NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Single technology appraisal (STA) of lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy with bortezomib (partial review of TA171) [ID667]

Dear [redacted],

The Evidence Review Group, Peninsula Technology Assessment Group (PenTAG), and the technical team at NICE have now had an opportunity to take a look at the submission received on the 11th November by Celgene. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on 12th December. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Carl Prescott, Technical Lead (carl.prescott@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.powell@nice.org.uk) in the first instance.

Yours sincerely

Elisabeth George

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Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Decision Problem

A1. On page 13 of the submission it is stated that no additional evidence is likely to be available in the next 12 months. Could you please confirm that this is still the case?

Celgene confirms that no additional evidence is likely to be available in the next 12 months for the indication and position in the treatment pathway that is being appraised.

A2. On page 16 section 1.13, it is explained that a safety warning regarding an increased risk of AML progression for patients with MDS was issued on 10th June to health care professionals. Please provide detail about what the safety letter describes regarding the increased risk of AML progression for people with multiple myeloma.

The letter was issued in relation to the MDS indication. On page 7 of the letter, reference is made in the context of clinical trial studies of newly diagnosed multiple myeloma patients to the incidence of secondary primary malignancies (SPM). This has no relation to the population setting which is being appraised by NICE.

For information, lenalidomide was reviewed under Article 20 by the European Medicines Agency (EMA) in 2011 in its current indication for relapsed and refractory multiple myeloma and which concluded that the benefit-risk ration remains positive. In a retrospective pooled analysis (Dimopolous, 2012) of 11 clinical trials of lenalidomide-based therapy for relapsed/refractory multiple myeloma (N= 3846), the overall incidence rate SPMs were found to be consistent with the background incidence of developing cancer, with only one observation of AML.

Section B: Clarification on clinical-effectiveness data

B1. **Priority question**: The search strategy limits searches by themes such as 'relapse' and 'recurrence' (page 216, lines 6-12 of the MEDLINE strategy), which could affect the retrieval of potentially relevant studies (e.g. Bendamustine studies). Therefore:

- Please provide the rationale for this decision.
- Please re-run the effectiveness searches removing this cluster and list any additional studies not previously identified.

Two searches were conducted for clinical effectiveness:

1. The original search which included relapse/recurrence within the strategy
2. An update search with the relapse and recurrence terms removed

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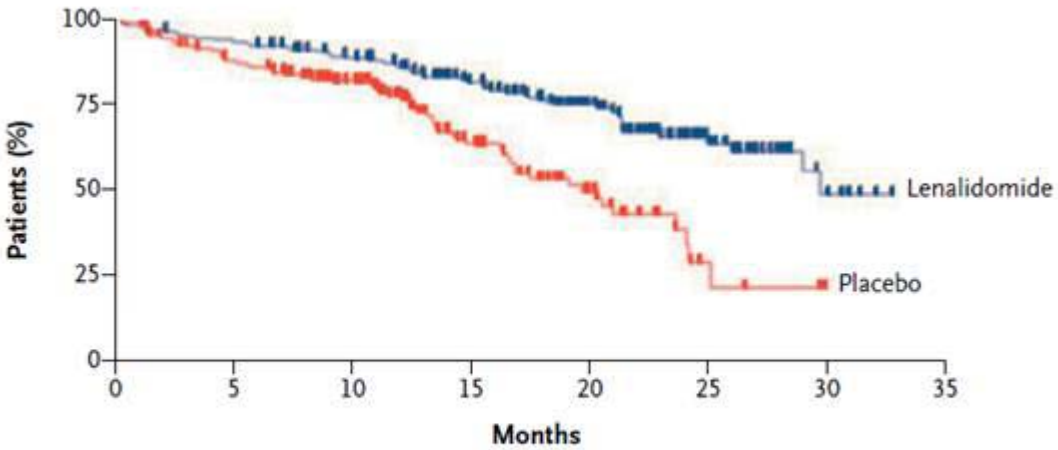
The update search was conducted with no date limits applied and therefore covers the entire date span of the original searches. The searches were conducted in this way was to avoid duplication in the reference management process. The attached spreadsheet provides the results with the relapse/recurrence terms removed (which were provided within the original submission).

B2. **Priority question**: All adverse event data provided is from the MM-010 and MM-009 clinical trials. Given the adverse event profile associated with lenalidomide, please provide the rationale for not conducting separate searches for adverse events.

The studies MM-009 and MM-010 were designed to capture any AE's associated with lenalidomide in this patient group. Additionally the AE's were presented for the duration of treatment and for longer term follow up at 48 months. The AE's presented were comparable and are consistent with those listed in the current SPC which was updated in 2013. Expert clinical view was that the AE profile of lenalidomide as presented in the submission is current and adequate.

B3. **Priority question**: Please provide the number at risk for figure 11 (as presented for figure 10)

The figure below presents the number at risk for Figure 11 (based on Weber 2007).



No. at Risk							
Lenalidomide	177	164	144	109	74	34	7
Placebo	175	144	115	51	26	5	1

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B4. **Priority question:** There are values in Table 19 (page 76) which appear counterintuitive (for example baseline plasma cell percentage and duration of MM). Please confirm whether the values in Table 19 are correct and provide the equations used in the Cox regression model.

The values in Table 19 were taken from the Dimopolous 2009 publication (reference 32, Table 3). The table below provides this analysis with more decimal places for the hazard ratios.

Variable	**Parameter estimate**	**SE**	**P-value**	**HR**	**95% CI**	
Treatment: Placebo/Dex vs. Rev/Dex	0.3489	0.1038	0.0008	1.418	1.157	1.737
BL % Plasma cells -- Aspirate/Biopsy: High vs. Low	0.00912	0.00195	<.0001	1.009	1.005	1.013
Beta-2M: >2.5 mg/L vs. <=2.5 mg/L	0.45634	0.14915	0.0022	1.578	1.178	2.114
Duration of MM (years)	-0.07632	0.02275	0.0008	0.927	0.886	0.969
Lytic bone lesion at baseline: Y vs. N	0.23758	0.12825	0.064	1.268	0.986	1.631
Number of earlier anti-myeloma therapies	0.1274	0.05726	0.0261	1.136	1.015	1.271
Previously treated with HDT/SCT: Y vs N	0.21224	0.10976	0.0532	1.236	0.997	1.533
Previously treated with Dex: Y vs. N	0.28843	0.12039	0.0166	1.334	1.054	1.689
ISS score at baseline (III vs II vs I)	0.38059	0.07964	<.0001	1.463	1.252	1.71

Shorter duration of disease and greater percentage of plasma cells in the bone marrow were all associated with a reduced OS in a long-term follow-up of the MM-009 and MM-010 trials.

The association between baseline plasma cells in bone marrow and overall survival may reflect changes within the tissue of the bone marrow. Bone marrow stromal cells are known to promote multiple myeloma cell proliferation and survival,[1,2] and an increase in stromal cell numbers at the time of multiple myeloma diagnosis has recently been shown to correlate closely with plasma cell burden.[3] Although the causal relationship among these factors is unclear, these findings suggest a correlation between plasma cell numbers and changes in the bone marrow microenvironment which are associated with rapid disease progression. Plasma cell percentage at baseline may therefore represent a significant prognostic factor in patients with multiple myeloma, although analysis of MM-009 and MM-010 data shows that the prognostic importance is low (even though the significance is high).

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An analysis of UK MRC trial patients (Auguston et al) with MM found a considerable degree of early mortality (10% within two months). [4] In another retrospective multi-centre registry analysis (Kumar et al, 2012), whilst the overall median OS reported was 9 months, almost half of patient alive at 12 months seemed to be still alive at month 60.[5] It would therefore seem reasonable that if a substantial proportion of patients are dying early then those who survive the early stages of disease may have a higher median OS since their disease is controlled and they have a better propensity to treatment response.

Following the question on the above two points from ERG, we also sought clinical expert opinion and their view was that such an association was clinically valid.

All other results are as would be expected:

- OS is reduced for patients with lytic bone lesions at baseline
- OS is reduced the more therapies patients have previously received
- OS is reduced if patients have previously received (and therefore perhaps stopped responding to) dexamethasone
- OS is reduced if patients have previously received a stem cell transplant
- OS is reduced the higher the ISS risk stage score

1. Wong TW, Kita H, Hanson CA *et al.* Induction of malignant plasma cell proliferation by eosinophils. *PLoS One* 2013;8:e70554.
2. Pellegrino A, Ria R, Di Pietro G et al. Bone marrow endothelial cells in multiple myeloma secrete CXC-chemokines that mediate interactions with plasma cells. Br J Haematol 2005;129:248-56.
3. Noll JE, Williams SA, Tong CM et al. Myeloma plasma cells alter the bone marrow microenvironment by stimulating the proliferation of mesenchymal stromal cells. Haematologica 2013.
4. Augustson B, Begum G, Dunn JA et al. Early Mortality After Diagnosis of Multiple Myeloma: Analysis of Patients Entered Onto the United Kingdom Medical Research Council Trials Between 1980 and 2002—Medical Research Council Adult Leukaemia Working Party. *J Clin Oncol*. 2005;23:9219-9226
5. Kumar SK, Lee JH, Lahuerta JJ et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: A multicenter international myeloma working group study. *Leukemia.* 2012;26:149–157.

Section B: Clarification on cost-effectiveness data

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B5. **Priority question**: Given the sensitivity of the cost-effectiveness estimates to the data sources in TA171, please explore the impact of using different data sources for the effectiveness data on the final ICER. More specifically, please conduct sensitivity analysis using MM-009 data only and pooled data (from MM-009 and MM-0010).

Results based upon the MM-009 study are provided below. Please note the ICERs presented have been updated to take into account adjusted PFS from the Taverna paper (see answer to T3 for further details). Comparative efficacy estimates for bortezomib retreatment, calculated using the same methodology as employed for MM-010 data, are as follows:

- OS: 1.70
- PFS: 1.35

MM-009 clinical data

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Bortezomib	123,575	5.11	2.99	-	-	-	-
Lenalidomide	128,275	5.52	3.36	4,700	0.41	0.37	12,567
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Mean outcomes, weighted by the number of patients in the MM-010 and MM-009 studies, are provided below. These are used to calculate a combined-study ICER. This methodology has been employed as directly pooling clinical studies is not appropriate (breaks randomisation) and would result in approximately the same results (given that the trials contained roughly the same number of patients receiving lenalidomide).

Model outcomes using MM-010 and MM-009 clinical data

Technologies	Total lenalidomide costs (£)	Total bortezomib costs (£)	Total lenalidomide QALYs	Total bortezomib QALYs	Weighted incremental costs (£)*	Weighted incremental QALYs*	ICER (£) incremental (QALYs)
MM-010	121,422	123,207	3.42	2.85	-	-	-
MM-009	128,275	123,575	3.36	2.99	0.47	1,467	3,122
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. * Weighted by number of patients on the Len/Dex arm in each study (MM-010 = 176, MM-009 = 177).							

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B6. **Priority question**: On page 136 of the submission there is reference to the multivariate equations developed to model OS, PFS and TTF. These equations are said to be used to adjust for differences in baseline characteristics of the populations (page 136, page 138 and page 148). Please provide these equations in full detail. Please provide the calculations performed to "improve exchangeability…and to adjust median survival estimates for lenalidomide" (page 148).

For clarification 1 set of multivariate equations are used within the model both to predict OS, PFS and TTF for lenalidomide and to estimate comparative efficacy. The following process was used:

Fit Curves for Lenalidomide using Trial Data

Parametric equations were fit solely to MM-010 data (and now also MM-009 in response to these questions) to produce the baseline curve shapes for second line patients:

- A piecewise curve fit was also applied to the OS data which was the best fitting curve and is applied to model OS in the base case
- A log-logistic curve fit was the best fitting curve for the PFS data (and TTF data)

Calculate Comparative efficacy

The parametric equation which was the best fit was used within the model to calculate the median for lenalidomide adjusting for patient characteristics to match the source paper for OS and PFS as closely as possible in order to derive a hazard ratio for the comparator vs lenalidomide:

- This was the weibull with time dependent effect for OS (as it is not possible to produce an equation of the required format to produce a median for comparative efficacy using a piecewise exponential curve) and the log-logistic curve for PFS
- It was assumed that the HR for TTF would be the same as for PFS as the curve fits for lenalidomide because these two variables are similar and no information on TTF was presented in any of the evidence identified

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Regression equation for the prediction of OS – MM-010 – weibull[1]

Variable	Coefficient	Standard Error	P value
MM duration (centred on the mean)	-0.0622146	0.0252462	0.014
Beta 2M count ≥2mg/L	0.6111748	0.179955	0.001
2+ prior treatments	-0.5556985	0.4228444	0.189
ECOG performance status: 0 or 1	0.1014312	0.1642646	0.537
ECOG performance status: 2	0.6250442	0.2084904	0.003
ECOG performance status: unknown	-0.0201439	0.7315625	0.978
Presence of bone lesions	0.4318573	0.197072	0.028
Constant term	-4.450569	0.4717471	0.000

Regression equation for the prediction of PFS – MM-010 – log-logistic[2]

Variable	Coefficient	Standard Error	P value
MM duration (centred on the mean)	0.0501873	0.0204727	0.014
Beta 2M count ≥2mg/L	-0.7790044	0.1425477	0.000
2+ prior treatments	-0.1852167	0.1463218	0.206
Constant term	3.115807	0.1837414	0.000

Regression equation for the prediction of OS – MM-009 – weibull [3]

Variable	Coefficient	Standard Error	P value
MM duration (centred on the mean)	-0.0705927	0.0300944	0.019
Beta 2M count ≥2mg/L	1.129541	0.1744345	0.000
2+ prior treatments	0.0424577	0.5009001	0.932
Constant term	-5.953292	0.5390546	0.000

[1] The parts of this equation relevant to predicting OS for lenalidomide can be found in the sheet MM10 Progression & Survival rows 92 – 98. MM duration and 2+ prior treatments are not included in the model sheet as these are not required to be used in the model (all patients are 1 prior treatment & MM duration was centered on the mean during the analysis)

[2] The parts of this equation relevant to predicting PFS for lenalidomide can be found in the sheet MM10 Progression & Survival rows 21-23. MM duration and 2+ prior treatments are not included in the model sheet as these are not required to be used in the model (all patients are 1 prior treatment & MM duration was centered on the mean during the analysis)

[3] The parts of this equation relevant to predicting OS for lenalidomide can be found in the sheet MM09 Progression & Survival rows 88-90. MM duration and 2+ prior treatments are not included in the model sheet as these are not required to be used in the model (all patients are 1 prior treatment & MM duration was centered on the mean during the analysis)

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Regression equation for the prediction of PFS – MM-009 – log-logistic[4]

Variable	Coefficient	Standard Error	P value
MM duration (centred on the mean)	0.0686768	0.0233338	0.003
Beta 2M count ≥2mg/L	-0.5875301	0.1354660	0.000
2+ prior treatments	-0.3483372	0.1323018	0.008
Constant term	3.132012	0.1627754	0.000

To improve the exchangeability of the studies of interest, that is, MM-010 or MM-009 and the study being used to predict comparator efficacy relative to Len/Dex, available prognostic characteristics from these studies were entered into the regression equations above. This had the effect of altering the MM-010 (or MM-009) dataset to be in line with the comparator study of interest in terms of the available prognostic characteristics (for example MM duration). This method was employed as it is not possible to adjust the information in the relevant studies to match the MM-010 (or MM-009) patient population. The patient level data from the trials could be adjusted however.

With inputs set to match the comparator study, the regression equations above predicted new OS and PFS estimates. These can be interpreted as showing what OS or PFS would have prevailed if the MM-010 (or MM-009) population had the same prognostic characteristics as the comparator study of interest. The resulting values were the Len/Dex 'adjusted OS' or 'adjusted PFS' estimates, from which hazard ratios were calculated to apply comparative efficacy in the economic analysis.

B7. **Priority question**: Pages 139 to 146 describe six parametric distributions for each clinical outcome (PFS, TTF and OS). The observed KM survival plots and parametric curves are provided. For the 3 outcomes PFS, TTF and OS, please provide the raw data used to produce:

- 1) the KM curves
- 2) the parametric curves
- 3) the log cumulative hazard plots

[4] The parts of this equation relevant to predicting PFS for lenalidomide can be found in the sheet MM09 Progression & Survival rows 21-23. MM duration and 2+ prior treatments are not included in the model sheet as these are not required to be used in the model (all patients are 1 prior treatment & MM duration was centered on the mean during the analysis)

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Please see the response to question 3 in the 'Textual clarifications and additional points', as the changes made for that clarification directly impact our response to the present question.

The raw KM data are provided in a separate Excel spreadsheet. Parameters for each of the models for OS, PFS and TTF are provided below.

OS parametric model coefficients

Variable	Coefficient	Standard Error	P-value
Piecewise exponential			
Beta-2m >2mg/L	0.613	0.180	0.001
ECOG score = 1	0.101	0.164	0.539
ECOG score = 2, 3	0.621	0.209	0.003
ECOG score unknown	-0.046	0.732	0.950
Bone lesions present	0.440	0.197	0.026
Time: ≥6 <12 months	-0.327	0.468	0.485
Time: ≥12 <18 months	-1.316	0.611	0.031
Time: ≥18 <24 months	-1.003	0.619	0.105
Time: ≥24 <30 months	-0.730	0.608	0.230
Time: ≥30 months	-0.449	0.430	0.297
Constant	-4.673	0.364	0.000
Exponential model			
Beta-2m >2mg/L	0.629	0.180	0.000
ECOG score = 1	0.111	0.164	0.500
ECOG score = 2, 3	0.646	0.208	0.002
ECOG score unknown	-0.066	0.731	0.928
Bone lesions present	0.447	0.197	0.023
Constant	-5.173	0.277	0.000
Weibull model (time dependent effect)			
Beta-2m >2mg/L	0.611	0.180	0.001
ECOG score = 1	0.101	0.164	0.537
ECOG score = 2, 3	0.625	0.208	0.003
ECOG score unknown	-0.020	0.732	0.978
Bone lesions present	0.432	0.197	0.028
Constant	-4.451	0.472	0.000
Ln(gamma)	-0.240	0.134	0.073
Weibull model			
Beta-2m >2mg/L	0.615	0.180	0.001
ECOG score = 1	0.113	0.164	0.491
ECOG score = 2, 3	0.619	0.209	0.003

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ECOG score unknown	-0.081	0.731	0.912
Bone lesions present	0.440	0.197	0.025
Constant	-5.039	0.420	0.000
Ln(gamma)	-0.031	0.090	0.733
Log-logistic model			
Beta-2m >2mg/L	-0.824	0.209	0.000
ECOG score = 1	-0.183	0.197	0.352
ECOG score = 2, 3	-0.898	0.275	0.001
ECOG score unknown	-0.014	0.765	0.985
Bone lesions present	-0.549	0.230	0.017
Constant	5.124	0.337	0.000
Ln(gamma)	-0.138	0.088	0.116
Log-normal model			
Beta-2m >2mg/L	-0.952	0.225	0.000
ECOG score = 1	-0.154	0.210	0.463
ECOG score = 2, 3	-0.909	0.286	0.002
ECOG score unknown	0.096	0.820	0.906
Bone lesions present	-0.580	0.244	0.018
Constant	5.195	0.358	0.000
Ln(sigma)	0.452	0.078	0.000
Gompertz model			
Beta-2m >2mg/L	0.626	0.626	0.001
ECOG score = 1	0.116	0.164	0.482
ECOG score = 2, 3	0.628	0.209	0.003
ECOG score unknown	-0.093	0.731	0.899
Bone lesions present	0.445	0.197	0.024
Constant	-5.264	0.323	0.000
Gamma	0.005	0.008	0.507
Gamma model			
Beta-2m >2mg/L	-0.784	0.225	0.001
ECOG score = 1	-0.159	0.191	0.404
ECOG score = 2, 3	-0.721	0.278	0.010
ECOG score unknown	0.090	0.786	0.909
Bone lesions present	-0.521	0.227	0.022
Constant	5.420	0.363	0.000
Ln(gamma)	0.123	0.236	0.602
Ln(kappa)	0.857	0.471	0.069

PFS parametric model coefficients

Variable	Coefficient	Standard Error	P-value

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Log-logistic model			
Constant	3.116	0.184	0.000
Beta-2m >2mg/L	-0.779	0.143	0.000
Ln(gamma)	-0.218	0.080	0.007
Log-normal model			
Constant	3.151	0.186	0.000
Beta-2m >2mg/L	-0.813	0.151	0.000
Ln(sigma)	0.308	0.072	0.000
Exponential model			
Constant	-3.619	0.165	0.000
Beta-2m >2mg/L	0.711	0.147	0.000
Weibull model			
Constant	-3.184	0.267	0.000
Beta-2m >2mg/L	0.669	0.149	0.000
Ln(gamma)	-0.145	0.077	0.060
Gompertz model			
Constant	-3.085	0.202	0.000
Beta-2m >2mg/L	0.576	0.148	0.000
Gamma	-0.038	0.011	0.000
Gamma model			
Constant	2.724	0.292	0.000
Beta-2m >2mg/L	-0.809	0.152	0.000
Ln(sigma)	0.331	0.073	0.000
Ln(kappa)	-0.670	0.339	0.048

TTF parametric model coefficients

Variable	Coefficient	Standard Error	P-value
Log-logistic model			
Constant	2.678	0.169	0.000
Beta-2m >2mg/L	-0.731	0.130	0.000
Ln(gamma)	-0.153	0.067	0.022
Log-normal model			
Constant	2.663	0.207	0.000
Beta-2m >2mg/L	-0.858	0.152	0.000
Ln(sigma)	0.669	0.057	0.000
Exponential model			
Constant	-3.262	0.141	0.000
Beta-2m >2mg/L	0.687	0.127	0.000
Weibull model			
Constant	-2.642	0.213	0.000
Beta-2m >2mg/L	0.637	0.128	0.000

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Ln(gamma)	-0.217	0.064	0.001
Gompertz model			
Constant	-2.813	0.171	0.000
Beta-2m >2mg/L	0.579	0.128	0.000
Gamma	-0.031	0.008	0.000
Gamma model			
Constant	3.312	0.193	0.000
Beta-2m >2mg/L	-0.809	0.139	0.000
Ln(sigma)	0.207	0.077	0.007
Ln(kappa)	1.022	0.172	0.000

Model results using all available parametric survival models are provided below.

Scenario analysis results using all available parametric models for OS, PFS and TTF

Parameter	Base-case Assumption	Scenario analysis	ICER MM-010 data	ICER MM-009 data
Curve fit for OS	Piecewise exponential	Exponential multivariable	Lenalidomide dominates	£24,379
		Weibull with time dependent effect (time horizon 38 years)		Lenalidomide dominates
		Weibull multivariable (time horizon 38 years)		
		Log-normal multivariable		£17,337
		Log-logistic multivariable		£13,123
		Gompertz multivariable		Lenalidomide dominates
		Gamma multivariable		
Curve fit for PFS	Log-logistic multivariable	Log-normal multivariable	Lenalidomide dominates	£12,468
		Exponential multivariable		£14,042
		Weibull multivariable		£13,657
		Gompertz multivariable		£10,465
		Gamma multivariable		£12,349
Curve fit for TTF	Log-logistic multivariable	Log-normal multivariable	Lenalidomide dominates	Lenalidomide dominates
		Exponential multivariable		
		Weibull multivariable		
		Gompertz multivariable	£6,576	
		Gamma multivariable	Lenalidomide	

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Parameter	Base-case Assumption	Scenario analysis	ICER MM-010 data	ICER MM-009 data
			dominates	

B8. **Priority question**: Please clarify which of the following approaches were taken in the economic analysis:

- The dataset was stratified and so only data (clinical and cost) for the second-line treatment population was included in the economic analysis.
- Data (clinical and cost) from the full MM-010 population was used (as suggested in page 137 - 139), and then the covariate estimate for the second-line setting was used to adjust the models results
    a. If this approach was used please present sensitivity analysis using only data from patients treated in the second-line setting

Please see the response to question 3 in the 'Textual clarifications and additional points', as the changes made for that clarification directly impact our response to the present question.

The second approach listed above was taken in the economic analysis. Results using survival analysis inputs from only patients who were treated in the second-line setting (for OS, PFS and TTF) are provided below for both MM-010 and MM-009 clinical data. It is assumed that comparative efficacy estimates are equal to those calculated for the wider MM-010 and MM-009 populations respectively.

Second-line population: MM-010 clinical data

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Bortezomib	137,138	6.85	3.63	-	-	-	-
Lenalidomide	148,831	8.23	4.48	11,693	1.38	0.85	13,771
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Second-line population: MM-009 clinical data

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Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Bortezomib	130,691	5.73	3.25	-	-	-	-
Lenalidomide	138,378	6.26	3.73	7,587	0.53	0.48	15,699
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

B9. **Priority question**: The Gamma distribution visually seems to be as good (or better) a fit to the KM data for PFS and TTF than the lognormal distribution, which was included in sensitivity analyses. Please clarify why the Gamma distribution was not considered in the sensitivity analysis.

Please find model results using the gamma distribution in response to clarification B7.

B10. **Priority question**: Please clarify why the Markov trace figures for OS provided in the appendix appear to be substantially different from Figure 28 in the submission, presenting the predicted survival?

The Markov trace presented in the submission differed to Figure 28 in the submission because Figure 28 showed the overall survival Kaplan-Meier chart and piecewise exponential plot for the entire ITT population. This was provided as analysis was conducted using the full (ITT population) with the curve fit for second-line patients then analysed by including the line of treatment (second or third or more) as a covariate within the regression analysis (see answer to B8).

The Kaplan-Meier chart and parametric model for the ITT population adjusted to reflect patients treated in the second-line setting (based upon the second approach described in clarification B8) is provided below.

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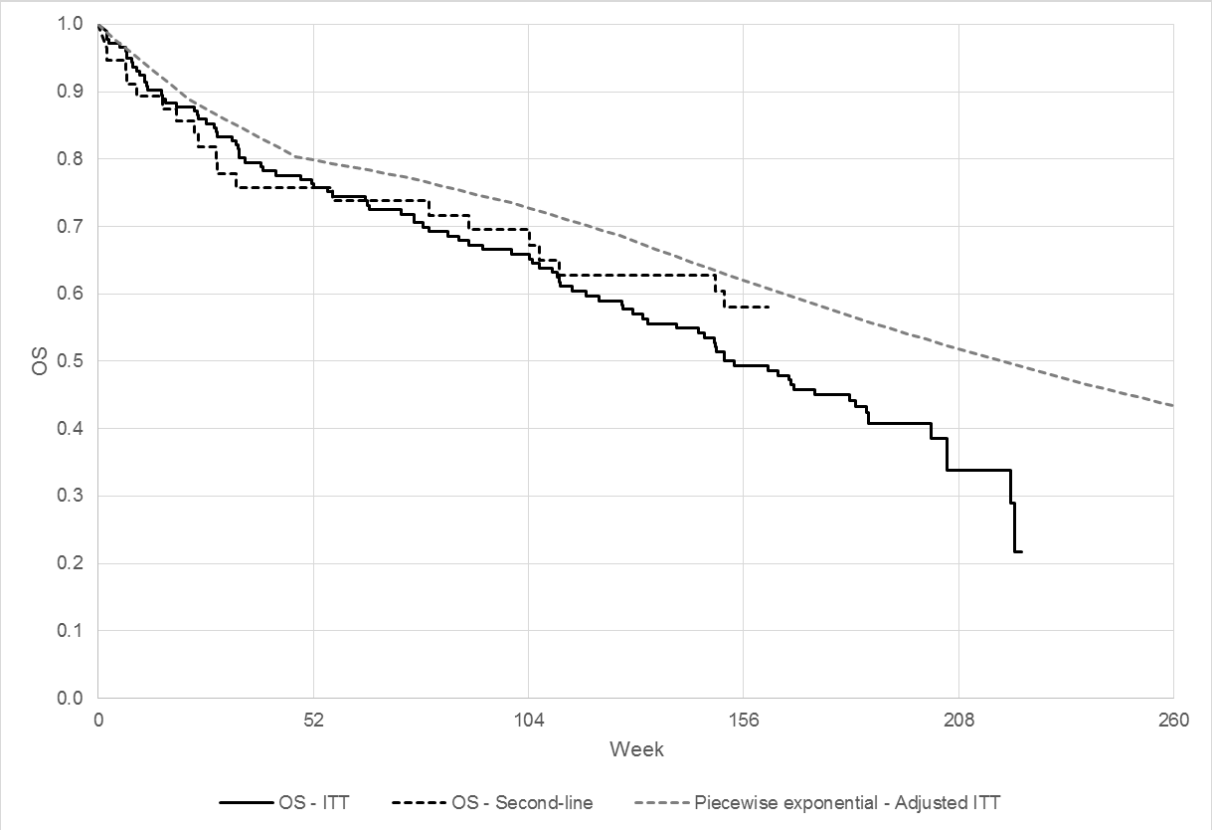
Corrected Figure 28 – Kaplan-Meier chart and fitted piecewise exponential model (MM-010)



It is not possible to adjust a Kaplan-Meier chart to show the OS of the ITT population adjusted for if it were a second-line population. The exponential model above was estimated this way, using the full MM-010 dataset. The Kaplan-Meier plot and piecewise exponential model for the second-line only population are provided below. These two charts are also provided for the MM-009 dataset.

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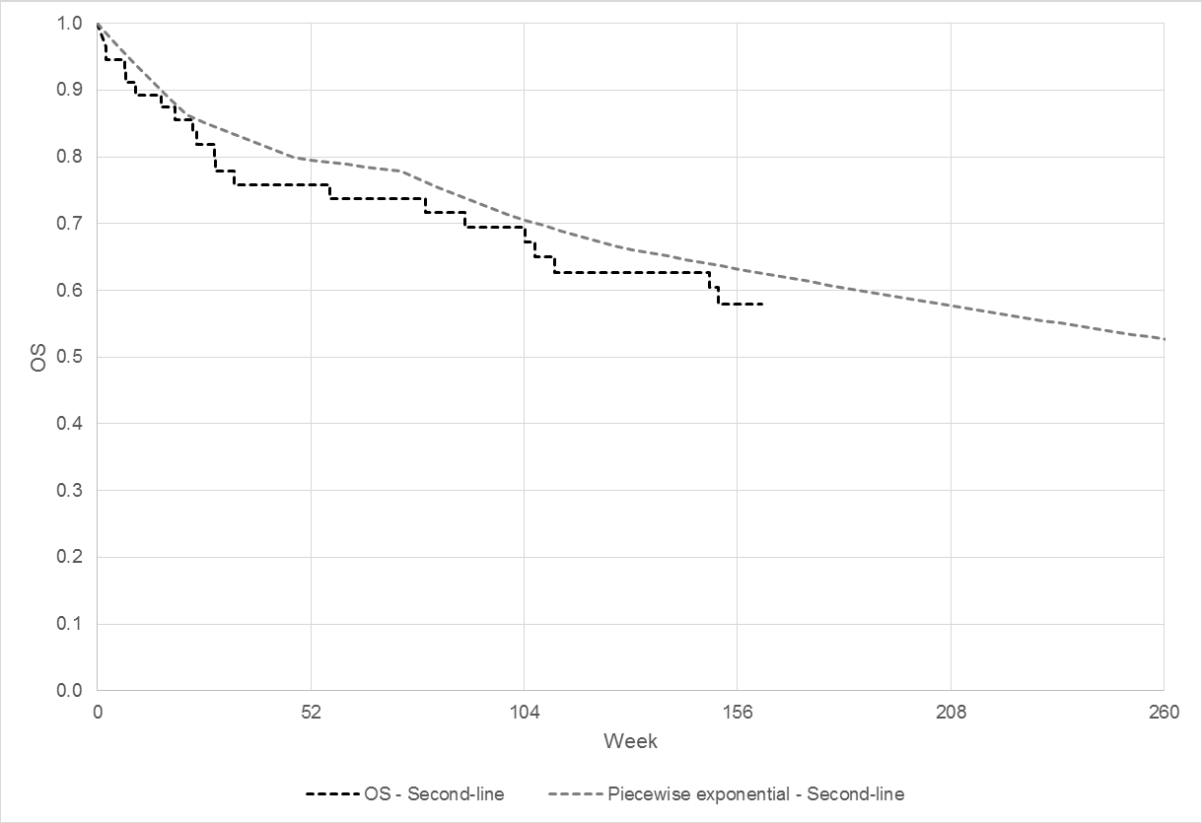
Kaplan-Meier chart and fitted piecewise exponential model – second-line patients only (MM-010)



The predicted survival curve does not appear to fit precisely to the observed data for the lenalidomide group in the 2nd line subgroup population as survival has been estimated using mean covariate values from the full 2nd line population (lenalidomide and dexamethasone patients). Due to some small imbalances in patient characteristics between treatment groups and differences in population characteristics between 2nd line patients between the treatment groups this has resulted is a slight shifting of the predicted curve for lenalidomide away from the observed estimate. For example in MM10, the mean value for the duration of multiple myeloma (MM) for 2nd line lenalidomide patients 2.73 years, whilst the mean value for the entire MM10 population is 3.08 years. It is also noted that the 2nd line population relies on a small sample size and thus the Kaplan-Meier curve is more sensitive to censoring and appears less 'smooth' than Kaplan-Meier survival curves based on the larger ITT population resulting in somewhat poorer fitting curve.

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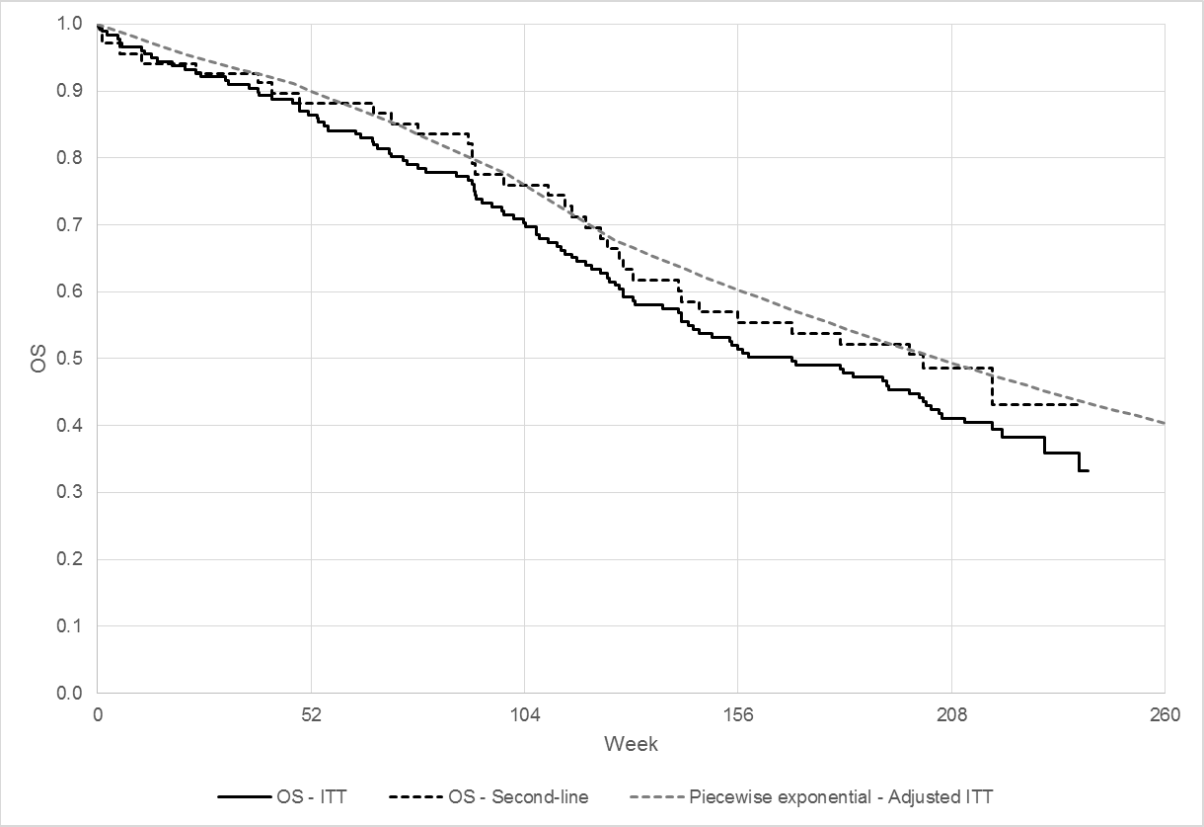
Kaplan-Meier chart and fitted piecewise exponential model (MM-009)



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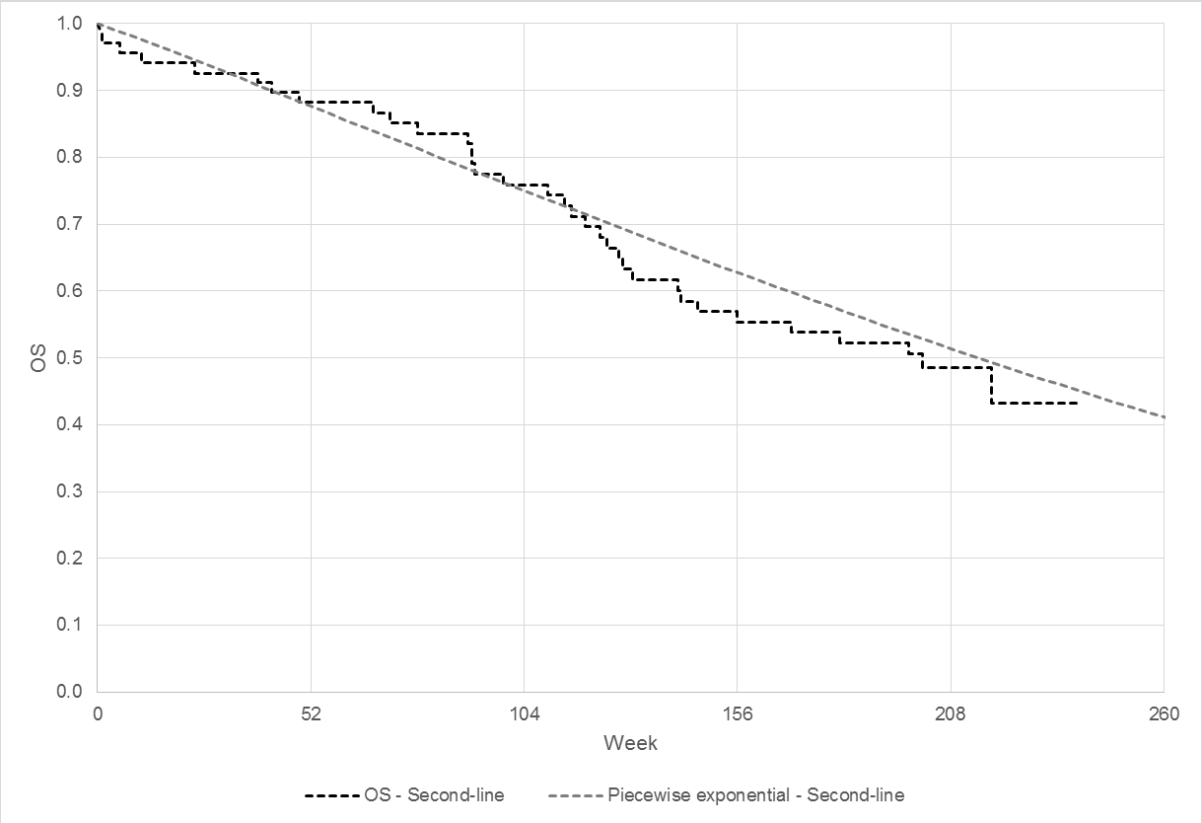
Kaplan-Meier chart and fitted piecewise exponential model – second-line patients only (MM-009)



B11. **Priority question**: Please outline why no search terms for health related quality of life were included in the searches?

The explicit terms were mistakenly excluded. The searches have been repeated with the correct terms included (see below for the filter used for utilities). 195 papers were found (see Excel spreadsheet provided). 1 additional paper which was not found in the original searches was identified after filtering: Crott 2013. This paper reports a utility of 0.69 (SD = 0.26) using the EQ-5D for multiple myeloma based upon 172 patients (717 observations).

The utilities in the paper identified in the original review are 0.81 pre-progression, 0.77 pre-progression after 2 years and 0.64 post-progression. The utility in the Crott paper falls within this range and given the large number of observations per patient would be expected to include more post-progression than pre-progression observations. Unfortunately the Crott

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paper does not report utility by pre and post-progression therefore it would not be possible to use this reference within the economic modelling.

MEDLINE filter

Quality-Adjusted Life Years/
quality adjusted life.tw.
(qaly$ or qald$ or qale$ or qtime$).tw.
disability adjusted life.tw.
daly$.tw.
Health Status Indicators/
(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
(euroqol or euro qol or eq5d or eq 5d or eq-5d).tw.
(hql or hqol or h qol or hrqol or hr qol).tw.
(hye or hyes).tw.
"Value of Life"/
health$ year$ equivalent$.tw.
health utilit$.tw.
(hui or hui1 or hui2 or hui3).tw.
disutili$.tw.
rosser.tw.
quality of wellbeing.tw.
quality of well-being.tw.
qwb.tw.
willingness to pay.tw.
standard gamble$.tw.
time trade off.tw.
time tradeoff.tw.
tto.tw.
(fact-an or fact-g or fact an or fact g).tw.

Cochrane Library Filter

MeSH descriptor: [Quality-Adjusted Life Years] this term only
quality adjusted life:ti,ab,kw (Word variations have been searched)

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disability adjusted life:ti,ab,kw (Word variations have been searched)
daly*:ti,ab,kw (Word variations have been searched)
MeSH descriptor: [Health Status Indicators] explode all trees
(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six):ti,ab,kw (Word variations have been searched)
(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve):ti,ab,kw (Word variations have been searched)
sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen:ti,ab,kw (Word variations have been searched)
(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty):ti,ab,kw (Word variations have been searched)
sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six:ti,ab,kw (Word variations have been searched)
euroqol or euro qol or eq5d or eq 5d:ti,ab,kw (Word variations have been searched)
hql or hqol oe h qol oe hrqol or hr qol:ti,ab,kw (Word variations have been searched)
hye or hyes:ti,ab,kw (Word variations have been searched)
MeSH descriptor: [Value of Life] explode all trees
qaly* or qald* or qale* or qtime*:ti,ab,kw (Word variations have been searched)
health* year* equivalent*:ti,ab,kw (Word variations have been searched)
health utilit*:ti,ab,kw (Word variations have been searched)
hui or hui1 or hui2 or hui3:ti,ab,kw (Word variations have been searched)
disutili*:ti,ab,kw (Word variations have been searched)
rosser:ti,ab,kw (Word variations have been searched)
quality of wellbeing:ti,ab,kw (Word variations have been searched)
quality of well-being:ti,ab,kw (Word variations have been searched)
qwb:ti,ab,kw (Word variations have been searched)
willingness to pay:ti,ab,kw (Word variations have been searched)
standard gamble*:ti,ab,kw (Word variations have been searched)
time trade off:ti,ab,kw (Word variations have been searched)
time tradeoff:ti,ab,kw (Word variations have been searched)
tto:ti,ab,kw (Word variations have been searched)
fact-an or fact-g or fact an or fact g:ti,ab,kw (Word variations have been searched)

EMBASE filter

quality adjusted life year/
quality adjusted life.tw.
(qaly$ or qald$ or qale$ or qtime$).tw.
disability adjusted life.tw.
daly$.tw.
health status indicator/

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(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
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(euroqol or euro qol or eq5d or eq 5d or eq-5d).tw.
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health utilit$.tw.
(hui or hui1 or hui2 or hui3).tw.
disutili$.tw.
rosser.tw.
quality of wellbeing.tw.
quality of well-being.tw.
qwb.tw.
willingness to pay.tw.
standard gamble$.tw.
time trade off.tw.
time tradeoff.tw.
tto.tw.
(fact-an or fact-g or fact an or fact g).tw.

CINAHL Filter

TI (fact-an or fact-g or fact an or fact g) OR AB (fact-an or fact-g or fact an or fact g)
TI tto OR AB tto
TI time tradeoff OR AB time tradeoff
TI time trade off OR AB time trade off
TI standard gamble* OR AB standard gamble*
TI willingness to pay OR AB willingness to pay
TI qwb OR AB qwb
TI quality of well-being OR AB quality of well-being
TI quality of wellbeing OR AB quality of wellbeing
TI rosser OR AB rosser
TI disutilit* OR AB disutilit*
TI (hui or hui1 or hui2 or hui3) OR AB (hui or hui1 or hui2 or hui3)
TI health utilit* OR AB health utilit*

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TI health* year* equivalent* OR AB health* year* equivalent*
(MH "Health Status Indicators")
TI (hye or hyes) OR AB (hye or hyes)
TI ((hql or hqol oe h qol oe hrqol or hr qol)) OR AB ((hql or hqol oe h qol oe hrqol or hr qol))
TI ((hye or hyes)) OR AB ((hye or hyes))
TI ((hql or hqol oe h qol oe hrqol or hr qol)) OR AB ((hql or hqol oe h qol oe hrqol or hr qol))
TI ((euroqol or euro qol or eq5d or eq 5d)) OR AB ((euroqol or euro qol or eq5d or eq 5d)
TI ((sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six)) OR AB ((sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six))
TI ((sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty)) OR AB ((sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty))
TI ((sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen)) OR AB ((sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen))
TI ((sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve)) OR AB ((sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve))
TI ((sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six)) OR AB ((sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six))
(MH "Health Status Indicators")
TI daly* OR AB daly*
TI disability adjusted life OR AB disability adjusted life
TI (qaly* or qald* or qale* or qtime*) OR AB (qaly* or qald* or qale* or qtime*)
TI quality adjusted life OR AB quality adjusted life
(MH "Quality-Adjusted Life Years")

B12. The ICERs in this submission differ significantly from those presented in TA171. It will be beneficial to the Appraisal Committee to understand the reasons for this. Therefore please provide reasoning for this difference.

While some aspects of the economic model have been employed for their similarity with the analysis in TA171, the ICERs submitted here differ to those presented in TA171 because it is based upon a new economic model, with updated clinical inputs (later data cut), updated

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costs inputs, and with a different (active) comparator therapy at a different position in the treatment pathway.

When only results for the lenalidomide arm are studied (Table 56 from the manufacturer submission for TA171) the comparison is as follows:

Comparison of Lenalidomide Results between TA171 and Current Model Using Similar Data

	TA171	**Analysis presented in B8 using only second line patients (as per TA171)**
Discounted QALYs	4.49	4.48
Undiscounted Lys	8.33	8.23
Discounted Costs	£115,775	£148,831

B13. Please confirm that in Table 41 the intercept term coefficient value is 3.116 and the Beta-2 microglubin coefficient -0.779 for the log-logistic model (The same applies for the lognormal model coefficients). Please provide the p-values used to assess the statistical significance of the predictors.

This is correct. A table containing the coefficients of all PFS predictors, and associated standard errors and p-values, is provided in B7.

<u>Textual clarifications and additional points</u>

1. **Priority question**: Please consider the following and provide an updated model if necessary:
    - The values on tab “Comparative efficacy” could not be traced back in the submission. The values for median OS and median PFS for the Len/Dex arm of the model do not match the values provided in Section 6 of the submission. Please present these outcomes and the sources.
    - Within the same excel tab, there is potential mislabelling in the tables from cells C32-J78. Please provide a clear, corrected table with sources included.

Values for median OS, TTP and PFS for the Len/Dex arm were obtained from the MM-010 clinical study report. The can be found in Table 24 (p 73), Table 25 (p 75) and Table 26 (p 76) respectively. The outcomes presented in Section 6 of the submission were based on a

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2005 earlier analysis of the trial data (up to unblinding), whereas model inputs use the extended, open-label follow-up data (until 2008). Outcomes from the extended follow up period are provided in Appendix D of the submission, though these were stratified by number of prior anti-myeloma therapies received.

Note that as the economic analysis has now also been performed for the MM-009 clinical study, the MM-009 CSR should be consulted to obtain the values shown in the "Comparative efficacy" model worksheet. Median OS, TTP and PFS can be found in Table 23 (p 71), Table 24 (p 73) and Table 25 (p 74) respectively.

2. **Priority question**: The Excel model provided indicates that there are extra calculations to adjust for the crossing of the fitted PFS and OS curves, which may have led to an overestimation of PFS. Please provide the rationale for these calculations.

Crossing of fitted parametric curves for PFS and OS is possible when the curves lie close together. To avoid the implausible scenario of PFS exceeding OS a Markov approach was undertaken rather than an area under the curve (AUC) approach in modelling PFS. The Markov approach was a three state model in which patients were modelled to be in a health state of pre-progression, post-progression or dead. Transition probabilities were calculated from MM10 data for the movement of subjects between these health states.

Importantly the Kaplan-Meier plots for PFS and OS do not cross at any point; crossing is the result of the fitted curve lying close together when extrapolated to future time points.

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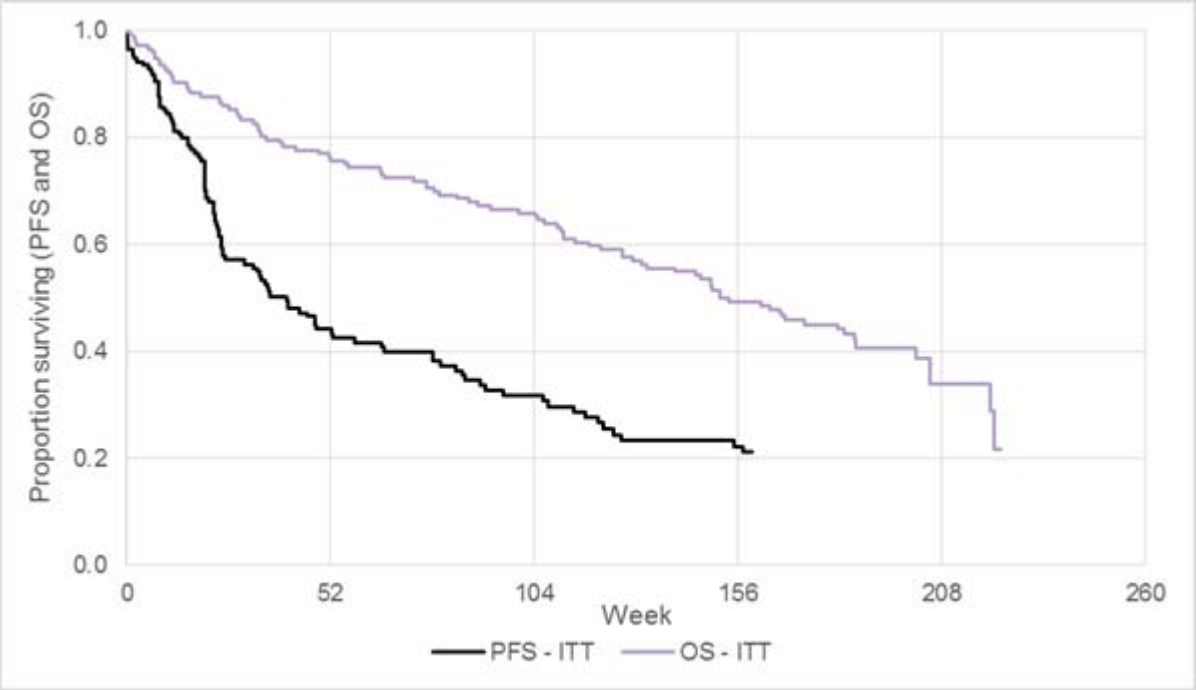
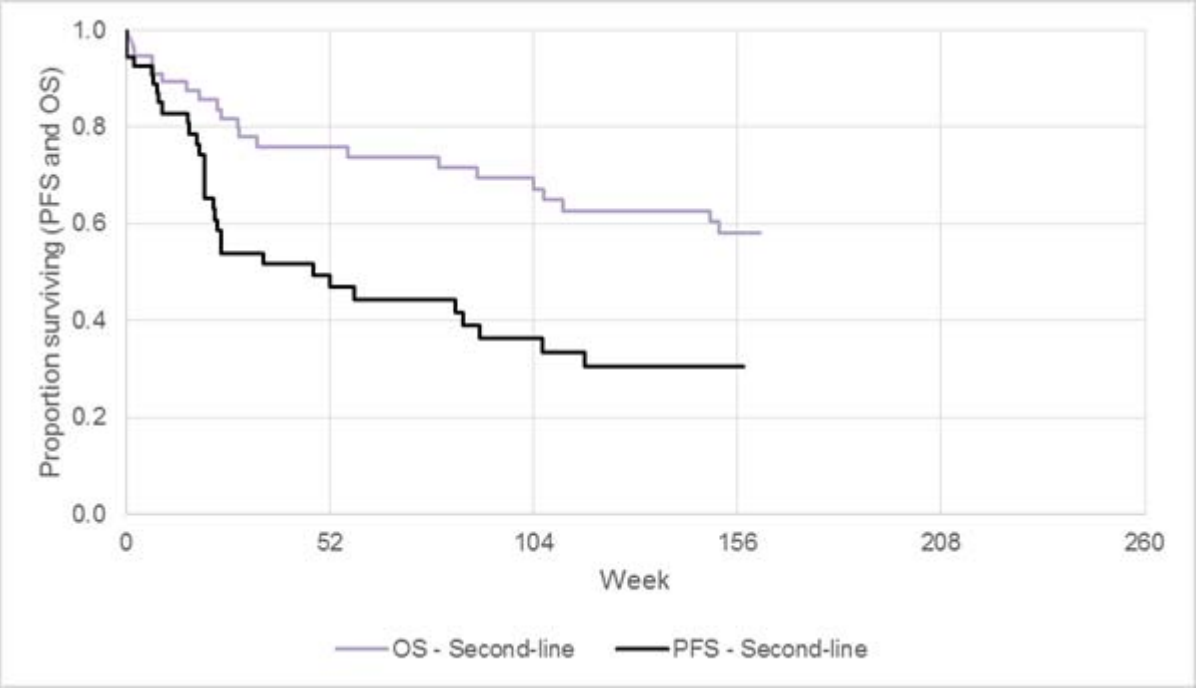
OS and PFS curves for ITT population



OS and PFS Curves Second Line Patients



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3. **Priority question**: In the Excel model provided, there is a possible inconsistency in the approaches to adjust for patient characteristics. The median observed PFS and TTP (tab "Comparative Efficacy", cells F44 and F45) are not adjusted for patients characteristics reported in the Taverna study, whilst the median OS estimate was. Please provide median PFS and TTP from trial MM-010, adjusted for patient characteristics from the Taverna study.

Unfortunately, failure to adjust comparative PFS estimates for the MM duration information available in Taverna et al (2012) was an oversight. This analysis has now been performed. The resulting estimated hazard ratio of bortezomib retreatment relative to Len/Dex is 0.90. This has been incorporated into the base case analysis, and as such, a complete set of model results is provided below.

The resulting base case ICER takes a negative value, because lenalidomide provides a gain in QALYs and lower total costs relative to bortezomib retreatment. The clinical explanation for this result, with a PFS hazard ratio <1 and OS hazard ratio>1, is that while it appears using the Taverna paper that patients are more likely to experience an initial response to bortezomib having already responded previously, the response duration and therefore resulting OS is shorter (as these patients have been previously treated with and lost response to bortezomib). Bortezomib patients remain on treatment for longer and incur the associated acquisition and administration costs, and fewer patients go on to receive subsequent therapy, and therefore subsequent lenalidomide which provides a survival benefit.

Model outputs by clinical outcomes – lenalidomide

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
Progression-free survival	2.48	1.73	£110,582
Post-progression survival	3.25	1.68	£10,840
Total	5.74	3.42	£121,422
LY, life years; QALY, quality-adjusted life year.			

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Model outputs by clinical outcomes – bortezomib

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
Progression-free survival	1.42	1.06	£76,611
Post-progression survival	3.48	1.79	£46,596
Total	4.89	2.85	£123,207
LY, life years; QALY, quality-adjusted life year.			

Summary of QALY gain by health state

Health state	QALY intervention (lenalidomide)	QALY comparator (bortezomib)	Increment	Absolute increment	% absolute increment
Pre-progression	1.73	1.06	0.67	0.67	86.5%
Post-progression	1.68	1.79	-0.10	0.10	13.5%
Total	3.42	2.85	0.57	0.78	100%
QALY, quality-adjusted life year. Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.					

Summary of costs by health state

Health state	Cost intervention (lenalidomide)	Cost comparator (bortezomib)	Increment	Absolute increment	% absolute increment
Pre-progression	£110,582	£76,611	£33,971	£33,971	48.7%
Post-progression	£10,840	£46,596	-£35,756	£35,756	51.3%
Total	£121,422	£123,207	-£1,785	£69,727	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.					

Summary of predicted resource use by category of cost

Item	Cost intervention (lenalidomide)	Cost comparator (bortezomib)	Increment	Absolute increment	% absolute increment
Technology cost	£104,211	£57,832	£46,379	£46,379	45.1%
Administration & transport cost	£168	£15,396	-£15,228	£15,228	14.8%
Monitoring & test costs	£11,949	£9,291	£2,658	£2,658	2.6%

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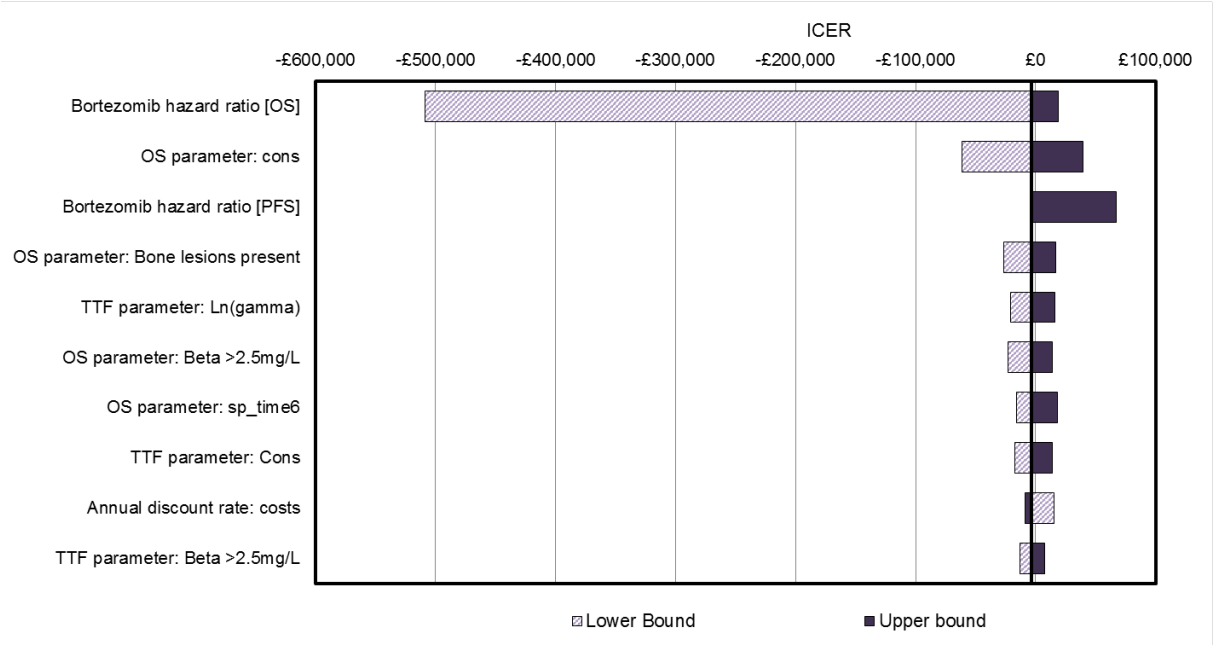
3rd line therapy cost (inc. admin and transport)	£204	£37,046	-£36,842	£36,842	35.8%
4th line therapy cost (inc. admin and transport)	£3,428	£1,898	£1,530	£1,530	1.5%
Adverse event costs	£420	£671	-£252	£252	0.2%
Terminal care costs	£1,042	£1,072	-£30	£30	0.0%
Total	£121,422	£123,207	-£1,785	£103,327	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.					

Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Bortezomib	123,207	4.89	2.85	-	-	-	-
Lenalidomide	121,422	5.74	3.42	-1,785	0.85	0.71	Lenalidomide dominates
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Tornado diagram – top 10 parameters in terms of ICER sensitivity



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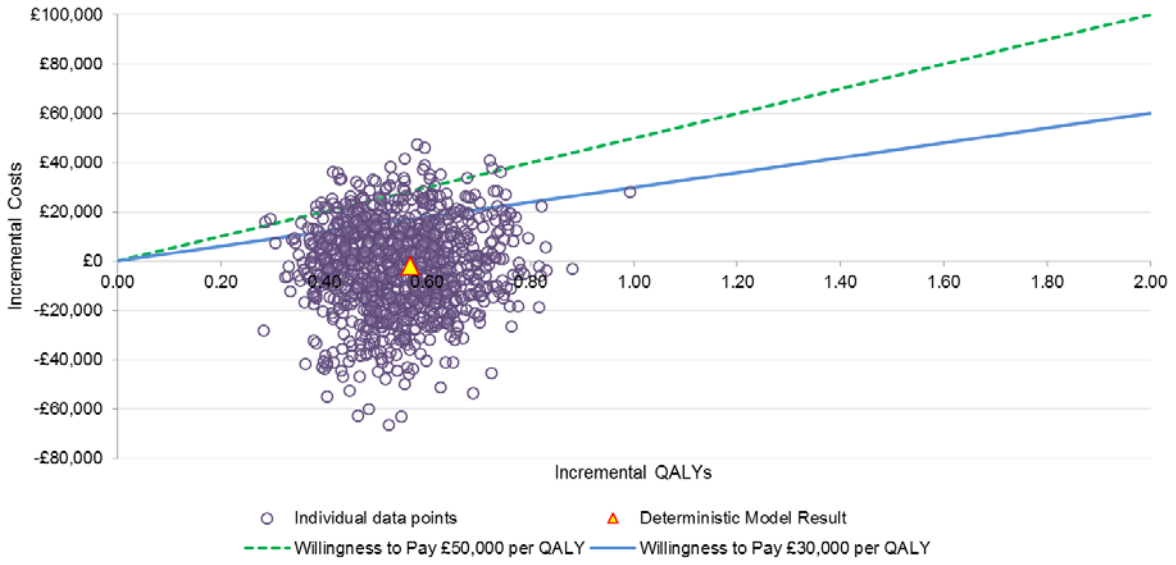
Results from 1,000 PSA simulations

Model outcome	PSA result
Mean incremental costs (SD)	-£2,150 (18,291)
Mean incremental QALYs (SD)	0.54 (0.10)
Mean ICER	Lenalidomide dominates
Observations cost-effective at £20,000 threshold	74.5%
Observations cost-effective at £30,000 threshold	85.0%
ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; SD, standard deviation; QALY, quality-adjusted life year.	

Cost-effectiveness scatter plot



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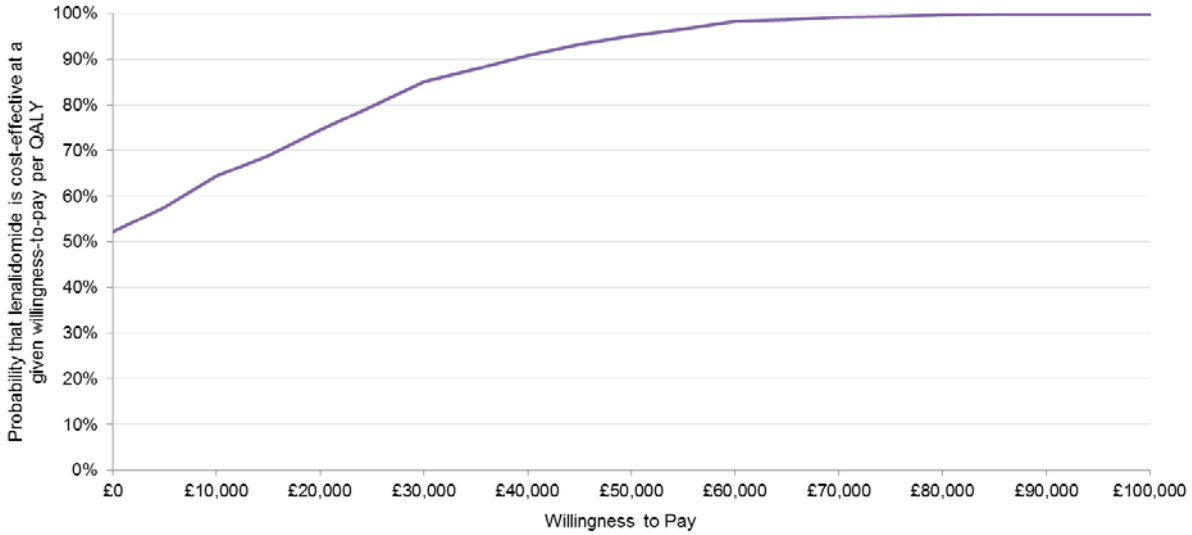
Cost-effectiveness acceptability curve



Scenario analysis 1 – time horizon

Parameter	Base Case Assumption	Scenario analysis	ICER
Time horizon	25 years	5 years	Lenalidomide dominates
		10 years	Lenalidomide dominates
		15 years	Lenalidomide dominates
		20 years	Lenalidomide dominates
ICER, incremental cost-effectiveness ratio.			

Scenario analysis 2 – type of comparison

Parameter	Base case assumption	Scenario analysis (market share)	ICER
Choice of comparator	Bortezomib retreatment	Bortezomib retreatment/dexamethasone (34%[a])	Lenalidomide dominates
		Bendamustine/prednisolone (6%[b])	£55,621
		Bendamustine/dexamethasone (6%[b])	£55,611
		Melphalan/prednisone (5%[c])	£60,246
		High-dose cyclophosphamide/dexamethasone (5%[c])	£67,660
		Low-dose	£64,345

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Parameter	Base case assumption	Scenario analysis (market share)	ICER
		cyclophosphamide/dexamethasone (5%[c])	
		Doxorubicin (5%[c])	£66,895
		Vincristine (5%[c])	£64,332
Comparator	Bortezomib retreatment	Blended comparator by market share	£20,769
The use of Len/Dex at third line	As per NICE recommendations (i.e. earlier use of lenalidomide)	As per historical best supportive care (i.e. sub-100% lenalidomide use at third line)	£27,703
Include dexamethasone with 3rd and 4th line treatments where applicable	Yes	No	Lenalidomide dominates
ICER, incremental cost-effectiveness ratio. a, bortezomib market share includes monotherapy and combination with dexamethasone; b, bendamustine market share includes combination with prednisolone and dexamethasone; c, chemotherapy agents' market shares include all chemotherapies listed			

Scenario analysis 3 – modelling lenalidomide efficacy

Parameter	Base-case Assumption	Scenario analysis	ICER
Parameter used to model treatment discontinuation	TTF	PFS	£12,122
ICER, incremental cost-effectiveness ratio.			

Note: the impact of different parametric curve fits is presented in response to B7.

Scenario analysis 4 – treatment efficacy assumptions

Parameter	Base-case Assumption	Scenario analysis	ICER
Comparative efficacy of bortezomib	OS from Taverna (2012)[45]	OS from White (2013)[42]	Lenalidomide dominates
	PFS from Taverna (2012)	PFS from Petrucci (2013)[53]	£21,053
		PFS from Hrusovsky (2010)[50]	£10,743
		PFS from Dispenzieri (2010)[80]	£22,288
		PFS from White (2013)	£43,331
ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.			

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Scenario analysis 5 – bortezomib patient access scheme

Parameter	Base-case Assumption	Scenario analysis	ICER
Bortezomib patient access scheme	Not included	15% discount at 2nd line applied for all bortezomib 2nd line patients	£12,170
		15% price discount applied for 55% of bortezomib 2nd line patients	£5,275
ICER, incremental cost-effectiveness ratio.			