including wastage of part of a package in each cycle. This is unlikely to be realistic.

Finally, the ERG is of the opinion that the costs of subsequent treatment should be included in the model as the effects of these subsequent treatments are implicitly incorporated in the OS results, and thus it would be rational to also include the costs required to achieve those effects. However, the two estimates of these costs provided in the CS for scenario analyses differ greatly and which should be preferred is difficult to determine based on the information provided in the CS.

8.3 Suggested research priorities

Given the lack of direct evidence comparing POM with BTD and PANO a three arm trial comparing these options for people with RRMM at third line or beyond would be helpful. Ideally such trial would include the EQ-5D, in order to create a more robust regression model for HRQoL.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from Kleijnen Systematic Reviews to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Friday 23 September** 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 **Disregarding of pairwise comparisons**

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P117: “there is no convincing reason why different relevant patient populations should be considered for different comparisons, e.g. for POM+LoDEX vs BTD and for POM+LoDEX vs PANO+BOR+DEX.”	Removal of statements.	Celgene believe that the difference in trials and the limited effect of adjusting for covariates is reason enough that a pooled population across all trials should not be considered for all comparisons.	Not a factual error The ERG does not agree with the proposed amendment. Firstly, the statement on P117 concerns the indicated patient population for POM+LoDEX, and not the differences in the trial characteristics. Secondly, the underlying reasons of the ERG critique as well as the implications of the pairwise comparisons were explained in the same paragraph.
P157: “in the CS a different dataset is used for each of the three comparisons. The ERG considers that this pairwise approach is not that informative, because it implies a slightly different population for each comparison, without being able to clearly define these sub populations”.		As stated in the submission, MM-002 is most similar to the BEN data whilst MM-003 and MM-010 contain higher levels of refractoriness to LEN and BOR. The ERG report states on page 157 that ‘[use of pooled data] it does mean that the data used for comparison with BTD might not be the most comparable to the BTD trials.’ The ERG continue to say that this is offset through adjustment for confounding and the benefits from a larger dataset. We do not believe that the benefits of the larger dataset outweigh the reduced comparability.	Not a factual error The ERG does not agree with the removal of the statements as the underlying reasons of the critique were given in the ERG report.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		A further point to note is that the application of the HR from the within-trial comparison to HiDex (as a proxy to conventional chemotherapy) to a pooled dataset further increases uncertainty and should be avoided when a reliable within-trial comparison is possible (as is the case here).	Not a factual error Even though the ERG agrees with the point that the within trial comparison is more certain than the indirect treatment comparison with HiDEX (as a proxy to conventional chemotherapy), the ERG still considers that this point does not justify the removal of the statements proposing a full incremental analysis based on a common dataset instead of pairwise analyses.

Issue 2 **Description of direction of bias within indirect comparisons**

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Whilst a good summary of the direction of bias is presented within Section 4.3 for each of the indirect comparisons (e.g. on page 68 it is stated that the patients in the bendamustine studies are less refractory and have had fewer lines of therapy) this does not translate to the executive summary or later economic sections.	Provide information on the direction of bias of comparisons within the executive summary and economic sections	This is important for the Committee to understand as ICERs should be viewed within context of the bias present within the datasets used for comparison; as the ERG recognise covariate adjustment cannot account for the full scope of this bias, however, there is very good understanding which way the bias works.	Not a factual error The ERG does not agree with the proposed amendment. In the ERG report, differences of baseline characteristics were discussed both in the clinical and cost-effectiveness parts. Additional judgements on the direction of the bias and effects on ICER would not be evidence-based (e.g. there is no bendamustine study with higher refractory and more lines of previous therapy) and would contain a risk to be speculative.

Issue 3 **Issues with baseline characteristics**

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P14: “The number of centres located in the United Kingdom (UK) and patients recruited in the UK was unclear.”	Remove these statements as this information was provided	Page 154 of the Celgene submission states that 96 UK patients were recruited into MM003	Not a factual error. This was an issue of clarity. The ERG understood the statement on page 154 to be the total of UK patients enrolled in MM-003 and MM-010. The number of UK centres in MM-003 was not provided.
P47: The ERG noted that 68 of the 93 study sites were based in Europe but could not identify from the main submission how many centres and how many individual patients were from the UK”			
P47: “The ERG noted that over 50% of patients in the trial are aged 65 or under so may reflect a younger population than that typically seen in practice.”	Remove statement related to age	Whilst the average age may be older for newly diagnosed patients the age profile at this line of therapy is not the same. The data identified for UK patients at this line of therapy receiving BTD (presented in Table 31) indicated that patients had a similar age to those who received POM+LoDEX in the clinical trial.	Not a factual error. The ERG’s comment relates to generalisability of the trial to clinical practice. The ERG acknowledges that patients in the BTD trials were of a similar age to patients in MM-003.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P47: “The ERG noticed an inconsistency in relation to patients with renal insufficiency. It was noted in the company submission that patients with CrCl < 45ml/min were excluded from the trial. However the baseline characteristics showed that 48 of 455 (10.5%) patients had a baseline CrCl of < 45ml/m.”	Information provided for clarity	In relation to creatinine clearance patients were excluded if <45ml/min at screening; CrCl could change between screening and baseline assessment.	Not a factual error. However, the ERG has amended the report as follows: ‘*The ERG noticed an inconsistency in relation to patients with renal insufficiency. It was noted in the company submission that patients with CrCl < 45 ml/min were excluded from the trial. However the baseline characteristics showed that 48 of 455 patients (10.5%) had a baseline CrCl of < 45 ml/m. The company informed the ERG that this was due to the fact that CrCl could change between screening and baseline assessment.*’

Issue 4 **Use of covariate information within the economic model**

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 99 the ERG express concerns regarding inconsistency in information used in regards to number of prior lines of therapy	Amend to state that: - Within CGP analysis the patient characteristics are taken solely from the clinical trial selected to be used within the analysis (as patient level data on numbers within each group is used)	Current information is unclear and provides information on the number of lines used etc… which may not be accurate for all comparisons.	Not a factual error. The provided numbers are derived from the CGP analysis, which was used in the base case.
	- Within the mean of covariate and utility analysis patient characteristics are taken from user defined inputs (which include real world data on expected usage)	We wanted to clarify this for both the ERG and Committee.	Not a factual error. The provided numbers (from Table 5.4 of the ERG report), are used in utility calculations (in all analyses) as well as OS/PFS calculations in one of the scenario analyses (where mean covariate method was used instead of CGP).

Issue 5 **Implementation of covariate adjustment within survival analysis**

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Justification of use of only two methods of adjustment for selection bias, p117: "For implementing these adjustments in the model, only two methods (CGP and mean covariate adjustment) were discussed. Another method might have been individual patient simulation given its availability for POM+LoDEX and BTD and that the curve for PANO+BOR+DEX was calculated by applying a HR to the curve for POM+LoDEX. Therefore, the selection of these methods seemed arbitrary, as no explanation was given in the CS for the selection of either of these methods and why the CGP method was selected in the base-case analysis rather than the mean covariate method."	Information on method selection provided for ERG understanding.	The CGP method was selected as published literature (Ghali 2001) indicates that use of the mean of covariates method may lead to misleading adjusted survival curves (this is particularly the case where there is correlation between covariates, for example age and sex are often correlated).	Not a factual error. This justification based on the published literature was missing in the Company submission.
	Comment regarding individual patient simulation should be removed or rewording. This is not a method to apply covariate adjustment for survival analysis.	Individual patient simulation is not a method for applying covariate adjustment – you would use one of these 2 methods and conduct the analysis within a simulation framework rather than a markov framework.	The ERG agrees to amend the text on page 117 to read *'For implementing these adjustments in the model, two methods (CGP and mean covariate adjustment) were discussed. The selection of these methods seemed arbitrary, as no explanation was given in the CS for the selection of either of these methods and why the CGP method was selected in the base-case analysis rather than the mean covariate method.'*

Issue 6 **Minor inaccuracies in the text**

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The following textual inaccuracies were identified within the ERG report: P15: "the main direct evidence submitted in the CS (the MM-003 trial) compares pomalidomide in combination with low dose dexamethasone (POM+LoDEX) with high dose dexamethasone (HiDEX) which is no longer considered representative of conventional chemotherapy regimens"	Suggest amend to state no longer representative of current UK practice given this statement on page 17 "Therefore the comparator can only be viewed as a proxy for conventional chemotherapy which might constitute an alternative"	Aid in both the accuracy and clarity of the document.	Corrected as proposed
P16, p79: "Similarly, for patients receiving BTD median OS in the unadjusted analysis was 8.1 months (95% CI 5.3 to 13.5) compared to 10.5 months (95% CI 6.1 to 12.4) in the adjusted analysis."	"Similarly, for patients receiving BTD median OS in the unadjusted analysis was 8.1 months (95% CI 5.3 to 15.5) compared to 10.5 months (95% CI 5.8 to 14.8) in the adjusted analysis."		Corrected as proposed
P32: "In the MM-003 study the median number of prior anti-myeloma therapies was five with a range from 2 to 17. This implies that 50% of patients in the study received POM+LoDEX as sixth line treatment or greater"	At the ERGs request at clarification stage Celgene produced a histogram highlighting the percentage of patients who received Pd at each line within MM-003. The statement here ignores the amount of patients who received fifth line treatment. Therefore, this should read "34% of patients in the study received POM+LoDEX as sixth line treatment or greater" or "50% of patients in the study received POM+LoDEX as fifth line treatment or greater		Corrected as proposed.
P33: "The company also presented a comparison of OS and PFS for patients receiving HiDEX and patients receiving three alternative conventional chemotherapy regimens from the IFM 95-01 study. This study was conducted in patients receiving second line treatment therefore these results may not be applicable to the patient population for this appraisal"	"The company also presented a comparison of OS and PFS for patients receiving HiDEX and patients receiving three alternative conventional chemotherapy regimens from the IFM 95-01 study. This study was conducted in previously untreated patients therefore these results may not be applicable to the patient population for this appraisal"		Corrected as proposed

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
P39: “Following treatment discontinuation patients were assessed at 28 days then until death or five years after randomisation”	“Following treatment discontinuation patients were assessed at 28 days and then they entered long term follow up with 4 visits / year until death or 5 years after randomization”		Corrected as proposed
P69: “In order to be eligible to receive pomalidomide patients are required to be refractory to both bortezomib and lenalidomide”	The license does not require patients to be refractory to both of these treatments (only to have received them), however, the vast majority of patients enrolled into the clinical studies were refractory.		Corrected as proposed
P73: “These data were supplemented by patient level data on 14 patients from Gooding & Tarant datasets”	“These data were supplemented by patient level data on 21 patients from Gooding & Tarant datasets”		Corrected as proposed
P79, p87: “The company used covariate adjusted Cox proportional hazards regression to adjust for the differences between studies based on the set of covariates selected above.”	We did explore Cox PH models to assess differences in KM curves once adjusted for covariates, but these were for presentation purposes only and not used in any subsequent analysis, parametric survival models were used for later analysis.		The ERG understands this to mean that the survival results used in the cost-effectiveness analysis were based on parametric survival models. The results presented in section 4.10 for clinical effectiveness (p102 onwards) appear to be from a Cox proportional hazards model. These were the results included in the clinical effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
			section of the ERG report.
P79: “In the unadjusted analysis the hazard ratios for PFS were similar in the base case (HR=0.76, 95% CI 0.56 to 1.05) and in sensitivity analysis 1 (HR=0.80, 95% CI 0.80, 95% CI 0.62 to 1.03).”	“In the unadjusted analysis the hazard ratios for PFS were similar in the base case (HR=0.76, 95% CI 0.56 to 1.05) and in sensitivity analysis 1 (HR=0.80, 95% CI 0.62 to 1.03).”		Corrected as proposed
P79: “In the adjusted analysis of PFS POM+LoDEX showed a greater improvement relative to BTD in sensitivity analysis 1 (HR=0.61, 95% CI 0.45 to 0.84) compared to the base case (HR=0.79, 95% CI 0.45 to 0.84).”	“In the adjusted analysis of PFS POM+LoDEX showed a greater improvement relative to BTD in sensitivity analysis 1 (HR=0.61, 95% CI 0.45 to 0.84) compared to the base case (HR=0.79, 95% CI 0.52 to 1.22).”		Corrected as proposed
P79: “given the fact that the confidence interval in sensitivity analysis 1 is contained entirely within the confidence interval for the base case this difference may not be clinically relevant”	“given the fact that the confidence interval in the base case is mostly contained entirely within the confidence interval for sensitivity analysis 1 this difference may not be clinically relevant”		Corrected as proposed
P79: “The hazard ratios for overall survival were similar in both sensitivity analysis 2 which included ISS stage (HR=0.72, 95% CI 0.47 to 1.11) and sensitivity analysis 3 which excluded ISS stage (HR=0.82, 95% CI 0.53 to 1.27).”	“The hazard ratios for overall survival were similar in both sensitivity analysis 2 which included ISS stage (HR=0.72, 95% CI 0.47 to 1.11) and sensitivity analysis 3 which excluded ISS stage (HR=0.82, 95% CI 0.54 to 1.27).”		Corrected as proposed
P82, Table 4.26, Line 5, Column 3: “8.1 (5.3, 13.5) 10.5 (5.8, 13.5)”	“8.1 (5.3, 15.5) 10.5 (5.8, 14.8)”		Corrected as proposed
P82, Table 4.26, Line 6, Column 8: “NR, 0.82 (0.53, 1.27)”	“NR, 0.82 (0.54, 1.27)”		Corrected as proposed
P87: “The selection of different datasets for POM+LoDEX does alter the results for OS. In the base-case using only the MM-002 study the median OS in the covariate adjusted analysis was 16.6 months (95% CI 12.6 to 19.8) for patients receiving POM+LoDEX”	“The selection of different datasets for POM+LoDEX does alter the results for OS. In the base-case using only the MM-002 study the median OS in the covariate adjusted analysis was 16.6 months (95% CI 12.6 to 21.3) for patients receiving POM+LoDEX.”		Corrected as proposed
P126, Table 5.13, Line 6, Column 2: “£691”	P126, Table 5.13, Line 6, Column 2: “£679”		Corrected as proposed

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section, 5.3.1 correction of programming errors, p150: "For the comparison with CC, POM+LoDEX is associated with a gain of 0.68 incremental life years and [redacted] incremental QALYs per patient, and an increase in overall costs of [redacted] per patient, which resulted in an ICER of £49,235 per QALY gained. For the comparison with PANO+BOR+DEX, POM+LoDEX is associated with a reduction of 0.49 incremental life years and a reduction of [redacted] incremental QALYs per patient, and a decrease in overall costs of [redacted] per patient, which resulted in an ICER of £139,954 per QALY gained (in the southwest quarter of the plane)."	The tables below the text on p150 (5.37 and 5.38) present different results to those quoted in the text and the text should be amended to be the same as those in the table. The tables appear to be correct. The ERG model gives the same results under the conditions described in this section as those appearing in the table, but not as those appearing in the text. Therefore, it seems reasonable to change these values to reflect what is in the table and output by the ERG model.		The ERG agrees with the proposed amendment and suggests that "[redacted]" be replaced with "[redacted]" and "£49,235" replaced with "£45,082" for incremental costs and ICER of POM+LoDEX vs CC and "[redacted]" be replaced with "[redacted]" and "£139,954" with "£142,930 " for incremental costs and ICER of POM+LoDEX vs PANO+BOR+DEX, respectively

Issue 7 **CIC marking in ERG report**

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In a number of places the ERG report does not mark costs and QALYs as CIC. I.e., - P137: incremental QALYS and costs. - P138: incremental QALYs and costs. - P139: incremental QALYs and costs.	Marking of all incremental costs and QALYs as CIC to prevent back-calculation of PAS levels.	To maintain confidentiality of PAS.	The ERG agrees with the proposed amendment and suggests CIC highlighting of the incremental costs and QALYs on p137, p138 and p139.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

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

- Erratum -

This document contains errata in respect of the ERG report in response to the company's factual accuracy check. It should be noted that none of these changes affect the overall conclusions of the ERG report. The table below lists the pages to be replaced in the original document and the nature of the change.

Page(s)	Change
15	Paragraph 2, sentence 2 now reads 'However the main direct evidence submitted in the CS (the MM-003 trial) compares pomalidomide in combination with low dose dexamethasone (POM+LoDEX) with high dose dexamethasone (HiDEX) which is no longer representative of current UK practice.'
16	Indirect Evidence Point 1, sentence 4 now reads 'Similarly, for patients receiving BTD median OS in the unadjusted analysis was 8.1 months (95% CI 5.3 to 15.5) compared to 10.5 months (95% CI 5.8 to 14.8) in the adjusted analysis.'
32	ERG comment paragraph 2, sentence 2 now reads 'This implies that 50% of patients in the study received POM+LoDEX as fifth line treatment or greater.'
33	ERG comment paragraph 2, sentence 3 now reads 'This study was conducted in previously untreated patients therefore these results may not be applicable to the patient population for this appraisal.'
39	Table 4.3 Follow-up, sentence 2 now reads 'Following treatment discontinuation patients were assessed at 28 days and then they entered long term follow up with 4 visits / year until death or 5 years after randomisation'
47	Addition to the final bullet point: 'The company informed the ERG that this was due to the fact that CrCl could change between screening and baseline assessment.'
69	ERG comment, sentence 2 now reads 'In order to be eligible to receive pomalidomide patients are required to have received both bortezomib and lenalidomide and demonstrated disease progression on the most recent therapy.'
73	Section 4.4.2, Paragraph 2, sentence 3 now reads 'These data were supplemented by patient level data on 21 patients from Gooding & Tarant datasets.'
79	Paragraph 2, final sentence now reads 'Similarly, for patients receiving BTD median OS in the unadjusted analysis was 8.1 months (95% CI 5.3 to 15.5) compared to 10.5 months (95% CI 5.8 to 14.8) in the adjusted analysis.' Paragraph 5, final 3 sentences now read 'In the unadjusted analysis the hazard ratios for PFS were similar in the base case (HR=0.76, 95% CI 0.56 to 1.05) and in sensitivity analysis 1 (HR=0.80, 95% CI 0.62 to 1.03). In the adjusted analysis of PFS POM+LoDEX showed a greater improvement relative to BTD in sensitivity analysis 1 (HR=0.61, 95% CI 0.45 to 0.84) compared to the base case (HR=0.79, 95% CI 0.52 to 1.22). Since the median PFS times remain similar between the adjusted and unadjusted analyses and given the fact that the confidence interval in sensitivity analysis 1 is almost entirely contained within the confidence interval for the base case this difference may not be clinically relevant. Paragraph 6, sentence 3 now reads 'The hazard ratios for overall survival were similar in both sensitivity analysis 2 which included ISS stage (HR=0.72, 95% CI 0.47 to 1.11) and sensitivity analysis 3 which excluded ISS stage (HR=0.82, 95% CI 0.54 to 1.27)'
82	Table 4.26, Line 5, Column 3 now reads '8.1 (5.3, 15.5) 10.5 (5.8, 14.8)' Table 4.26, Line 6, Column 8 now reads 'NR, 0.82 (0.54, 1.27)'

87	Paragraph 4, sentence 2 now reads ‘In the base-case using only the MM-002 study the median OS in the covariate adjusted analysis was 16.6 months (95% CI 12.6 to 21.3) for patients receiving POM+LoDEX.’
117	Paragraph 4, sentences 3 and 4 now read ‘For implementing these adjustments in the model, two methods (CGP and mean covariate adjustment) were discussed. The selection of these methods seemed arbitrary, as no explanation was given in the CS for the selection of either of these methods and why the CGP method was selected in the base-case analysis rather than the mean covariate method.’
126	Table 5.13, Line 6, Column 2 has been changed from ‘£691’ to ‘£679’
137-139	The commercial in confidence costs and QALY data on these pages have now been marked.
150	The two paragraphs immediately above table 5.36 now read ‘For the comparison with CC, POM+LoDEX is associated with a gain of 0.68 incremental life years and [redacted] incremental QALYs per patient, and an increase in overall costs of [redacted] per patient, which resulted in an ICER of £45,082 per QALY gained. For the comparison with PANO+BOR+DEX, POM+LoDEX is associated with a reduction of 0.49 incremental life years and a reduction of [redacted] incremental QALYs per patient, and a decrease in overall costs of [redacted] per patient, which resulted in an ICER of £142,930 per QALY gained (in the southwest quarter of the plane).’

1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The patient population described in the final scope issued by the National Institute for Health and Care Excellence (NICE) was '*Adults with relapsed and refractory multiple myeloma who have had at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and whose disease progressed on the last therapy*'. Panobinostat in combination with bortezomib and dexamethasone (PANO+BOR+DEX) was a comparator for patients who had two or more prior therapies. Bendamustine and conventional chemotherapy regimens are comparators at fourth line of treatment or greater, i.e. patients who have received at least three prior treatements. Outcomes included overall survival, progression free survival, response rates, adverse effects of treatment and health-related quality of life.

The decision problem in the company submission (CS) is broadly in line with the final scope. However the main direct evidence submitted in the CS (the MM-003 trial) compares pomalidomide in combination with low dose dexamethasone (POM+LoDEX) with high dose dexamethasone (HiDEX) which is no longer representative of current UK practice. Furthermore, the trial is not representative of third line treatment with pomalidomide as only 17 out of 455 patients had received exactly two prior treatments. The median number of prior treatments received by patients in the MM-003 study was five (interquartile range = 4 to 6, minimum = 2, maximum = 17). Any conclusions on the role of pomalidomide at third line would be based on an assumption of a better response in less treated patients rather than robust evidence.

[redacted]

1.2 Summary of clinical effectiveness evidence submitted by the company

Direct evidence

The company conducted a systematic review to inform the submission. The aim of the systematic review was '*to understand the relative efficacy and safety of POM+LoDEX compared to alternative therapies for adult patients with RRMM who were previously treated with LEN and BOR.*'

The company identified four randomised controlled trials (RCTs) and nine non-RCTs of pomalidomide. The company also described '*a retrospective real world data collection project on prescribing of BEN, BOR retreatment and POM+LoDEX at third line onwards with the aim of increasing the comparator evidence available to NICE.'*

The main evidence presented was the MM-003 randomised controlled trial as this was the only study that compared POM+LoDEX with any of the comparators listed in the final scope. This trial compared POM+LoDEX to HiDEX which the company considered a proxy for conventional chemotherapy. It included 455 participants and was a multinational trial including participants recruited in 93 study sites, 68 of which are located in Europe. The number of centres located in the United Kingdom (UK) and patients recruited in the UK was unclear.

Using the latest data cut-off of MM-003 (1 September 2013, investigator assessment) at 15.4 months follow-up, there was an increase in median survival with pomalidomide. Overall survival (OS) was significantly better for patients treated with POM+LoDEX compared to those receiving HiDEX (13.1 months vs. 8.1 months, hazard ratio (HR) 0.72, 95% CI: 0.56 to 0.92). POM+LoDEX significantly extended progression-free survival (PFS) compared to HiDEX (4 months vs. 1.9 months, HR 0.50, 95% CI: 0.41 to 0.62).

Almost all of the patients across the trial had at least one adverse event (99% POM+LoDEX, 99.3% HiDEX). The company found that 247 of 300 patients (82.3%) in the POM+LoDEX group had at least one adverse event (AE) considered by the investigator to be related to POM. Furthermore 190 patients (63.3%) had Grade 3-4 treatment-emergent adverse events (TEAEs) considered related to POM. However the company stated that '*with dose modifications and supportive care the safety profile was predictable, manageable and generally well tolerated.*' Events occurring more frequently in the POM+LoDEX group included neutropaenia (51.3% versus 20.0% for neutropenia and 9.3% versus 0% for febrile neutropenia). The main cause of treatment discontinuation was progressive disease and discontinuations related to adverse events were uncommon. There were more dose interruptions in the POM group than in the HiDEX group (67% vs. 30%).

Indirect evidence

Limitations of the available studies precluded a conventional mixed treatment comparison (MTC) or indirect meta-analysis. There were no studies that directly compared POM+LoDEX with either bendamustine (BEN) or PANO+BOR+DEX. Furthermore, there were no studies that could provide a common comparator to support indirect comparison or MTC. As a consequence the company selected individual treatment arms from the available studies and performed separate analyses comparing POM+LoDEX to each of the comparators independently. These were as follows:

1. Comparison of individual patient data (IPD) from the POM+LoDEX arms of the MM-003, MM-002 and MM-010 studies with IPD from the MUK-One, Gooding and Tarant studies of bendamustine using regression models to adjust for factors thought to be prognostic of OS and PFS. In the base case analysis covariate adjustment had little impact on the relative effect of POM+LoDEX compared to bendamustine+thalidomide+dexamethasone (BTD) on OS. The unadjusted hazard ratio was 0.55 (95% CI 0.38 to 0.81) compared to 0.58 (95% CI 0.36 to 0.94) in the covariate adjusted analysis. The median OS for patients receiving POM+LoDEX was 16.5 months (95% CI 12.6 to 19.8) in the unadjusted analysis and 16.6 months (95% CI 12.6 to 21.3) in the adjusted analysis. Similarly, for patients receiving BTD median OS in the unadjusted analysis was 8.1 months (95% CI 5.3 to 15.5) compared to 10.5 months (95% CI 5.8 to 14.8) in the adjusted analysis. Covariate adjustment also had little effect on PFS results. The unadjusted hazard ratio for POM+LoDEX relative to BTD was 0.76 (95% CI 0.56 to 1.05) compared to 0.79 (0.52 to 1.22) in the covariate adjusted analysis. The unadjusted median PFS for patients treated with POM+LoDEX was 4.2 months (95% CI 3.7 to 5.8) compared to 4.7 months (95% CI 3.7 to 6.6) in the adjusted analysis. The corresponding results for patients treated with BTD were 3.3 months (95% CI 2.5 to 5.5) in the unadjusted analysis and 3.7 months (95% CI 2.8 to 5.6) in the adjusted analysis.
2. Comparison of IPD from the POM+LoDEX arms of the MM-003, MM-002 and MM-010 studies with aggregate data from the single-arm PANORAMA-2 study of PANO+BOR+DEX using matching adjusted indirect comparison (MAIC) to adjust for adjust for factors thought to be prognostic of OS and PFS. As above this amounts to a direct comparison between two sets of observational studies. The application of the MAIC method resulted in a one month increase in median OS for patients receiving POM+LoDEX (13.4 months, 95% CI 11.4 to 15.6) compared to the unweighted analysis (12.4 months, 95% CI 11.1 to 13.4). In both cases the median OS was shorter than those patients receiving PANO+BOR+DEX (17.5 months, 95% CI 10.8 to 22.22). The hazard of death was reduced by a similar amount for patients receiving PANO+BOR+DEX compared to POM+LoDEX in both the unweighted analysis (HR=0.73, 95% CI 0.52 to 1.02) and in the MAIC (HR=0.78, 95% CI 0.56 to 1.09). The application of MAIC had little effect on the median PFS time of patients treated with POM+LoDEX (4.2 months, 95% CI 3.7 to 4.8) compared

3.1 Population

The patient population defined in the final scope is '*Adults with relapsed and refractory multiple myeloma who have had at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and whose disease progressed on the last therapy*'[30]

In the CS the company states that the population is '*as defined in the scope*'[3]

ERG comment: The patient population for the comparison of POM+LoDEX with HiDEX which forms the main focus of the submission is based on the MM-003 study. Evidence from the MM-002 and MM-010 studies was also included in Section 4.10 of the CS to inform the comparison of POM+LoDEX with bendamustine (BEN) or with panobinostat+bortezomib+dexamethasone (PANO+BOR+DEX).

In the MM-003 study the median number of prior anti-myeloma therapies was five with a range from 2 to 17.[31]This implies that 50% of patients in the study received POM+LoDEX as fifth line treatment or greater. This is higher than the two prior therapies specified in the scope.[30]

The MM-002 study was an open label randomised phase II study comparing POM with POM+LoDEX in adults with RRMM who had received at least two prior therapies and had undergone prior treatment with at least two cycles of lenalidomide and two cycles of bortezomib. The median number of prior lines of therapy actually received by patients in MM-002 was 5 (range 1 to 13).[32]

The MM-010 study was an open label, single arm observational study to assess the efficacy and safety of POM+LoDEX in patients with RRMM who had received ≥ 2 prior treatment lines, including ≥ 2 cycles of lenalidomide and bortezomib (alone or in combination). The median number of prior lines of therapy actually received was five (range 2-18).[33]

In Section 3.1 the CS states that '*With increasing lines of therapy, there is a decreasing DOR and ultimately development of refractory disease*'[34] therefore the population in the MM-003, MM-002 and MM-010 studies may underestimate the treatment effect relative to the population specified in the scope.[30]

3.2 Intervention

Pomalidomide '*in combination with dexamethasone is indicated in 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. The recommended starting dose of Imnovid is 4 mg once daily taken orally on Days 1 to 21 of repeated 28 day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on Days 1, 8, 15 and 22 of each 28day treatment cycle. '*[35]

The intervention in the MM-003 study was '*28-day cycles of POM (4 mg/day orally on days 1-21) + LoDEX (40 mg/day orally on days 1, 8, 15, and 22)*'.[31]

The intervention arm of the MM-002 study was '*POM (4 mg/day on days 1-21 of each 28-day cycle)*' with '*LoDEX (40 mg/week)*'.[32]

In the MM-010 study '*Patients were administered pomalidomide 4 mg on days 1-21 of a 28-day cycle. Patients also received low-dose dexamethasone 40 mg (if aged ≤ 75 years old) or 20 mg (if aged > 75 years old) on days 1, 8, 15, and 22 of a 28-day cycle*'[33]

The intervention specified in the scope was '*Pomalidomide in combination with dexamethasone*'[30]

ERG comment: The intervention arms of all three pomalidomide studies were consistent with the scope.[30]

3.3 Comparators

The comparators listed in the scope specified by NICE were:

'*For people who have had 2 prior therapies:*

- *panobinostat in combination with bortezomib and dexamethasone*

For people who have had 3 or more prior therapies:

- *panobinostat in combination with bortezomib and dexamethasone*
- *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)*
- *conventional chemotherapy regimens (for example, melphalan and cyclophosphamide)*'[30]

In the previous submission there was limited evidence available for these comparators. In this resubmission the company presented evidence from the PANORAMA-2 study for panobinostat in combination with bortezomib and dexamethasone. The company also presented evidence for bendamustine from the MUK-One study, the Gooding study and the Tarant study. The company stated in the CS that data from the high dose dexamethasone (HiDEX) arm could be considered a proxy for other conventional therapy regimens.[3]

ERG comment: The ERG agrees that the design of the available studies was such that neither standard direct comparisons nor network meta-analyses could be carried out to compare the intervention and the comparators. The ERG recognises the company's efforts to identify all available evidence and consider a variety of different analyses to obtained estimates of effectiveness for the intervention relative to the comparators. These analyses are discussed in detail in Section 4.4.

The company justified the choice of HiDEX as the control arm in the MM-003 study on the basis that it was standard anti-myeloma therapy at the time the trials were initiated. The company also presented a comparison of OS and PFS for patients receiving HiDEX and patients receiving three alternative conventional chemotherapy regimens from the IFM 95-01 study.[36] This study was conducted in previously untreated patients therefore these results may not be applicable to the patient population for this appraisal. The median overall survival for patients receiving HiDEX was similar to those on other conventional chemotherapy regimens. Patients receiving HiDEX had shorter PFS but longer survival post progression compared to patients on other conventional chemotherapy regimens.

3.4 Outcomes

All outcomes listed in the scope specified by NICE[30] were reported in the CS. In addition, time to treatment failure was added by the company as this was a key input to the economic model.[3]

3.5 Other relevant factors

[redacted]

- None of the included RCTs compared pomalidomide with a comparator outlined in the scope.[30]
- The main evidence presented in the clinical effectiveness section was the MM-003 trial which compared POM+LODEX with HiDEX.[31] HiDEX was assumed to be a proxy for conventional chemotherapy. The evidence supporting this assumption is discussed in Section 4.3.

4.2.2 Overview of the direct evidence: MM-003

According to the CS '*The Phase III study MM-003 was a multicentre, randomised, open-label study, which took place in 93 centres in Europe (including the UK), Russia, Australia, Canada and the United States. The trial was designed to compare the efficacy and safety of POM+LoDEX versus high-dose dexamethasone (HiDEX) in patients with RRMM who have received at least two prior treatment regimens, including both LEN and BOR.*'[3] An overview of the trial is given in Table 4.3.

In MM-003 455 participants either received pomalidomide (4 mg/day) plus dexamethasone (40mg on Days 1, 8, 15 and 22 of a 28-day cycle) (POM+LoDEX) or 40mg dexamethasone on Days 1 through 4, 9 through 12 and 17 through 20 of a 28-day cycle HiDEX. See Table 4.3.

Median follow-up was 15.4 months. The primary outcome was progression-free survival defined as *'Time from randomisation until documented disease progression, or death, whichever occurred earlier.'* The main measure used International Myeloma Working Group (IMWG) response criteria[56] as assessed by an independent adjudication committee. Progression-free survival was also assessed using European Society for Blood and Marrow Transplantation (EBMT) criteria[57] and by investigators.

Overall survival was assessed along with other efficacy and safety outcomes outlined in Table 4.3 and defined more fully in Table 4.4.

Table 4.1: Overview of MM-003

	MM-003
Trial Design	Multi-centre, open-label, randomised (in a 2:1 ratio) controlled trial
Participants	N = 455 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. Following treatment discontinuation patients were assessed at 28 days and then they entered long term follow up with 4 visits / year until death or 5 years after randomisation. 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

- assessor was used to determine progression-free survival and both investigator and independent assessor results are presented in the submission.
- Most importantly, the trial does not provide sufficient evidence for patients who have received only two prior therapies. Results were provided for 17 patients who had received exactly two therapies. However the results, as acknowledged by the company, are based on too small a number to be reliable. Hence the trial is not truly representative of third line treatment with pomalidomide. Any conclusions on the role of pomalidomide would be based on an assumption of a better response in less treated patients.
- The trial population is a heavily treated population. Participants had received an average of five prior treatments (most had received between three and seven).
- The trial population is a hard to treat population. Eighty-two per cent of the patients had disease progression on or within 60 days of both LEN and BOR based treatments.
- The ERG noted that 68 of the 93 study sites were based in Europe but could not identify from the main submission how many centres and how many individual patients were from the UK.
- The ERG noted that over 50% of patients in the trial are aged 65 or under so may reflect a younger population than that typically seen in practice.
- We also noted an under-representation of non-white participants. Under 1% were of Asian origin and 1.5% were of black or African American origin.
- The ERG noticed an inconsistency in relation to patients with renal insufficiency. It was noted in the company submission that patients with CrCl < 45ml/min were excluded from the trial. However the baseline characteristics showed that 48 of 455 (10.5%) patients had a baseline CrCl of < 45ml/m. The company informed the ERG that this was due to the fact that CrCl could change between screening and baseline assessment.

4.2.3 MM-003: Quality assessment

The quality rating of MM-003 as presented by the company is given in Table 4.7.

Table 4.2: Quality assessment of MM-003

Was randomisation carried out appropriately?	Yes. Patients were randomised in a 2:1 ratio by permuted block randomisation. Randomisation was undertaken using a validated interactive voice/web response system (IVRS/IWRS).
Was the concealment of treatment allocation adequate?	MM-003 is an open-label study.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Baseline characteristics of the study populations in both treatment groups were well balanced in terms of age, age distribution, sex, disease stage, performance status, cytogenic risk, median time since diagnoses, median number of prior anti-myeloma regimens, and previous treatments. Patients were also well balanced for baseline beta-2-microglobulin, baseline distribution of beta-2-microglobulin, baseline albumin, baseline distribution of albumin, baseline renal function and baseline ECG.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Although the study was open-label, the sponsor's study team was blinded to the study treatment code until the final analysis of the primary endpoint. An independent Response Adjudication Committee (IRAC) reviewed all efficacy data in a blinded manner, independent of investigator response to ensure an unbiased assessment of the data.
Were there any unexpected imbalances in drop-outs between groups?	No. The majority of patients in both treatment groups discontinued treatment due to progressive disease (61% of discontinuations for the POM+LoDEX group versus 62% for the HiDEX group). Similar percentages of patients in both treatment groups discontinued due to AEs or death. Similar percentages

patients in the PANORAMA-2 study are summarised in Table 4.22 alongside the characteristics of the pooled dataset from the POM+LoDEX studies.

The CS also notes that '*The PANORAMA 1 trial[71] which forms the main basis of the PANO+BOR+DEX submission to NICE (TA380), was not identified within the SLR as this represents a much less advanced patient population (as evidenced by the inclusion of LEN as a NICE comparator): only 19% of patients had received prior LEN in the study, and in the licensed subgroup (≥2 prior regimens including BOR and an IMiD) reporting for patients receiving prior IMiD still fails to meet the inclusion criteria for the SLR (86% of patients had received prior THAL versus 38% receiving prior LEN). There is a high likelihood of confounding of OS results from use of subsequent LEN in this trial within a patient population who have not received, let alone become refractory to, this treatment, which rules out use of this study when comparing to the POM+LoDEX trials*'[3]

Table 4.3: Comparison of baseline characteristics between the pooled trial dataset for POM+LoDEX (pomalidomide arm) and PANORAMA-2 (panobinostat arm)

	Panobinostat (PANORAMA-2)	**Pomalidomide Combined MM-002, MM-003 and MM-010 datasets (subgroup refractory to bortezomib but not primary refractory)**
N	55	886
Age: Median (range)	61 (41-88)	66 (34-88)
ECOG (%) 0 1 2 3	 47.3 (26/55) 45.5 (25/55) 7.3 (4/55) 0 (0)	 40.1 47.0 12.9 0.1
ISS stage (%) 1 2 3 Missing	 33.3 (18/54) 42.6 (23/54) 24.1 (13/54) 1/55	MM-003 and MM-010*: 23.5 (373/1588) 41.0 (651/1588) 35.5 (564/1588) 78/1666
Prior lines of therapy Median (range)	 4 (2-11)	 5 (2-18)
Prior thalidomide therapy (%)	69.1	56.9
Refractory to bortezomib (%)	100	100

Source: Based on Table 32 of the CS[3]
Note: * Not reported in MM-002
ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; POM, pomalidomide, LoDex, low-dose dexamethasone, MM, multiple myeloma.

ERG comment: The exclusion of the PANORAMA-1 study appears reasonable given the low percentage of patients who had received prior lenalidomide in this study (19%). In order to be eligible to receive pomalidomide patients are required to have received both bortezomib and lenalidomide and demonstrated disease progression on the most recent therapy. Since 81% of patients in PANORAMA-1

had not received lenalidomide these patients would not be considered comparable to patients who are eligible to receive pomalidomide.

randomisation of the RCTs is broken by selecting single treatment arms. There is no common comparator to link the two sets of studies which would make this an indirect comparison.

2. Comparison of IPD from the POM+LoDEX arms of the MM-003, MM-002 and MM-010 studies with aggregate data from the single-arm PANORAMA-2 study of PANO+BOR+DEX using matching adjusted indirect comparison (MAIC) to adjust for adjust for factors thought to be prognostic of OS and PFS. As above this amounts to a direct comparison between two sets of observational studies
3. Comparison of POM+LoDEX with HiDEX based on the MM-003 trial. In the CS the company argue that HiDEX can be used as a proxy for conventional chemotherapy. The evidence base for this assumption is discussed in Section 4.3. The results of the MM-003 trial are described in Section 4.2.

The details of these analyses are described below. The ERG recognises that although the evidence supporting the comparisons with bendamustine and with PANO+BOR+DEX is limited this is likely to be the best that could be achieved given the available studies.

4.4.1 Selection of studies for statistical analysis – POM+LoDEX

The CS stated that '*the decision whether to include or exclude studies for POM+LoDEX from quantitative analysis of comparative effectiveness was taken on the basis of study size (only studies with >50 patients were considered given the large body of evidence available), study population (studies analysing comorbidity subgroups were not considered), generalisability and comparability to comparator studies and availability of patient level data for analysis. Based on these criteria, three studies were considered for inclusion in analyses: the MM-003 Phase III trial, the MM-002 Phase II trial and the MM-010 Phase IIIb trial.*'[3] The MM-003 and MM-002 studies are described in section 4.2. The MM-010 study was '*an open-label, single-arm phase 3b study undertaken at 91 centers in 19 countries across Europe*'.[33] In the MM-010 study '*Patients were administered pomalidomide 4 mg on days 1-21 of a 28-day cycle. Patients also received low-dose dexamethasone 40 mg (if aged ≤ 75 years old) or 20 mg (if aged > 75 years old) on days 1, 8, 15, and 22 of a 28-day cycle*'.[33]

According to the CS the dataset for each analysis was selected '*based upon comparability with the available comparator datasets. The MM-002 Phase II trial represented the trial that was the most comparable to available comparator studies for BEN, whereas the full trial dataset (MM-002, MM-003 and MM-010) was most comparable to the data for PANO+BOR+DEX. The comparison to the pooled dataset of all three studies (MM-002, MM-003 and MM-010) is also presented as sensitivity analysis for comparison to BEN.'*[3]

4.4.2 Comparison of POM+LoDEX and bendamustine

The CS states that '*The systematic review did not identify any comparator RCTs allowing the formation of a traditional network meta-analysis: no RCTs have been run in this setting by any of the therapies listed within the NICE decision problem except for the MUK-one trial, which compared two doses of BEN.*'

The company obtained patient level trial data from the MUK-one study which compared 60 mg/m^2 bendamustine with 100 mg/m^2 bendamustine in patients with RRMM. All patients in both arms received oral thalidomide 100 mg on days 1-28 and oral dexamethasone 20 mg on days 1, 8, 15 and 22 of each 28 day cycle.[67] These data were supplemented by patient level data on 21 patients from the Gooding and Tarant datasets.[68, 69] Based on these data the company constructed a series of covariate adjusted IPD regression models to compare the relative effects of POM+LoDEX and bendamustine.

Results

The company used covariate adjusted Cox proportional hazards regression to adjust for the differences between studies based on the set of covariates selected above. The company reported results for OS and PFS comparing POM+LoDEX in the base case and in three sensitivity analyses as described above. The results of these analyses are summarised in Table 4.26 below. For the base case and sensitivity analysis 1 the company reported adjusted and unadjusted results for both OS and PFS. For sensitivity analyses 2 and 3 only adjusted hazard ratios were reported.

In the base case analysis covariate adjustment had little impact on the relative effect of POM+LoDEX compared to BTD on OS. The unadjusted hazard ratio was 0.55 (95% CI 0.38 to 0.81) compared to 0.58 (95% CI 0.36 to 0.94) in the covariate adjusted analysis. The median OS for patients receiving POM+LoDEX was 16.5 months (95% CI 12.6 to 19.8) in the unadjusted analysis and 16.6 months (95% CI 12.6 to 21.3) in the adjusted analysis. Similarly, for patients receiving BTD median OS in the unadjusted analysis was 8.1 months (95% CI 5.3 to 15.5) compared to 10.5 months (95% CI 5.8 to 14.8) in the adjusted analysis.

Covariate adjustment also had little effect on PFS results. The unadjusted hazard ratio for POM+LoDEX relative to BTD was 0.76 (95% CI 0.56 to 1.05) compared to 0.79 (0.52 to 1.22) in the covariate adjusted analysis. The unadjusted median PFS for patients treated with POM+LoDEX was 4.2 months (95% CI 3.7 to 5.8) compared to 4.7 months (95% CI 3.7 to 6.6) in the adjusted analysis. The corresponding results for patients treated with BTD were 3.3 months (95% CI 2.5 to 5.5) in the unadjusted analysis and 3.7 months (95% CI 2.8 to 5.6) in the adjusted analysis.

The results of sensitivity analysis 1 showed that the inclusion of additional POM+LoDEX data from MM-003 and MM-010 reduced the benefit observed for patients treated with POM+LoDEX compared to BTD on OS. The covariate adjusted hazard ratio for POM+LoDEX relative to BTD was 0.64 (95% CI 0.45 to 0.91) compared to 0.58 (95% CI 0.36 to 0.94) in the base case. The unadjusted results were 0.68 (95% CI 0.51 to 0.92) in sensitivity analysis 1 and 0.55 (95% CI 0.38 to 0.81). The difference between the base case and the sensitivity analysis is also apparent in the median overall survival time. Patients treated with POM+LoDEX had a shorter median OS in sensitivity analysis 1 compared to the base case by approximately four months in both the adjusted and the unadjusted results. In contrast patients treated with BTD had a similar median OS in both the base case and the sensitivity analysis.

The inclusion of additional POM+LoDEX data from MM-003 and MM-010 did not substantially alter the results for PFS. The median PFS time was similar in the base case and in sensitivity analysis 1 for patients treated with POM+LoDEX and for patients treated with BTD regardless of covariate adjustment. In the unadjusted analysis the hazard ratios for PFS were similar in the base case (HR=0.76, 95% CI 0.56 to 1.05) and in sensitivity analysis 1 (HR=0.80, 95% CI 0.62 to 1.03). In the adjusted analysis of PFS POM+LoDEX showed a greater improvement relative to BTD in sensitivity analysis 1 (HR=0.61, 95% CI 0.45 to 0.84) compared to the base case (HR=0.79, 95% CI 0.52 to 1.22). Since the median PFS times remain similar between the adjusted and unadjusted analyses and given the fact that the confidence interval in sensitivity analysis 1 is almost entirely contained within the confidence interval for the base case this difference may not be clinically relevant.

Sensitivity analyses 2 and 3 were designed to assess the impact of including ISS stage as a prognostic factor in those studies where data were available. The MM-002 and Gooding studies did not report ISS stage therefore these studies were excluded from the analysis. The hazard ratios for overall survival were similar in both sensitivity analysis 2 which included ISS stage (HR=0.72, 95% CI 0.47 to 1.11) and sensitivity analysis 3 which excluded ISS stage (HR=0.82, 95% CI 0.54 to 1.27). The company highlighted that '*ISS stages two and three show an increased hazard of death versus stage*

Table 4.4: Summary of the comparison of POM+LoDEX with BTD – OS and PFS

Outcome	Base-case		Sensitivity analysis 1		Sensitivity analysis 2		Sensitivity analysis 3	
	POM+LoDEX	BTD	POM+LoDEX	BTD	POM+LoDEX	BTD	POM+LoDEX	BTD
Overall Survival								
Included studies Study, N	MM-002, 113	Tarant, 4 Gooding, 17 MUK-one, 57	MM-002, 113 MM-003, 302 MM-010, 682	Tarant, 4 Gooding, 17 MUK-one, 57	MM-003, 290 MM-010, 650	Tarant, 3 MUK-one, 56	MM-003, 290 MM-010, 650	Tarant, 3 MUK-one, 56
Total N	113	78	1097	78	940	59	940	59
Median OS[1] Unadjusted Adjusted	 16.5 (12.6, 19.8) 16.6 (12.6, 21.3)	 8.1 (5.3, 15.5) 10.5 (5.8, 14.8)	 12.6 (11.6, 13.8) 12.7 (11.9, 13.9)	 8.1 (5.3, 15.5) 8.1 (6.1, 12.4)	 NR NR	 NR NR	 NR NR	 NR NR
HR (95%CI) Unadjusted Adjusted	 0.55 (0.38, 0.81) 0.58 (0.36, 0.94)		 0.68 (0.51, 0.92) 0.64 (0.45, 0.91)		 NR 0.72 (0.47, 1.11)		 NR 0.82 (0.54, 1.27)	
Progression free survival								
Included studies Study, N	MM-002, 113	Gooding, 17 MUK-one, 57	MM-002, 113 MM-003, 302 MM-010, 682	Gooding, 17 MUK-one, 57	MM-003, 290 MM-010, 650	MUK-one, 56	MM-003, 290 MM-010, 650	MUK-one, 56
Total N	113	74	1097	74	940	56	940	56
Median PFS[1] Unadjusted Adjusted	 4.2 (3.7, 5.8) 4.7 (3.7, 6.6)	 3.3 (2.5, 5.5) 3.7 (2.8, 5.6)	 4.3 (3.9, 4.7) 4.6 (3.9, 48)	 3.3 (2.5, 5.5) 2.8 (2.2, 3.8)	 NR NR	 NR NR	 NR NR	 NR NR
HR (95%CI) Unadjusted Adjusted	 0.76 (0.56, 1.05) 0.79 (0.52, 1.22)		 0.80 (0.62, 1.03) 0.61 (0.45, 0.84)		 NR 0.62 (0.43,		 NR 0.62 (0.43,	

4.6 Conclusions of the clinical effectiveness section

The company conducted a systematic review to identify studies comparing pomalidomide to comparators outlined in the NICE scope.[30] Although a number of limitations were identified in relation to the systematic review of evidence (particularly in relation to the search for studies), overall the ERG is satisfied that all the relevant evidence has been presented. The evidence is limited as patients had to have received previous treatment with BOR and LEN. The main evidence in the submission came from the MM-003 trial which compares POM+LoDEX to HiDEX. Although this was a reasonably large, well conducted multi-centre trial, the main comparator is no longer optimal in current practice. Therefore the comparator can only be viewed as a proxy for conventional chemotherapy which might constitute an alternative. The trial was in a heavily treated population who had received a median of five therapies (range 2 to 17). Only 25 patients had received two prior therapies only, thus the trial is not representative of POM as a third line therapy. It could be assumed that POM might perform better at third line in a less treated population but this is an assumption. At third line patients can be offered PANO and there is no direct evidence comparing the two treatments. Within these constraints, pomalidomide appears to extend OS and PFS in comparison with HiDEX in a heavily treated population who are refractory to BOR and LEN. The adverse event profile appears to be manageable with appropriate dose reductions and interruptions. The ERG has drawn attention to those adverse events occurring more frequently in the POM arm, notably neutropaenia.

There were limited data available to inform the comparison of POM+LoDEX with treatments other than HiDEX. There were no studies that directly compared POM+LoDEX with either BTD or PANO+BOR+DEX. In addition the available studies did not include a common comparator that would permit an indirect comparison or mixed treatment comparison (MTC). As a result the company presented evidence based on comparisons of observational data.

In the base case the POM+LoDEX arm of the MM-002 study was compared to BTD arms from the MUK-one, Gooding and Tarant studies. The company also reported a sensitivity analysis that included POM+LoDEX data from MM-002, MM-003 and MM-010. The company used covariate adjusted Cox proportional hazards regression to adjust for the differences between studies in patient characteristics. The covariate adjusted results were very similar to the unadjusted results in terms of both PFS and OS for the base case and the sensitivity analysis. This indicates that the differences between studies in the selected covariates (patient characteristics) have relatively little impact on the outcomes observed.

The selection of different datasets for POM+LoDEX does alter the results for OS. In the base-case using only the MM-002 study the median OS in the covariate adjusted analysis was 16.6 months (95% CI 12.6 to 21.3) for patients receiving POM+LoDEX. In the sensitivity analysis based on data from MM-002, MM-003, MM-010 the median OS in the covariate adjusted analysis was 12.7 months (95% CI 11.9 to 13.9) for patients receiving POM+LoDEX. The median OS for patients receiving BTD was similar in both the base-case and the sensitivity analysis. As a result the covariate adjusted relative effect of POM+LoDEX versus BTD was reduced in the sensitivity analysis (HR=0.64, 95% CI 0.45 to 0.91) compared to the base-case (HR=0.58, 95% CI 0.36 to 0.94). In combination these results suggest the survival benefit of POM+LoDEX was less for patients in the MM-003 and MM-010 studies than for patients in the MM-002 study.

For the comparison with PANO+BOR+DEX the POM+LoDEX arms of the MM-002, MM-003 and MM-010 studies were compared with the PANO+BOR+DEX arm of the PANORAMA-2 study in a matching adjusted indirect comparison. The matching adjusted results for patients receiving POM+LoDEX were similar to the unadjusted results in terms of OS and PFS. The matching adjusted median OS for patients receiving POM+LoDEX was 13.4 months (95% CI 11.4 to 15.6) compared to

ERG comment: The main issues and critique given in Section 4.4 apply for this section, as well. The results should be interpreted with caution, because even though some of the baseline covariates were adjusted, there can be still some unmeasured confounders or other factors that add uncertainty to the treatment effectiveness results of the CS (e.g. the fact that refractoriness to BOR was not in the dataset, the representativeness of the HiDEX efficacy for the conventional care, etc.).[3]

In the CS[3], a different dataset is used for each of the three comparisons (bendamustine trials and MM-002 only for POM+LoDEX vs BTD, PANORAMA-02 and MM-002, MM-003 and MM-010 and for POM+LoDEX vs PANO+BOR+DEX and MM-003 trial for POM+LoDEX vs CC). The ERG considers that this pairwise approach is not that informative, because the decision for POM+LoDEX should be based on a fully incremental analysis. Furthermore, the pairwise approach is more prone to bias, for instance due to differences in baseline characteristics of the three datasets used, different cost and QALY outcomes were estimated for the same treatment (POM+LoDEX), in the three different comparisons. It might be reasonable to have three different estimates if they related to three different populations. However, the ERG considers that the differences between the baseline characteristics of the datasets cannot be directly generalised to UK clinical practice, i.e. it is not possible to define an exact subgroup for whom only POM+LoDEX vs BTD is relevant as opposed to any of the other comparators. Moreover, there is no convincing reason *why* different relevant patient populations should be considered for different comparisons, e.g. for POM+LoDEX vs BTD and for POM+LoDEX vs PANO+BOR+DEX.

Therefore, the ERG requested the company to provide a full incremental analysis using a single source of data for POM+LoDEX and applying any treatment effect between POM+LoDEX and the other compactors as required. The company did this using pooled data from all POM+LoDEX (MM-002, MM-003 and MM-010) and all BTD trials. After the OS and PFS of POM+LoDEX and BTD are obtained, the OS and PFS of both PANO+BOR+DEX and CC were estimated using proportional hazards assumption, by applying the corresponding treatment effects (HR) for OS/PFS on the POM+LoDEX OS/PFS. This approach enables a full incremental analysis between comparisons.

For the effect of treatment on survival, to adjust for selection bias, with PANO+BOR+DEX, the 'MAIC' based on aggregate trial data method was used and for BTD, regression analysis based on individual patient data (IPD) was used. Matching and regression analysis based on IPD are given as options in the NICE Decision Support Unit Document 17 on the use of observational data and, as such, appear to be reasonable approaches.86 For implementing these adjustments in the model, two methods (CGP and mean covariate adjustment) were discussed. The selection of these methods seemed arbitrary, as no explanation was given in the CS for the selection of either of these methods and why the CGP method was selected in the base-case analysis rather than the mean covariate method.

Moroever, prediction can also be used to incorporate real world data on baseline characteritics.In Ghali et al. 2001, which is the main reference that the company cited for the definition of CGP and mean covariate adjustment methods, it was mentioned that for the latter method, the mean value of the covariates (derived from the dataset analysed) should be inserted into the survival function.[83] However, in the model, the company did not insert the mean covariate values from the dataset to the survival function, but instead used real world data obtained from a number of UK centres.[46, 47] Technically it is not wrong to use real world data for the baseline characteristics (it is actually preferable), but then the difference between CGP and mean covariate methods in the CS is not only

Table 5.5: Drug acquisition costs of POM+LoDEX and its comparators per treatment cycle

	Cost per treatment cycle	Cost is applied every
POM+LoDEX		
POM	[redacted]	4 weeks
LoDEX	£5.07 to £8.83[a]	4 weeks
BTD[a]		
BEN	£679	4 weeks
THAL	£597	4 weeks
DEX	£20	4 weeks
PANO+BOR+DEX		
PANO	£4,656	3 weeks
BOR (first 8 cycle)	£3,050[b]	3 weeks
BOR (subsequent cycles)	£1,525[c]	3 weeks
DEX (first 8 cycle)	£40	3 weeks
DEX (subsequent cycles)	£10	3 weeks
CTD		
CYC	£139	4 weeks
THAL	£1,1194	4 weeks
DEX	£61	4 weeks

Notes: [a] In POM+LoDEX, the dose of DEX was based on a weighted average dose per cycle from trials MM-010, MM-002 and MM-003 [MM-002 only for the comparison with BTD].[b] The model submitted by Company used £4,574 here, in the response to the CL this was corrected; [c] The model submitted by Company used £3,050 here, in the response to the CL this was corrected.
BEN, bendamustine; BOR, bortezomib; BTD, bendamustine + thalidomide + dexamethasone; CYC, cyclophosphamide; DEX, dexamethasone; LoDEX, low-dose dexamethasone; PANO, panobinostat; POM, pomalidomide; THAL, thalidomide

Costs of monitoring and tests, concomitant medications and adverse events

As the cost and resource use SLR did not identify any treatment-specific resource use, a questionnaire was sent out to clinical experts to collect data about resource use associated with the treatment of patients with RRMM in the UK. The questionnaire consisted of questions related to current treatment practice (including dosing schedules), (treatment-specific) routine follow-up care, subsequent treatment use and resource use associated with adverse events.

Six clinical experts completed the questionnaire. Average annual resource use associated with POM+LoDEX, BTD, PANO+BOR+DEX, off active treatment (pre-progression) and off active treatment (post-progression) was derived from the questionnaire, and implemented in the economic model. Resource use related to conventional chemotherapy was assumed equal to the resource use related to BTD. Resource use was combined with unit costs derived from either the TA228 NICE review[19] or NHS reference costs[100].

The costs of monitoring and tests per cycle are presented in Table 5.14, just as the costs of concomitant medications and adverse events. With respect to concomitant medications, only costs associated with granulocyte-colony stimulating factor (G-CSF) were taken into account, as it is assumed that no differences exist in the use of other concomitant medications across treatments or between pre- and post-progression.

5.2.11 Sensitivity analyses

Probabilistic sensitivity analyses

To examine the impact of the joint uncertainty across all model inputs probabilistic sensitivity analyses were conducted for POM+LoDEX vs. BTD, POM+LoDEX vs. PANO+BOR+DEX and POM+LoDEX vs. CC. In these analyses, all inputs vary simultaneously, based upon their distributional information. The PSA also included the uncertainty around the choice of parametric OS, PFS and TTF curves (see Section 5.2.6).

The results of 1,000 PSA iterations are shown in the figures below. Cost effectiveness planes show the incremental QALYs and costs of POM+LoDEX relative to the relevant comparators (Figures 5.19, 5.21 and 5.23). Additionally, cost effectiveness acceptability curves (CEACs) are presented, showing the likelihood of POM+LoDEX cost effectiveness at different willingness-to-pay thresholds (Figures 5.20, 5.22 and 5.24).

POM+LoDEX vs. BTD

Mean incremental QALYs from POM+LoDEX were [redacted] (SD: 0.08; 95% CI: [redacted]). Mean incremental costs were [redacted] (SD: £1,198; 95% CI: [redacted]). The resulting probabilistic ICER from 1,000 iterations was £39,317 (comparable to the deterministic, base-case ICER of £39,665).

The CEAC in Figure 5.20 suggests that there is an 8% likelihood of POM+LoDEX cost effectiveness at a willingness-to-pay threshold of £30,000/QALY and a 85% likelihood of POM+LoDEX cost effectiveness at a willingness-to-pay threshold of £50,000/QALY.

Figure 5.1: Cost effectiveness plane – vs. BTD

[redacted]

Figure 5.2: Cost effectiveness acceptability curve – vs. BTD

POM+LoDEX vs. PANO+BOR+DEX

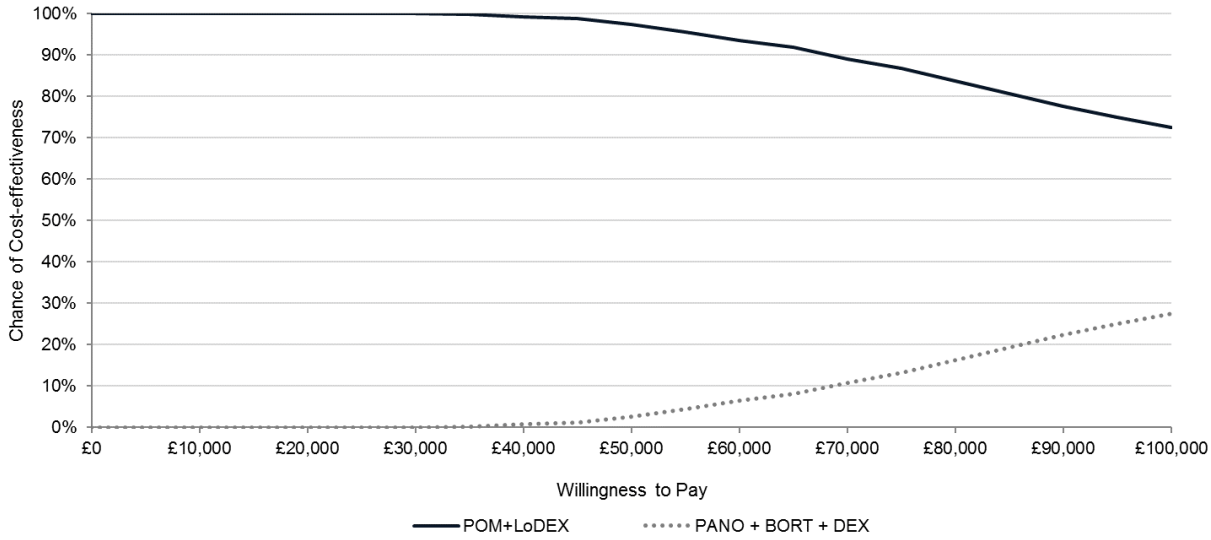
Mean incremental QALYs from POM+LoDEX were [redacted] (SD: 0.27; 95% CI: [redacted]). Mean incremental costs were [redacted] (SD: £5,967; 95% CI: [redacted]. The resulting probabilistic ICER from 1,000 iterations was £134,379 (comparable to the deterministic, base-case ICER of £141,793); NMB of £31,953.

The CEAC in Figure 5.22 suggests that there is a n almost 100% likelihood of POM+LoDEX cost effectiveness at a willingness-to-pay threshold of £30,000/QALY and a 97% likelihood of POM+LoDEX cost effectiveness at a willingness-to-pay threshold of £50,000/QALY.

Figure 5.3: Cost effectiveness plane – vs. PANO+BOR+DEX

[redacted]

Figure 5.4: Cost effectiveness acceptability curve – vs. PANO+BOR+DEX



POM+LoDEX vs. conventional chemotherapies

Mean incremental QALYs from POM+LoDEX were [redacted] (SD: 0.32; 95% CI: [redacted]). Mean incremental costs were [redacted] (SD: £4,880; 95% CI: [redacted]). The resulting probabilistic ICER from 1,000 iterations was £45,831 (comparable to the deterministic, base-case ICER of £44,811).

The CEAC in Figure 5.24 suggests that there is an 8% likelihood of POM+LoDEX cost effectiveness at a willingness-to-pay threshold of £30,000/QALY and a 60% likelihood of POM+LoDEX cost effectiveness at a willingness-to-pay threshold of £50,000/QALY.

2. As described in Section 5.2.6, the model did not use the CGP results that were obtained from the provided VBA macro, as described in the response to the clarification letter document.[38]
3. As described in Section 5.2.9, 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 this ERG-corrected model. Based on this model, the corrected base case results are given in Tables 5.36-5.38 below for POM+LoDEX vs. BTD, POM+LoDEX vs. PANO+BOR+DEX and POM+LoDEX vs. CC comparisons.

For the comparison with BTD, POM+LoDEX is associated with a gain of 0.67 incremental undiscounted life years and [redacted] incremental QALYs per patient, and an increase in overall costs of [redacted] per patient, which resulted in an ICER of £45,082 per QALY gained.

For the comparison with CC, POM+LoDEX is associated with a gain of 0.68 incremental life years and xxxx incremental QALYs per patient, and an increase in overall costs of [redacted] per patient, which resulted in an ICER of £45,082 per QALY gained.

For the comparison with PANO+BOR+DEX, POM+LoDEX is associated with a reduction of 0.49 incremental life years and a reduction of [redacted] incremental QALYs per patient, and a decrease in overall costs of [redacted] per patient, which resulted in an ICER of £142,930 per QALY gained (in the southwest quarter of the plane).

Table 5.6: Base-case results – 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]	-	-	-	-
POM+ LoDEX	[redacted]	1.80	[redacted]	[redacted]	0.67	[redacted]	£45,082
BTD, bendamustine, thalidomide and dexamethasone; ICER, incremental cost effectiveness ratio; LoDEX, low-dose dexamethasone; POM, pomalidomide; QALYs, quality-adjusted life years							

Table 5.7: Base-case results – 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]	-	-	-	-
POM+ LoDEX	[redacted]	1.55	[redacted]	[redacted]	-0.49	[redacted]	£142,930 (SW)
BOR, bortezomib; DEX, dexamethasone; PANO, panobinostat; ICER, incremental cost effectiveness ratio; LoDEX, low-dose dexamethasone; NMB, net monetary benefit; POM, pomalidomide; QALYs, quality-adjusted life years							