NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Lenalidomide for the treatment of multiple myeloma (part-review of TA171)

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists 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 is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

General considerations

- Should thalidomide be considered a comparator?
- How well do the populations in the trials match the decision problem?
    - Did not exclude people for whom thalidomide treatment is not appropriate, cannot be tolerated or is contraindicated (and a number of patients had previously received thalidomide)
    - Patients are younger than the average population with multiple myeloma (63 rather than 70)
    - The number of patients with prior stem cell therapies was higher than expected
    - Includes a high proportion of patients who have had two or three prior therapies

Clinical effectiveness

- Is lenalidomide more effective than the comparators?
    - No direct comparison

- Taking into account the population in the model (>1 prior therapies, younger population, high number of previous stem cell transplants), are the results likely to over or under-estimate the efficacy of lenalidomide?
- Time to failure data is used in the health economic model, but the data are not presented in the manufacturer's submission, do these data need to be considered?
- Are the sources selected for relative effectiveness of bortezomib appropriate?
    - The ERG noted a study (Hrusovsky) that was not used in the manufacturer's economic model.
- Are the included adverse events the most appropriate? Data was presented from MM-009 and MM-010 which have a short follow up, and no further searches were made.

Cost effectiveness

- Are the assumptions made in the manufacturer's model clinically plausible? Specifically:
    - The model assumes that patients move from treatment failure to subsequent treatment without a pause in treatment (immediately accruing the costs of subsequent treatment in both the lenalidomide and comparator arms, and immediately accruing the mortality benefit of third line treatment in the comparator arm).
    - Following disease progression, patients remain in the progressive disease state, patients cannot move to the progression free survival state and experience the associated utility
    - The modelled progression free survival is in favour of bortezomib whilst overall survival favours lenalidomide.
    - Patients receive third and fourth line treatments, is this representative of clinical practice?
    - The overall survival estimate for lenalidomide, has it been overestimated?
- Are the manufacturer's updates to the analyses appropriate?
    - Bortezomib progression free survival adjusted for baseline characteristics

  - Using log-logistic curves to prevent the curves crossing
  - Removing the 'min' function (used to prevent curves crossing) where possible
  - Corrected an inconsistency between the intervention and comparator arm in the patient flow sheet.
- Should third and fourth line treatments be modelled? If so:
  - Is having a different mix depending on previous treatment appropriate?
  - Are the modelled treatment mixes representative of clinical practice?
  - Should all costs and effects be modelled?
- The model includes crossing overall survival and progression free survival curves that cross on the comparator arm. What may be the impact of this on cost effectiveness and can this be addressed? Can the extrapolation be considered valid given the crossing of the curves?
- The manufacturers model does not include patient access schemes in the base case.
  - The bortezomib patient access scheme was included in a scenario, has it been correctly modelled (assumed a 15% discount)?
  - The patient access scheme for lenalidomide for patients at third line treatment has not been modelled. Is this appropriate? Would patients reach 26 cycles (and hence be eligible for the patient access scheme)?
- The utility values used in the model are higher than the general population. Is this appropriate?
- For lenalidomide, two trials are available (MM-009 and MM-010) however the model used only data from MM-009 in the economic model. The manufacturer stated that it was not appropriate to use pooled data in the economic model because of breaking randomisation; however, pooled clinical effectiveness data was presented. Is this appropriate to only use MM-009 data, or should the model include pooled data, or MM-010 only?
- Are the modelled costs appropriate?
  - Excluding dexamethasone (at 3rd/4th line of treatment)
  - Was the cost of bortezomib calculated appropriately?
  - Were lenalidomide monitoring costs calculated appropriately?

  - Should bortezomib be given until treatment failure, or should it be given for a fixed number (8) of cycles?
  - Are transport costs (50% of patients) modelled correctly?
- Why is there a change in the ICER to be more in favour of lenalidomide following an improvement in progression free survival that favours bortezomib?

1 Background: clinical need and practice

1.1 Multiple myeloma is a cancer that arises from plasma cells (white blood cells) in the bone marrow. The term multiple myeloma refers to the presence of more than one site of affected bone at the time of diagnosis. Myeloma cells produce large quantities of an abnormal antibody, known as paraprotein (which cannot fight infection), and suppress the development of normal red blood cells, white blood cells, and platelets. People with multiple myeloma can therefore experience bone pain, bone fractures, tiredness (because of anaemia), infections, hypercalcaemia (too much calcium in the blood) and kidney problems. Cancer Research UK estimated that the 2010 age-standardised incidence of multiple myeloma in England to be 6.7 per 100,000 men and 4.4 per 100,000 women.

1.2 Life expectancy for people with multiple myeloma is determined by the stage of the disease. In the UK about 70% of people with multiple myeloma live for at least 1 year after diagnosis, and 37% for 5 years. Ten year survival is between 15% and 19%. Life expectancy for multiple myeloma can be predicted based on the stage of the cancer. The stages are determined by the serum albumin and serum beta-2 microglobulin levels (Table 1).

Table 1 Stage of disease and overall survival

Stage	Median survival (months)
Stage I (albumin ≥ 3.5 & beta-2 microglobulin ≤3.5)	62
Stage II (beta-2 microglobulin levels 3.5 to 5.5)	44
Stage III (beta-2 microglobulin level > 5.5)	29

1.3 There is currently no cure for multiple myeloma. The aims of treatment are to control the disease and relieve symptoms. The primary management of multiple myeloma is stem cell transplant. However, due to factors including age, co-morbidities, and performance status, stem cell transplant is not appropriate for approximately 86% of people with multiple myeloma. For people with multiple myeloma for whom stem cell transplantation is not considered suitable, NICE Technology Appraisal guidance recommends the following:

- NICE Technology Appraisal guidance TA228 recommends thalidomide as a first line treatment, or bortezomib if thalidomide is contraindicated.
- NICE Technology Appraisal guidance TA129 recommends bortezomib following one prior therapy
- NICE Technology Appraisal guidance 171 recommends lenalidomide following two prior therapies.

Treatment with bendamustine and/or retreatment with bortezomib are commonly used following relapse if other treatments are contraindicated or inappropriate (sometimes via the Cancer Drugs Fund). The British Society for Haematology guidelines for the diagnosis and management of multiple myeloma recommend a number of options for the treatment of relapsed patients including thalidomide, lenalidomide and bortezomib (usually in combination with dexamethasone). The guidelines note that there is no defined sequence and combination of drugs.

1.4 Bortezomib is therefore recommended at both first and second line (i.e. retreatment) if thalidomide is contraindicated, and there are currently no recommended alternatives to bortezomib retreatment at second line.

2 The technology

2.1 Lenalidomide (Revlimid®) is an immunomodulating agent, and a structural derivative of thalidomide. Lenalidomide's mechanism of action is anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory. Lenalidomide is administered orally.

2.2 The summary of product characteristics lists the following adverse reactions for lenalidomide: neutropenia, anaemia and thrombocytopenia. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic substance that causes severe life-threatening birth defects. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide cannot be ruled out. For these reasons a risk minimisation plan was developed and agreed with the MHRA to ensure that there is no foetal exposure to lenalidomide. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Lenalidomide is available as a 21 tablet pack. The cost per pack varies according to tablet size: £3,570 (5 mg), £3780 (10mg), £3,969 (15 mg) and £4,368 (25 mg; British national Formulary [BNF] edition 65). The recommended starting dose is 25mg. Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was to appraise the clinical and cost effectiveness of lenalidomide within its licensed indication for treating multiple myeloma previously treated with bortezomib.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adults with multiple myeloma for whom thalidomide is contraindicated and whose disease has progressed after at least 1 prior treatment with bortezomib.	

The manufacturer estimated the size of the population stated in the decision problem, using the costing template from TA228. The manufacturer used a population of England and Wales, and assumed that annually there are 2,047 patients with multiple myeloma for whom stem cell transplantation is not appropriate, that 15% are unable to tolerate or are contraindicated to thalidomide, and that 86.5% progress to a second line treatment. Applying these assumptions, the population would include 266 people.

The ERG noted that the population in the scope differed from that presented in the decision problem by the manufacturer in terms of previous treatments. Only 4% of the population in the trial had also been previously treated with bortezomib. Additionally there were more people in the trial who had received 2 or more prior therapies, rather than just one prior therapy. The ERG stated that clinical advice indicated that the type of previous treatment should not impact the effectiveness of lenalidomide.

	Final scope issued by NICE	Decision problem addressed in the submission
Intervention	Lenalidomide in combination with dexamethasone.	
Comparators	• Bortezomib monotherapy and bortezomib in combination with high-dose dexamethasone • Chemotherapy including regimens based on melphalan, vincristine, cyclophosphamide and doxorubicin • Bendamustine	

The ERG noted that the manufacturers' decision problem differed from that in the scope as an incremental analysis of all the comparators was not presented, instead bortezomib was the comparator selected for the base case analyses, and the other comparators were explored in scenario analyses. In addition, it was unclear whether the base case comparator was bortezomib monotherapy or bortezomib in combination with dexamethasone. The ERG assumed the base case was

bortezomib monotherapy as a scenario was presented that included combination with dexamethasone, although 64% of people in the trial that was used to inform the effectiveness of bortezomib (in both analyses) received bortezomib in combination with dexamethasone.

The ERGs clinical expert commented that people for whom thalidomide was contraindicated in early treatment (for example because of poor renal function) may still be treated with thalidomide later on and after relapse.

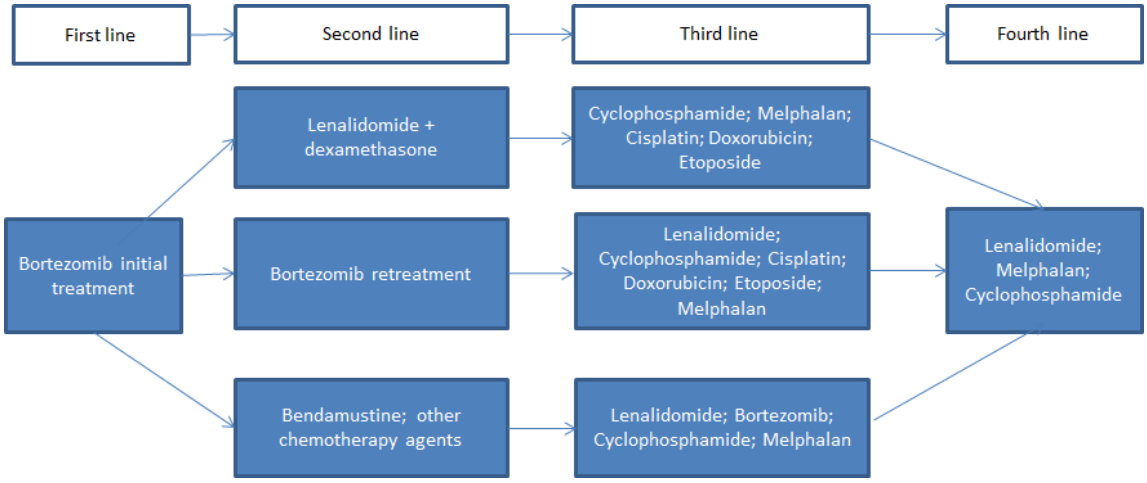
	Final scope issued by NICE	**Decision problem addressed in the submission**
Outcomes	The outcome measures to be considered include: • Progression free survival • Overall survival • Response rates • Time to next treatment • Adverse effects of treatment • Health related quality of life	All outcomes measures, excluding time to next treatment, will be addressed in the submission.

The manufacturer stated that time to next treatment was not included as it was not a reported outcome in the clinical trials presented in this submission.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Economic evaluation	The submission will provide an estimate of cost-effectiveness using the QALY as an output. The time horizon for estimating clinical and cost effectiveness will be appropriate for the indication and the population and in line with the reference case requirements. The costs will be considered from the perspective of the NHS and Personal Social Services. The costs will be presented excluding any patient access schemes for either the intervention or the comparators.	

3.2 Lenalidomide is being considered for treating multiple myeloma following one prior treatment with bortezomib, for those for whom treatment with thalidomide is contraindicated.

Figure 1: Current treatment pathway with the proposed introduction of lenalidomide as a second-line treatment



4 Clinical-effectiveness evidence

4.1 The manufacturer identified, through a systematic literature review, two identically designed randomised controlled trials that compared lenalidomide plus dexamethasone with placebo plus dexamethasone (MM-009 and MM-010). In addition, six subgroup and two updated analyses for the randomised controlled trials were identified (see sections 4.9-4.12). No randomised controlled trials were identified that directly compared lenalidomide with the comparators defined in the decision problem. The manufacturer presented data from the following studies, identified through systematic literature review, to show the efficacy of bortezomib and bendamustine:

- **Bortezomib:** 6 non-randomised clinical trials were identified. A study by Taverna et al (2012) was presented as the most relevant, which was a retrospective survey of people who had received bortezomib retreatment (see sections 4.13-4.14)

- **Bendamustine:** One retrospective study was identified that included people with relapsed or refractory multiple myeloma following prior treatment (Damaj et al (2012); see sections 4.15-4.16)

Lenalidomide plus dexamethasone compared with placebo plus dexamethasone (MM-009 and MM-010)

Clinical effectiveness

4.2 MM-009 and MM-010 compared treatment with lenalidomide plus dexamethasone with placebo plus dexamethasone in patients with multiple myeloma who had received at least 1 prior therapy. Patients received a starting daily dose of 25 mg oral lenalidomide or placebo on days 1–21 of each 28-day cycle. All patients also received 40 mg oral dexamethasone on days 1–4, 9–12 and 17–20 for the first 4 cycles. After the fourth cycle, 40mg of dexamethasone was administered on days 1–4 only. Treatment was continued until disease progression or discontinuation due to adverse effects. At disease progression or unblinding, patients in the placebo plus dexamethasone monotherapy group could switch treatment arms to receive lenalidomide. The study designs of MM-009 (n=353) and MM-010 (n=351) were identical other than study location (MM-009: United States and Canada; MM-010: Australia, Europe [including the UK] and Israel). The primary outcome was time to progression. Secondary outcomes included overall survival, response rates, adverse effects and time to decrease in performance status. Patients were stratified according to serum concentration of β2-microglobulin, previous stem-cell transplantation and number of previous anti-myeloma therapies. Table 1 summarises prior therapies; approximately 35% of patients had received one prior therapy (first relapse) and more than 65% had received at least two prior therapies. Exclusion criteria included those previously treated with lenalidomide or whose disease was refractory to dexamethasone. Response was assessed using the European Group for Blood and Marrow

Transplantation criteria. A number of post-hoc subgroups from the pooled populations were investigated, according to the number of prior therapies and patients who had received prior thalidomide or bortezomib therapy.

Table 2: Baseline characteristics for MM-009 and MM-010 and treatment history of patients

	Study MM-009			Study MM-010		
Type of Therapy	**Len/Dex N=170**	**Dex N=171**	**p-Value**	**Len/Dex N=176**	**Dex N=175**	**p-value**
Median age	64.0	62.0	0.505	63.0	64.0	0.453
Sex (% Male)	60.0	59.1	0.912	59.1	58.9	1.000
No. of prior anti-myeloma therapies 1 2 or 3	 64 (37.6%) 106 (62.4%)	 64 (37.4%) 107 (62.6%)	1.000	 56 (31.8%) 120 (68.2%)	 57 (32.6%) 118 (67.4%)	0.909
Prior SCT 0 1 2 3 >3	 68 (40.0%) 28 (16.5%) 25 (14.7%) 15 (8.8%) 34 (20.0%)	 69 (40.4%) 18 (10.5%) 28 (16.4%) 17 (9.9%) 37 (21.6%)	0.631	 77 (43.8%) 31 (17.6%) 30 (17.0%) 4 (2.3%) 34 (19.3%)	 81 (46.3%) 21 (12.0%) 23 (13.1%) 4 (4.0%) 43 (24.6%)	0.312
Prior thalidomide therapy Yes	 72 (42.4%)	 78 (45.6%)	0.586	 52 (29.5%)	 67 (38.3%)	0.091
Prior bortezomib (Velcade®) therapy Yes	 18 (10.6%)	 20 (11.7%)	0.864	 8 (4.5%)	 7 (4.0%)	1.000

SCT, stem cell transplant.

4.3 The manufacturer presented primary and secondary outcomes of the MM-009 and MM-010 trials individually and as a pooled dataset, using the intention to treat population. Table 2 below shows the results at unblinding for all patients. Lenalidomide plus dexamethasone was associated with statistically significantly reduced time to progression, statistically significantly increased progression free and overall survival and statistically significantly improved response rates compared with placebo plus dexamethasone, on both trials.

Table 3: Time to progression, progression free survival, and response rates for MM-009 and MM-010 at unblinding, and overall survival

		Study MM-009		Study MM-010	
		Len/Dex	Dex	Len/Dex	Dex
Time to progression (at unblinding)	N	177	176	176	175
	Median, weeks [95% CI]	48.1 [36.9, 1.4]	20.1 [16.7, 23.1]	48.7 [40.9, 72.1]	20.1 [18.1, 20.7]
	HR [95% CI]	2.822 [2.146, 3.701]		2.850 [2.159, 3.762]	
Progression free survival (at unblinding)	N	170	171	176	175
	Median [95% CI]	41.1 [29.4, NE]	20.1 [16.7, 24.1]	NE[34.1, NE]	20.1 [19.7, 21.7]
	HR [95% CI]	2.970 [2.089, 4.222]		2.567 [1.834, 3.592]	
Overall survival	N	177	176	176	175
	Median, months [95% CI]	29.6	20.2	NE	20.6
	HR [95% CI]	0.44 [0.30, 0.65]		0.66 [0.45, 0.96]	
Response (at unblinding)	N	177	176	176	175
	CR [c]	25 (14.1%)	1 (0.6%)	28 (15.9%)	6 (3.4%)
	RR	52 (29.4%)	16 (9.1%)	46 (26.1%)	16 (9.1%)
	PR	31 (17.5%)	18 (10.2%)	32 (18.2%)	20 (11.4%)
	SD	54 (30.5%)	102 (58.0%)	53 (30.1%)	97 (55.4%)
	PD	5 (2.8%)	25 (14.2%)	3 (1.7%)	25 (14.3%)
	NE [d]	10 (5.6%)	14 (8.0%)	14 (8.0%)	11 (6.3%)

ITT, intention to treat; TTP, time to progression; PFS, progression-free survival; NE, not estimable; CI, confidence interval; CR, complete response; PD, progressive disease ; PR, partial response; RR, remission response; SD, stable disease.

4.4 In a pooled analysis of MM-009 and MM-010 (see Table 3), at unblinding (median 17.5 months; n=704), lenalidomide plus dexamethasone was associated with a statistically significantly higher median time to progression, progression free survival and overall response rate[1]. Pooled overall survival data were presented after a median follow-up of 48 months. Overall survival was statistically significantly longer in patients treated with lenalidomide plus dexamethasone than in those treated with placebo plus dexamethasone.

[1] Assessed using the European Group for Blood and Marrow Transplantation criteria, with six response categories defined: complete response, near-complete response, partial response, stable disease, disease progression and 'response not evaluable'

Table 4 Pooled results showing response rates, time to progression, progression free survival and overall survival

	Len/Dex (n=353)	Dex (n=351)	p value
Up to unblinding (median 17.5 months) Response rate, %			
ORR	60.6	21.9	<0.001
CR	15.0	2.0	<0.001
VGPR	17.3	2.8	
PR	28.3	17.1	
Median TTP, months	13.4	4.6	<0.001
Median PFS, months	11.1	4.6	<0.001
Extended FU (median 48 months). Median OS (since randomisation), months	38.0	31.6	0.045

CR, complete response; DoR, duration of response; FU, follow-up; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TTP, time-to-progression; VGPR, very good partial response.

4.5 The median overall survival of patients on the placebo plus dexamethasone arms of MM-009 and MM-010 was higher than historical retrospective analyses, which were between 14 and 17 months from first relapse. The manufacturer stated that the results for overall survival were affected by crossover of patients at unblinding: 170 of 351 patients in the placebo plus dexamethasone arm received lenalidomide at disease progression or unblinding. These patients were included in the placebo plus dexamethasone arm for the overall survival analyses.

Health related quality of life

4.6 The manufacturer presented data on health-related quality of life, measured using the Eastern Cooperative Oncology Group-performance status (ECOG-PS; used to assess progression of disease and impact on daily living abilities). The median time to first worsening was longer in the lenalidomide plus dexamethasone arm (36.6 weeks) of MM-009 compared with placebo plus dexamethasone (12.1 weeks) and shorter in MM-010 (lenalidomide plus dexamethasone: 10.1 weeks, placebo plus dexamethasone: 12.3 weeks). However none of the results were statistically significant. The manufacturer stated that the different results from the two trials could be due to the subjectivity of the scoring.

Adverse events

4.7 The manufacturer presented adverse event data from MM-009 and MM-010 and the pooled analyses. The most common adverse events

associated with lenalidomide plus dexamethasone were haematological, and could be managed through dose reductions. Anaemia, neutropenia, thrombocytopenia, constipation, pneumonia, decreased weight, hypokalaemia, hypocalcaemia, tremor, rash, and deep vein thrombosis (DVT) were reported significantly more frequently in the lenalidomide plus dexamethasone group than in the placebo plus dexamethasone group.There was an increased risk of developing thromboembolic adverse events (DVT, pulmonary embolism) in lenalidomide plus dexamethasone arm compared with placebo plus dexamethasone arm (9.1% versus 4.3% and 4.0% versus 0.9%, respectively).

4.8 The manufacturer stated that peripheral neuropathy can be treatment limiting for other multiple myeloma treatments. The pooled analyses showed that lenalidomide was not associated with an increased risk of peripheral neuropathy. Grade 2 peripheral neuropathy was experienced by 1.4% of lenalidomide plus dexamethasone patients and 1.4% of placebo plus dexamethasone patients; grade 3 peripheral neuropathy occurred in 1.7% and 0.6% of the lenalidomide plus dexamethasone and placebo plus dexamethasone patients, respectively. There were no grade 4 peripheral neuropathic events in either group.

4.9 Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic substance that causes severe life-threatening birth defects. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide cannot be ruled out. For these reasons a risk minimisation plan was developed and agreed with the MHRA to ensure that there is no foetal exposure to lenalidomide.

4.10 The manufacturer outlined that a letter was issued to health care professionals in June 2013 regarding the safety of lenalidomide for the treatment of myelodysplastic syndromes associated with an isolated deletion 5q abnormality. This letter highlighted an increase in risk of progression to acute myeloid leukaemia in patients who had an isolated deletion 5q abnormality. The letter also discusses clinical trial studies of

newly diagnosed multiple myeloma and the incidence of second primary malignancies (including acute myeloid leukaemia). The manufacturer stated that neither of the populations described as having increases in risk were relevant to the population being appraised.

Subgroups

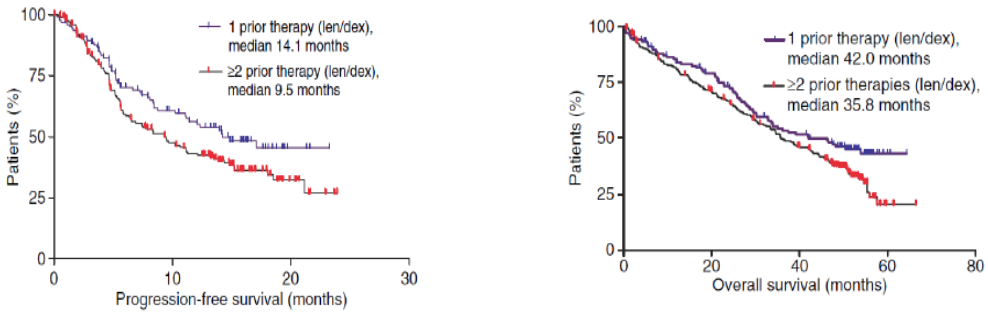
4.11 The manufacturer presented two subgroup analyses, using data from MM-009 and MM-010, which explored the effectiveness of lenalidomide plus dexamethasone after varying numbers of previous treatment. The first compared lenalidomide following one prior therapy with use following two or more prior therapies (Stadtmauer, 2009). The second looked at overall survival and progression free survival with lenalidomide use following one prior therapy only.

4.12 The manufacturer presented subgroup analyses of MM-009 and MM-010 that compared the efficacy of lenalidomide plus dexamethasone following one prior therapy with use following two or more prior therapies (Stadtmauer, 2009). This included 353 patients on lenalidomide plus dexamethasone, of whom 133 had received one prior therapy and 220 had received two or more prior therapies. Compared to those who had received two or more prior therapies, patients in the lenalidomide plus dexamethasone group who had received one prior therapy had statistically significantly longer:

- time to progression: 17.1 months versus 10.6 months [HR 0.68, 95% CI 0.48–0.97]; p=0.026
- progression free survival: median of 14.1 months versus 9.5 months [HR 0.71, 95% CI 0.2–0.99]; p=0.047 (Figure 3).
- overall survival from study enrolment: median overall survival of 42.0 versus 35.8 months; p=0.041 (Figure 3).

The manufacturer also stated that a pooled analysis by Dimopoulos et al showed that the type of previous therapy did not affect response rates to treatment with lenalidomide plus dexamethasone.

Figure 2 Kaplan-Meier curve progression free survival and overall survival, one prior therapy compared to two or more prior therapies



4.13 The manufacturer included a subset analysis of overall survival and progression free survival in those who had received one prior therapy only. This analysis did not included time to progression. In both MM-009 and MM-010, among patients who had one prior therapy only, median progression free survival was statistically significantly longer in the lenalidomide plus dexamethasone group compared with placebo plus dexamethasone (Table 5). For both MM-009 and MM-010, there were no statistically significant differences in median overall survival (Table 5).

Table 5: Progression free survival of second-line patients in studies MM-009 and MM-010

		Study MM-009		Study MM-010	
		Len/Dex	Dex	Len/Dex	Dex
PFS	N	68	67	56	57
	Died n (%)	37 (54.4)	48 (71.6)	31 (55.4)	48 (84.2)
	Median (months)	16.6	4.6	13.3	4.5
	[95% CI]	[11.0, 36.8]	[4.0, 5.7]	[5.1, 26.9]	[2.8, 5.6]
	Hazard ratio [95% CI]	0.30 [0.19, 0.47]		0.39 [0.24, 0.62]	
	Log-rank test p-value	<0.0001		<0.0001	
OS	Died n (%)	34 (50.0)	41 (61.2)	21 (37.5)	31 (54.4)
	Median (months)	50.1	37.6	NE	37.2
	[95% CI]	[8.3, 32.5]	[6.5, 21.5]	[34.3, NE]	[2.1, 23.5]
	Hazard ratio [95% CI]	0.70 [0.44, 1.10]		0.71 [0.41, 1.23]	
	Log-rank test p-value	0.1179		0.2175	

PFS, progression-free survival; CI, confidence interval; OS, overall survival; NE, not estimable.

Bortezomib

Clinical effectiveness and adverse events

4.14 The manufacturer presented data relating to the efficacy of bortezomib from 6 non randomised controlled trials. The most relevant was identified as the Taverna et al (2012) study, which was a retrospective survey of 42 patients across 26 centres in Switzerland. People included in the study had multiple myeloma that had responded to initial bortezomib therapy, but whose myeloma had subsequently progressed or relapsed, and who were then retreated with bortezomib (after a treatment-free interval). The study inclusion criteria specified that the initial treatment with bortezomib therapy had achieved complete response, near complete response or partial response, and that people had completed a retreatment regimen with bortezomib after relapse or disease progression. People had received a median of 2 prior therapies (range 1 to 11).

4.15 The 6 non- randomised controlled trials indicated:

- Response rates:
  - ◊ The response rate in the bortezomib trials ranged from 21% to 64.3%. Response to bortezomib was dependent upon initial response to bortezomib (a higher probability of response for patients who responded initially).
  - ◊ On the Taverna et al (2012) study bortezomib retreatment had a clinical benefit rate (complete response, (near) complete response and partial response and stable disease) of 83%.
  - ◊ In total, 85.7% of patients who attained complete response or near complete response with initial bortezomib treatment also attained complete response or near complete response with retreatment.
  - ◊ The median duration of response following bortezomib retreatment was 12.6 months (range 0–37.7 months), with 35% (95% CI 20.6–51.7) still responders at data cut-off.
- Treatment free interval:

  - ◊ Among the subgroup of patients with a first treatment free interval of >6 months, response rate to bortezomib retreatment was higher than in those with a first treatment free interval of ≤6 months (74.1% versus 46.7%; p=0.10).
- Progression free survival:
  - ◊ Median time to progression following bortezomib retreatment was 10.5 months (range 0.4–≥39.5 months).
- Overall survival:
  - ◊ Median overall survival from first diagnosis, after prior bortezomib and after bortezomib retreatment was 9.3, 3.5 and 1.7 years, respectively.
- Adverse events:
  - ◊ Bortezomib as retreatment was well tolerated, and the safety profile was consistent with previous studies of bortezomib in relapsed multiple myeloma. The most common adverse drug reactions attributed to bortezomib were nervous system disorders (including peripheral neuropathy) and blood/lymphatic system disorders.

Bendamustine

Clinical effectiveness

4.16 One retrospective study in France was identified that showed the clinical effectiveness of bendamustine, including people with relapsed or refractory multiple myeloma (n=110, Damaj et al (2012)). People in the study had received prior treatment with alkylators, steroids, IMiDs or bortezomib. Patients were participating in a compassionate use programme in which they received treatment with bendamustine. The aims of the study were to evaluate the response rate to bendamustine, the duration of response, progression free survival and overall survival. Response rates were assessed according to EBMT (European Society for Blood and Marrow Transplantation) criteria, overall survival was

calculated from the first dose of bendamustine and progression free survival included death from any cause or progression as events.

4.17 The Damaj et al (2012) study showed that following treatment with bendamustine, 33 patients (30%) had an overall response (≥PR); 22 patients (20%) had stable disease; and 55 patients (50%) did not respond. People with multiple myeloma that was refractory to treatment with lenalidomide or bortezomib plus thalidomide responded to treatment with bendamustine (30 (27%) refractory to lenalidomide, 33 (31%) refractory to thalidomide and bortezomib). After a median follow-up of 10 months, 49 patients who had received bendamustine had died following progression (or due to other causes related to myeloma) and 61 patients were still alive. At data cut-off, median duration of response had not been reached and 66% of patients responding to bendamustine therapy remained in response more than 6 months after initiation of bendamustine therapy. Following bendamustine treatment, median progression free survival was 9.3 months and median overall survival was 12.4 months.

ERG critique of clinical effectiveness

4.18 The ERG reviewed the literature review conducted by the manufacturer and concluded that overall, the searches presented were broadly suitable. The ERG reviewed the designs of MM-009 and MM-010 and concluded that they were high quality, the methodology used to assess the quality of the trials was adequate, and that the evidence submitted generally reflected the decision problem. However several issues were noted:

- Both trials were initiated in 2004, and since then management of multiple myeloma has undergone a lot of changes (specifically the introduction of novel agents such as bortezomib) and do not accurately reflect current clinical practice
- The mean age of patients in the clinical trials was substantially lower than of patients in clinical practice with multiple myeloma (63 rather than around 70)

- A significant proportion of patients had three or more prior stem cell transplants (based on expert clinical advice, the ERG expected this to be lower)
- The proportion of patients who received 2 or 3 prior therapies is higher than those who received one prior therapy only.

4.19 The ERG noted that there was no direct trial-based comparison between lenalidomide and the primary comparators, and the only evidence for comparator treatments was taken from non-randomised controlled trials. The ERG also commented that time to failure was not presented in the submission, despite this being an endpoint of MM-009 and MM-010.

4.20 The ERG identified a number of inconsistencies in the evidence presented. For example in the intention-to-treat analysis, the number of subjects considered in the progression free survival analysis (170 for lenalidomide plus dexamethasone, 171 for placebo plus dexamethasone) was different to those for time to progression (177 for lenalidomide plus dexamethasone, 176 for placebo plus dexamethasone), and for patient crossover, the manufacturer reported two different figures. Additionally, the TTP data were inconsistent when reported in weeks or months.

5 Comments from other consultees

5.1 Statements from a patient group supported the manufacturer's representation of the clinical pathway. That is, those not eligible for high-dose therapy and stem cell transplantation typically receive thalidomide, or bortezomib (if thalidomide is contraindicated or cannot be tolerated; approximately 20%). This is then followed by bortezomib (potentially retreatment) at second line.

5.2 The patient group highlighted that the population includes those who responded successfully to bortezomib, and therefore were likely to respond again, but also those who had not. The group commented that bortezomib retreatment would not be appropriate if it had been previously

ineffective, was contraindicated or could not be tolerated. The patient group emphasised that for these patient there were currently no treatment options on the NHS, as to be eligible for lenalidomide they needed to have a second relapse, but that they could obtain lenalidomide through the Cancer Drug Fund. The patient group commented that it was important to appraise lenalidomide in this setting, especially for those patients for whom retreatment with bortezomib is not appropriate.

5.3 The patient group commented on the advantages of lenalidomide. They stated that as an oral treatment, it was easy and convenient to use and did not need invasive procedures. They stated that this could also lead to NHS savings from reduced outpatient visits and staff time. They stated that there was also a benefit to patients, as it reduces the need for regular travel to hospital. Although they noted this was perceived as a disadvantage to some patients, because regular visits to the hospital gives confidence in the quality of care and ensures there is medical support available. Some patients also reported problems with committing to oral dosing schedules. Overall, however, the patient group concluded that the data was compelling and the potential advantages to patients significantly outweigh any disadvantages.

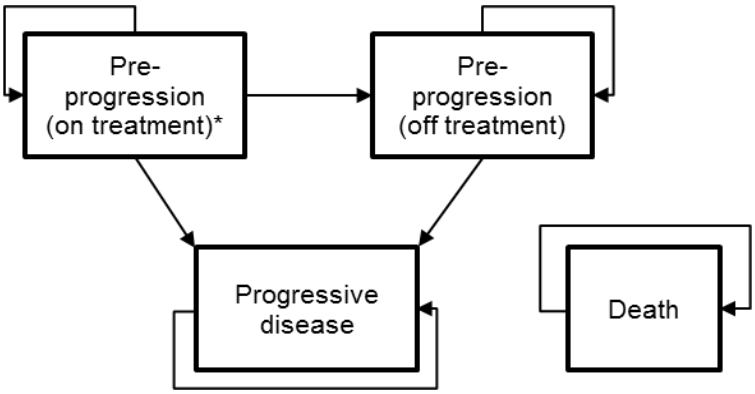
5.4 Finally the patient group noted that the decision problem defined that the population included those for whom thalidomide was not tolerated or is contraindicated. Thalidomide, like lenalidomide, is an immunomodulatory drug. Therefore, if thalidomide is contraindicated or cannot be tolerated, patients may have a similar response/reaction to lenalidomide.

6 Cost-effectiveness evidence

6.1 The cost-effectiveness evidence consisted of a systematic literature review and a de novo Markov model. The systematic review did not identify any relevant cost-effectiveness studies. The model compared lenalidomide with bortezomib for patients with multiple myeloma for whom thalidomide is contraindicated, and whose disease has progressed after at

least one prior therapy with bortezomib. The model had 3 health states: pre-progression (on treatment), pre-progression (off treatment), post-progression, and a death state (Figure 1). A lifetime time horizon (25 years) was used, the cycle length was 28 days, and discounting (3.5%) of costs and QALYs was included. The model took an NHS and PSS perspective. Patient access schemes available for bortezomib following one prior therapy and lenalidomide following two prior therapies were not included in the model base case.

Figure 3. Model structure



6.2 Patients enter the model having been treated with bortezomib at first-line, and receive second-line treatment with lenalidomide plus dexamethasone, or the comparator, for the duration of the pre-progression (on treatment) health state. The manufacturer used bortezomib retreatment as the base-case comparator. Alternative second line treatment options, including bendamustine and other chemotherapy agents, were explored in scenario analyses. The manufacturer's model also included third and fourth line treatments. The manufacturer developed a best supportive care mix for third and fourth line treatment (Table 6), the composition of which depended on previous treatments.

Table 6 Treatment mix used in the model for third and fourth line therapies

Drug	3rd-line therapy				4th-line therapy
	Len/Dex arm	Base case comparator arm	Following bortezomib	Other 2nd line comparator	All arms
Bortezomib				22.2%	
Dexamethasone	56.3%		31.3%	5.6%	
Melphalan	18.8%		10.4%	11.1%	20%
Cyclophosphamide	62.5%		34.7%	22.2%	20%
Cisplatin	12.5%		6.9%		
Doxorubicin	12.5%		6.9%		
Etoposide	31.3%		17.4%		
Prednisolone	6.3%		3.5%	11.1%	
Prednisone	6.3%		3.5%		
Lenalidomide		100.0%	44.4%	44.4%	60%

*Base case model assumes dexamethasone also given in combination; BSC, best supportive care; Columns sum to more than 100% as patients use more than one treatment

6.3 The transition probabilities in the model were based on the overall survival, progression free survival, and time to failure curves, and were derived as follows:

- **Lenalidomide:** The full MM-010 dataset was used to estimate progression free survival, time to failure and overall survival for lenalidomide (see section 6.4 for further details). These data were used to determine the transition between the health states, as follows:
  - ◊ Transition from ‘pre-progression on treatment’ to either pre-progression off treatment’ or ‘progressive disease’ was determined using progression free survival and time to failure
  - ◊ Transition from ‘pre-progression off treatment’ to ‘progressive disease’ was determined by progression free survival and time to failure
  - ◊ Transition from any health state to the death state was determined by overall survival.
- **Comparators:** Transitions on the comparator arm were modelled in a similar way to the lenalidomide arm. The overall survival, progression free survival and time to failure estimates for the comparators were derived by applying a hazard ratio to the MM-010 data. Progression free survival and overall survival estimates were

obtained from the literature (identified through systematic literature review). Hazard ratios for lenalidomide compared with each comparator were crudely approximated by comparing the median progression free survival or overall survival estimates between the studies of interest (Table 7). It was assumed that time to failure had the same hazard ratio as progression free survival. In the progressive disease health state, on the comparator arm, patients could receive lenalidomide as a third line treatment (such as in the base case). This impacted the transitions between the health states in that when the 3rd line treatment was lenalidomide, transition to the death state was based on the MM-010 trial overall survival data.

Table 7 Comparative efficacy estimates included in the model

Treatment	Variable	Evidence source	Hazard ratio (>1 favours lenalidomide)
Bortezomib retreatment	OS	Taverna 2012[45]	1.70
		White 2013[42]	1.42
	PFS	Taverna 2012	1.15
		White 2013	1.76
		Hrusovsky 2010[50]	1.09
		Dispenzieri 2010[80]	1.28
		Petrucci 2013[53]	1.26
		Min 2007[122]	0.84
Bendamustine (and chemotherapy agents)	OS	Damaj 2012[46]	3.00
	PFS	Damaj 2012	1.09

6.4 The manufacturer estimated overall survival and progression free survival from MM-010 rather that MM-009, because it had a European population, and stated that pooling the trials was not feasible because of breaking randomisation. Scenarios that used MM-009 data and pooled data were provided after clarification. The manufacturer presented six parametric distributions (exponential, Weibull, log-logistic, log-normal, Gompertz and gamma) for overall survival, progression free survival, and time to failure for lenalidomide plus dexamethasone. Log-logistic distribution was used in the model base case for progression free survival and time to failure, and

exponential piecewise was used for overall survival. The other distributions were considered in scenario analyses.

6.5 Overall survival and progression free survival associated with bortezomib retreatment was obtained from the Taverna (2012) study (see sections 4.14 and 4.15). Overall survival was adjusted for patient characteristics in the manufacturer's base case, however, progression free survival was not. A scenario that included progression free survival that was adjusted for patient characteristics was provided in response to clarification. Further sources of overall survival and progression free survival were used in scenario analyses (White 2013, Petrucci 2013, Hrusovsky 2010, Dispenzieri 2010, Min 2007). In addition, further comparators were explored in scenario analyses. Overall survival and progression free survival for bendamustine were derived from Damaj et all 2012 (see section 4.16). These values were also used for the other chemotherapies (melphalan, cyclophosphamide, doxorubicin and vincristine based regimens).

6.6 The manufacturer accounted for adverse events in the model. The adverse events included within the pre-progression health states of the manufacturer's model were taken from NICE Technology Appraisal 171 (Table 8).The event rates were estimated from MM-010 for lenalidomide plus dexamethasone and the VISTA trial for bortezomib. The melphalan and prednisolone arm of the VISTA trial was used to estimate the adverse event rates for all other chemotherapies. An average rate was estimated and applied to each model cycle. No adverse events were modelled in the post-progression health state, other than for patients in the comparator arm who receive lenalidomide plus dexamethasone as a third line treatment and then experience the associated adverse event rates.

Table 8 Adverse event rates applied in the economic analysis

Adverse event	Grade	Annual rate (cycle rate) Len/Dex	Bortezomib	Other comparators
Anaemia	3	8.3% (0.6%)	17.7% (1.3%)	26.2% (2.0%)
	4	0.5% (<0.1%)	3.0% (0.2%)	10.3% (0.8%)
Constipation	3	1.4% (0.1%)	0.7% (0.1%)	0.0% (0.0%)
	4	0.0% (0.0%)	0.0% (0.0%)	0.0% (0.0%)
Diarrhoea	3	2.3% (0.2%)	7.7% (0.6%)	0.8% (0.1%)
	4	0.0% (0.0%)	0.7% (0.1%)	0.0% (0.0%)
Deep vein thrombosis	3	3.2% (0.5%)	1.0% (0.1%)	0.8% (0.1%)
	4	0.5% (<0.1%)	0.0% (0.0%)	0.0% (0.0%)
Hypercalcaemia	3	0.5% (<0.1%)	0.0% (0.0%)	0.0% (0.0%)
	4	0.0% (0.0%)	0.0% (0.0%)	0.0% (0.0%)
Neutropenia	3	59.3% (4.4%)	34.0% (2.6%)	31.4% (2.4%)
	4	5.1% (0.4%)	11.3% (0.9%)	19.5% (1.5%)
Peripheral neuropathy	3	1.4% (0.1%)	14.3% (1.1%)	0.0% (0.0%)
	4	0.0% (0.0%)	0.3% (<0.1%)	0.0% (0.0%)
Pneumonia	3	4.6% (0.4%)	5.3% (0.4%)	5.2% (0.4%)
	4	0.5% (<0.1%)	2.0% (0.2%)	1.6% (0.1%)
Thrombocytopenia	3	11.0% (0.8%)	22.7% (1.7%)	21.8% (1.7%)
	4	1.4% (0.1%)	19.4% (1.5%)	18.7% (1.4%)

6.7 The manufacturer used utility values from the literature to estimate QALYs (Table 9). Health related quality of life data were not collected in the MM-009 and MM-010 clinical trials. Instead, the manufacturer identified health related quality of life studies from the literature. Of the 8 studies identified only 2 (Khanna 2006 (SF-36, USA), van Agthoven 2004 (EQ-5D, Netherlands)) were primary studies, the other 6 reported utility values from the van Agthoven study. The manufacturer used utility values from the van Agthoven study in the model. The pre-progression utility value was 0.81, which decreased after 2 years to 0.77. The post-progression utility value was 0.64. Utility values were adjusted for age, based upon published UK EQ-5D values. The manufacturer also included adverse event utility decrements to each model cycle. These were applied in the pre-progression health state for all treatments, or post-progression for patients receiving lenalidomide plus dexamethasone third-line. The utility decrements for each treatment per model cycle were 0.013 for lenalidomide plus dexamethasone, 0.033 for bortezomib, and 0.025 for bendamustine or chemotherapy agents.

Table 9 Summary of quality-of-life values for cost-effectiveness analysis

Variable	Value	Justification
Utility value: pre-progression	0.810	van Agthoven et al, 2004
Utility value: pre-progression after 2 years	0.770	
Utility value: post-progression	0.640	
Utility decrement associated with:		
Anaemia	0.310	Only decrement obtained through systematic search. Brown et al, 2013
Hypercalcaemia	0.000	
Pneumonia	0.190	
Thrombocytopenia	0.310	
Neutropenia	0.145	
Diarrhoea	0.000	
Constipation	0.000	
Peripheral neuropathy	0.065	Only decrement obtained through systematic search. Coffey et al, 2002[132]
Deep vein thrombosis	0.150	Only decrement obtained through systematic search. Brown et al, 2013

CI, confidence interval.
* Standard error 10% of the mean; ** Standard error 20% of the mean.

6.8 The manufacturer's model included treatment costs, resource use costs, and costs associated with adverse events. Treatment acquisition costs were obtained from the department of Health Electronic Market Information Tool (eMIT) or the BNF. The cost of lenalidomide included dose reductions and interruptions, based on those observed on MM-010. Bortezomib has a patient access scheme, whereby there is a rebate for patients who do not respond to treatment. This was not accounted for in the manufacturers base case, however, a scenario analysis was presented that assumed an overall discount of 15%. The adverse event costs included in the model were a weighted average of adverse events, the costs of which were based on where each adverse event was treated (inpatient, hospital day case, outpatient, and general practice; see Table 8 for adverse event proportions). The unit cost of treatment in primary care was that of a GP visit. Other costs were obtained from NHS reference costs.

Table 10 List of health states and associated costs in the economic model

Health states		Lenalidomide arm (cost per cycle)	Base case comparator arm, bortezomib (cost per cycle)
Pre-progression (typically on treatment)	Technology	Len: £3,773 Dex (cycles 1-4): £7.76 Dex (cycles 5+): £2.59	£4,067.30
	Concomitant G-CSF and administration	£473.62	n/a
	Monitoring and tests	£153.34	
	Administration	£161.85 (first cycle only)	£1,065.76
	Transport	£6.39 (first cycle only)	£17.04
	Adverse events	£17.11	£29.26
	Additional monitoring for lenalidomide (annual rate)	£824.26	n/a
Post-progression	3rd line treatment	£70.20 IV administration: £69.63 Transport: £3.06 Duration: maximum 4 cycles (17.2 weeks)	£3,772.88 IV administration: £0.00 Transport: £0.00 Duration: Lenalidomide PFS from MM-010
	4th line treatment	Therapy: £2,277.28 IV administration: £0.00 Transport : £0.00 Duration: maximum 4 cycles (16.8 weeks)	
	Monitoring and tests	£175.86	
	Adverse events	£0.00	£17.11
	Terminal care	£1,235 on death	
Alternative 3rd line treatment scenarios	Treatment mix after bortezomib 2nd line	n/a	Drug cost £1,716.99 IV administration: £49.45 Transport: £2.20
	Treatment mix after other 2nd line comparators	n/a	£2,592.00 IV administration: £203.00 Transport: £3.25

Results of the economic analyses

6.9 The manufacturer presented their initial results in the manufacturer's submission. During clarification, however, the ERG noted a number of issues with the manufacturer's initial base case modelling and consequently two rounds of clarification were undertaken and further revised analyses and results were presented by the manufacturer (the analyses are termed as follows: Initial modelling (base case), modelling after clarification 1 (base case A) and modelling after clarification 2 (base case B)). Each set of analyses is presented below.

Manufacturer's initial analyses and results

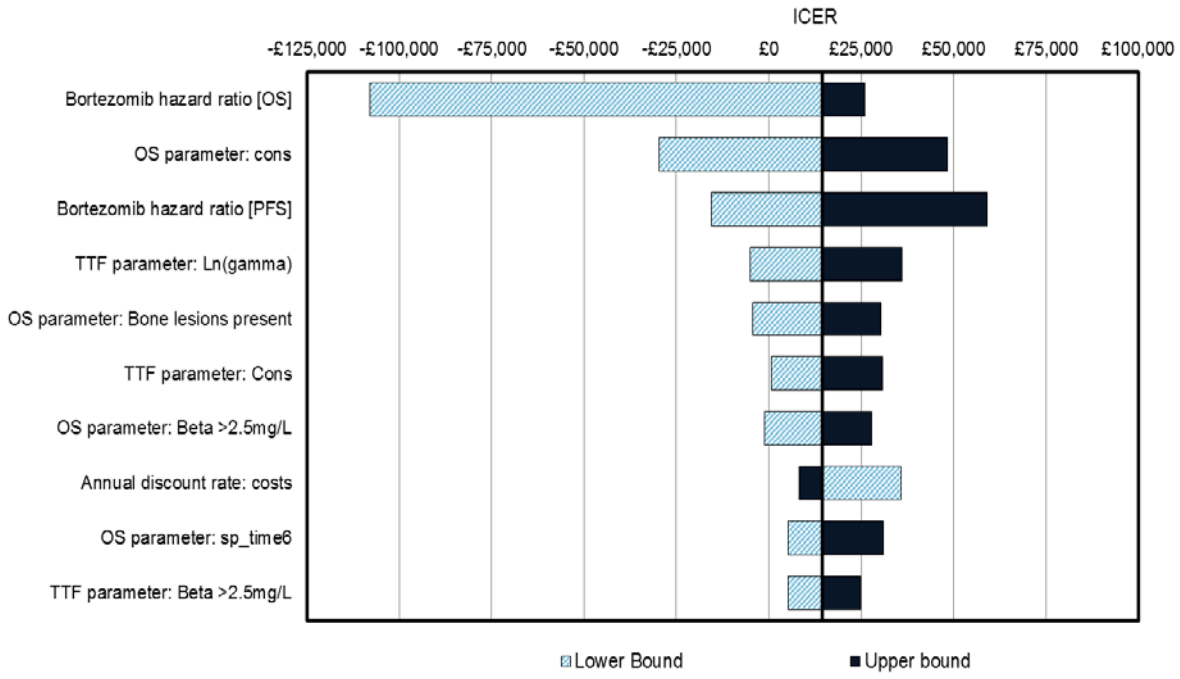
6.10 The manufacturer presented a base case deterministic ICER, comparing lenalidomide plus dexamethasone with bortezomib retreatment, of £14,535 per QALY gained (incremental costs £7682, incremental QALYs 0.53), and a mean probabilistic ICER of £13,930 per QALY gained (Table 11). The probability of lenalidomide being cost effective at £20,000 and £30,000 per QALY gained were 58.6% and 73.1% respectively (Figure 3). The manufacturer's deterministic sensitivity analysis showed that the ICER was most sensitive to the bortezomib hazard ratio for overall survival, with a range of ICERs for lenalidomide compared with bortezomib from -£107,892 to £26,121 per QALY gained (Figure 3). Other model drivers included which overall survival and time to treatment failure models were applied.

Table 11: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Base case							
Bortezomib	113,740	5.03	2.89	7,682	0.71	0.53	14,535
Lenalidomide	121,422	5.74	3.42				
Probabilistic sensitivity analysis							
Bortezomib	NS	NS	NS	7,123	NS	0.51	13,930
Lenalidomide	NS	NS	NS				

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NS: Not stated

Figure 4 Tornado diagram – top 10 parameters in terms of ICER sensitivity (base case)



6.11 The manufacturer presented several scenario analyses, including exploring the time horizon, comparator, lenalidomide efficacy, comparator efficacy and variance in bortezomib patient access scheme (Table 12). The ICERs ranged from lenalidomide dominating to £80,180.

Table 12 Scenario Analyses (base case)

Parameter	Base Case	Scenario analysis	ICER
Base case			£14,535
Time horizon	25 years	5 years	Len dominates
		10 years	Len dominates
		15 years	£4,336
		20 years	£10,736
Choice of comparator	Bortezomib retreatment	Bortezomib retreatment/dex	£14,444
		Bendamustine/prednisolone	£80,108
		Bendamustine/dexamethasone	£55,621
		Melphalan/prednisone	£60,246
		High-dose cyclophosphamide/dex	£67,660
		Low-dose cyclophosphamide/dex	£64,345
		Doxorubicin	£66,895
		Vincristine	£64,332
Comparator	Bortezomib retreatment	Blended comparator by market share	£32,462
The use of Len/Dex at third line	100% len	As per historical best supportive care (i.e. less than100% len)	£38,330
Include dex with 3rd and 4th line treatments where applicable	Yes	No	£14,533
Parameter used to model treatment discontinuation	TTF	PFS	£29,077
Curve fit for OS	Piecewise exponential	Weibull (time horizon set to 38 years)	Len dominates
Curve fit for PFS	Log-logistic multivariable	Log-normal multivariable	£14,667
Curve fit for TTF	Log-logistic multivariable	Log-normal multivariable	£56,145
Curve fit for PFS and TTF	Log-logistic multivariable	Log-normal multivariable	£56,274
Comparative efficacy of bortezomib	OS from Taverna (2012)	OS from White (2013)	£3,905
	PFS from Taverna (2012)	PFS from Petrucci (2013)	£21,053
		PFS from Hrusovsky (2010)	£10,743
		PFS from Dispenzieri (2010)	£22,288
		PFS from Min (2007)	Len dominates
		PFS from White (2013)	£43,331
Bortezomib patient access scheme	Not included	15% discount at 2nd line applied for all bortezomib 2nd line patients	£27,898
		15% price discount applied for 55% of bortezomib 2nd line patients	£21,885

Dex: dexamethasone; Len: lenalidomide

Manufacturers revised analyses after clarification round 1

6.12 In the manufacturers submission, the bortezomib progression free survival derived from Taverna (2012) was not adjusted for patient characteristics (see section 6.3), and therefore in response to the first clarification, the manufacturer adjusted the bortezomib hazard ratio. Adjusting for patient characteristics reduced the hazard ratio from 1.15 to 0.9; now favouring bortezomib. This resulted in a gain in QALYs and reduction in total costs for lenalidomide. The new base case ICER (referred to from this point as revised base case A) was dominant in favour of lenalidomide plus dexamethasone. The manufacturer explained this counterintuitive result by explaining that people receiving bortezomib had a longer progression free survival, but shorter overall survival than those receiving lenalidomide plus dexamethasone. The manufacturer stated that this could be due to the nature of re-treatment. That is, they have previously responded to bortezomib and so are likely to have a response again, and therefore have a good progression free survival response, but that because they have been exposed to bortezomib treatment before, the progression free survival benefit may not translate to an overall survival benefit.

6.13 In response to the first clarification, the manufacturer explored the impact of using MM-009 data only, or combining the results of MM-009 and MM-010 by using mean outcomes weighted by mean number of patients in the trials (the ERG asked for data that was pooled, however the manufacturer stated that it was not possible to do this due to breaking randomisation). The manufacturer presented ICERs of £12,567 (MM-009 only) and £3,122 (combined trial results) per QALY gained. The results presented include the updated progression free survival hazard ratio adjusted for bortezomib characteristics (an overall survival hazard ratio of 1.7 and progression free survival hazard ratio of 1.35)).

6.14 In response to the first clarification, the manufacturer presented several updated scenario analyses of base case A. These included the scenarios presented in the original analyses as well as different curve fits, using trial data from patients who has one prior therapy only and using MM-009 rather than MM-010 for lenalidomide clinical effectiveness estimates. The ICERs for lenalidomide plus dexamethasone compared with bortezomib retreatment ranged from lenalidomide dominating, to an ICER of £43,331 per QALY gained. The highest ICER was £67,660 per QALY gained for lenalidomide plus dexamethasone compared with high-dose cyclophosphamide plus dexamethasone. The mean probabilistic results showed that lenalidomide plus dexamethasone dominated bortezomib retreatment with a probability of cost effectiveness at £20,000 and £30,000 per QALY gained of 74.5% and 85%, respectively.

Manufacturers revised analyses after clarification round 2

6.15 Following the response to the first clarification, the ERG identified a number of further issues and therefore initiated a second round of clarification. The ERG highlighted that the progression free survival and overall survival curves crossed in the manufacturers model, which would result in more people in progression free survival than still alive in the model. The manufacturer's model used a 'min' function to correct for this, such that the minimum value (between overall survival and progression free survival) was used when overall survival was greater than progression free survival (i.e. progression free survival = overall survival; all those alive would be in progression free survival). The manufacturer subsequently changed the curve fitting for overall survival of lenalidomide, and removed the min function from the model. In the base case model a piecewise exponential curve was fitted to overall survival, and log-logistic curves fitted to progression free survival and time to failure. To prevent the curves crossing, the manufacturer changed the fitted overall survival curve to log-logistic.

6.16 In response to the second clarification, the manufacturer presented a revised base case (from this point referred to as revised base case B) that:

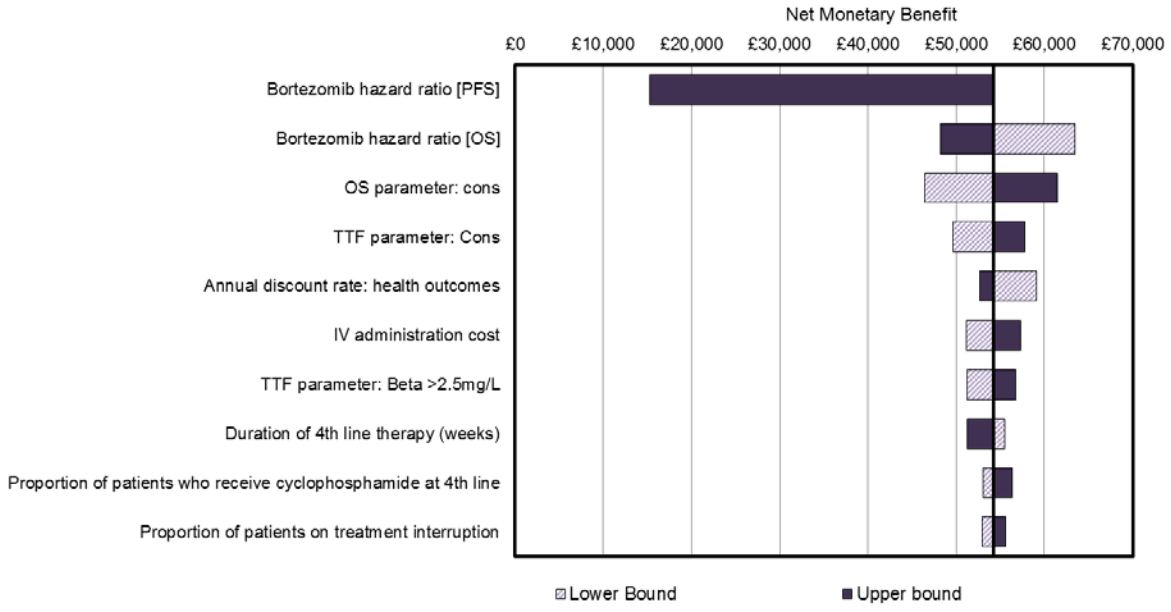
- corrected an inconsistency in the intervention and comparator arm in the patient flow sheets
- used the log-logistic curve for overall survival, progression free survival and time to failure for the intervention arm, to prevent the curves from crossing
- removed the use of the minimum function (previously used to ensure modelled progression free survival was never higher than overall survival) where possible to minimise potential issues with patient flow calculations
- used a progression free survival hazard ratio for bortezomib that was adjusted for patient characteristics, as in base case A, (0.9 in favour of bortezomib; see section 6.12)

6.17 The revised probabilistic and deterministic base case results (Table 13) showed that lenalidomide plus dexamethasone dominated bortezomib plus dexamethasone. The probability of cost-effectiveness was 100% at a threshold of £20,000 per QALY gained. The manufacturer performed one way sensitivity analyses (Figure 7), using net monetary benefit (assuming a maximum acceptable ICER of £30,000 per QALY gained), because of negative ICERs. The results were most sensitive to the bortezomib hazard ratios for PFS.

Table 13 Model outputs by clinical outcomes base case B

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Updated base case							
Bortezomib	131,111	6.50	3.45	-38,337	1.07	0.53	Lenalidomide dominates
Lenalidomide	92,774	7.56	3.98				
Probabilistic sensitivity analysis							
Bortezomib	NS	NS	NS	-37,584	NS	0.53	Lenalidomide dominates
Lenalidomide	NS	NS	NS				
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NS: Not stated							

Figure 5 Deterministic sensitivity analysis base case B



6.18 The manufacturer conducted several scenario analyses, as detailed in Table 14. Lenalidomide plus dexamethasone dominated bortezomib plus dexamethasone in the following scenarios in the revised base case B:

- Reducing the time horizon
- Including dexamethasone in 3rd and 4th line treatments
- Parameter used to model treatment failure (time to treatment failure or progression free survival)

- Source for comparative efficacy of bortezomib
- Including the bortezomib patient access scheme

The following scenarios increased the ICER:

- Enabling a mixture of 3rd line treatments on the comparator arm, rather than just lenalidomide (essentially reducing lenalidomide use from 100% to 44% at 3rd line) increased the ICER to £26,665 per QALY gained.

When lenalidomide was compared with bendamustine or other chemotherapies, the ICER increased up to £36,718 per QALY gained.

Table 14 Scenario analyses following clarification round 2 (base case B)

Parameter	Base Case Setting	Scenario Setting	ICER
Base case	N/A	N/A	Len Dominates
Time horizon	25 years	5 years	Len Dominates
		10 years	Len Dominates
		15 years	Len Dominates
		20 years	Len Dominates
Type of comparison			
Use of 3rd line lenalidomide	100% len	As per historical BSC (<100% len)	£26,665
Choice of comparator	Bortezomib retreatment	Bortezomib retreatment + dex	Len Dominates
		Bendamustine + dex	£23,435
		Bendamustine + presnisolone	£23,424
		Melphalan + prednisone	£28,516
		HD Cyclophosphamide + LD-dex	£36,718
		LD Cyclophosphamide + MD-dex	£33,088
		Doxorubicin	£35,836
		Vincristine	£33,013
Include dexamethasone with 3rd and 4th line treatments	Yes	No	Len Dominates
Varying modelling of lenalidomide efficacy			
Parameter used to model treatment failure	Time to treatment failure	Progression-free survival	Len dominates
Varying treatment efficacy assumptions			
Comparative efficacy of bortezomib	Overall survival from Taverna 2012	White 2013	Len Dominates
	Progression free survival from Taverna 2012	Petrucci 2013	Len Dominates
		Hrusovsky 2010	Len Dominates
		Dispenzieri 2010	Len Dominates
		White 2013	Len Dominates
Varying cost assumptions			
Bortezomib PAS	Not included	15% discount received by all patients	Len Dominates
		15% discount received by 55% of patients	Len Dominates
Using clinical inputs for the second-line population			
Source of lenalidomide data for clinical inputs in second line population	All patients in MM-009	Second-line population only	Len Dominates
Varying source of data			
Source of lenalidomide data for base case	MM-009	MM-010	Len Dominates
Source of lenalidomide data for clinical inputs in second line population	MM-009	MM-010	Len Dominates
Varying curve fits			
Results with non-crossing parametric curve fits	Log-logistic	Gompertz	Len Dominates
		Gamma	Len Dominates
Varying subsequent treatment options			
Subsequent treatment options	Third and fourth line therapy included	No subsequent treatment modelled	Len Dominates

ERG critique of cost effectiveness

6.19 The ERG stated that the search terms and databases in the systematic literature review used were appropriate.

6.20 The ERG reviewed the manufacturer's approach to the de novo model and highlighted a number of important logical errors in the original model. A number of these issues were not resolved following the two rounds of clarification.

Model structure.

6.21 The ERG noted that there were differences between how the 3rd and 4th line treatment of the intervention and the comparator arms in the manufacturer's model were modelled (Figure 6), as follows:

- In the intervention arm, when 3rd and 4th line treatments were modelled, only the costs of the treatments are included. However, in the comparator arm, when lenalidomide was included as a 3rd line treatment, as well as the treatment costs, the cost of adverse events were included. In addition, disutility of adverse events was incurred, and efficacy (in terms of overall survival) was changed to being that of lenalidomide (that is, determined from the MM-010 trial).
- The time period of 3rd line treatment was different between the intervention and the compactor arm. On the intervention arm it was fixed duration. On the comparator arm, when lenalidomide was a 3rd line treatment the duration of treatment was derived from MM-010 progression free survival.

6.22 The ERG reviewed the transition from the 'progression-free (on treatment)' health state to the 'progression-free (off treatment)' and 'progressive disease' health states.

- In both the lenalidomide and comparator arm, following the end of the 'progression-free (on treatment)' health state, patients immediately move on to receive third line treatment when in the

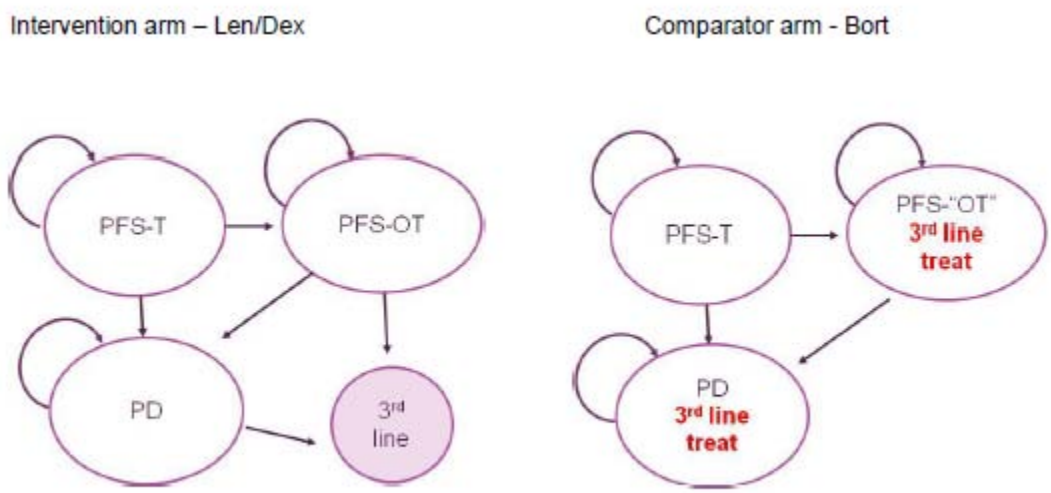
'progression-free (off treatment)' and 'progressive disease' health state. Patients immediately begin to accrue the costs associated with subsequent lines of treatment, without a treatment break.

- In the comparator arm, following the end of the progression-free (on treatment) health state, in addition to accruing the costs associated with third line treatment, patients also accrue the mortality benefit associated with lenalidomide.

Expert clinical opinion sought by the ERG was that these scenarios were not clinically plausible. In clinical practice, patients experience a treatment break following the end of the 'progression-free survival (on treatment) health state', and, following the start of a subsequent treatment line of treatment, there would be 4-6 months before any mortality benefit of subsequent treatments would be seen.

6.23 The ERG noted further issues with the way the 3rd and 4th line treatments were modelled. The ERG commented that the manufacturer's current treatment pathway (Figure 1) was not consistent with the 3rd and 4th line treatments included in the model (Table 5), and a number of the treatments included in the model were no longer routinely used in clinical practice. The ERG questioned whether 3rd or 4th treatment lines would be used in clinical practice. The ERG also noted that it was predominantly only cost data that was included at the 3rd and 4th line treatments (with the exception of lenalidomide), and therefore questioned whether these treatment lines should be included in the model.

Figure 6 ERG presentation of the manufacturer's model



6.24 The ERG noted that in the 'progressive disease' health state in the model, patients incur the progressive disease utility for all of the time in the health state. However, whilst in the progressive disease health state, patients can receive 3rd and 4th line treatments which, in clinical practice, could result in a progression free state and therefore an improvement in health and an increase in utility. The ERG noted that this clinical benefit is not captured in the model as they remain in the 'progressive disease' health state with no utility change.

Data extrapolation.

6.25 The manufacturer extrapolated progression free survival, time to progression and overall survival data from MM-010 using the mean of covariates method. The ERG noted that the mean of covariates method may skew the results, and stated that alternative approaches could have been used to adjust for baseline characteristics. Further, the ERG stated that it was not clear why each of the covariates had been chosen as some, such as ECOG score of 1, were not statistically significant predictors. The ERG stated that it was not clear if all potential predictors were included in the model (number of prior therapies was not included), and that pre-selection may have biased the model.

6.26 The ERG commented that overall survival with lenalidomide was likely to have been overestimated in the model. The ERG noted that after approximately 25 years, 11% of patients were still alive. The ERG commented that given patients enter the model at 63 years old, this indicated that approximately 11% of patients would live beyond the age of 88 years.

Comparative efficacy.

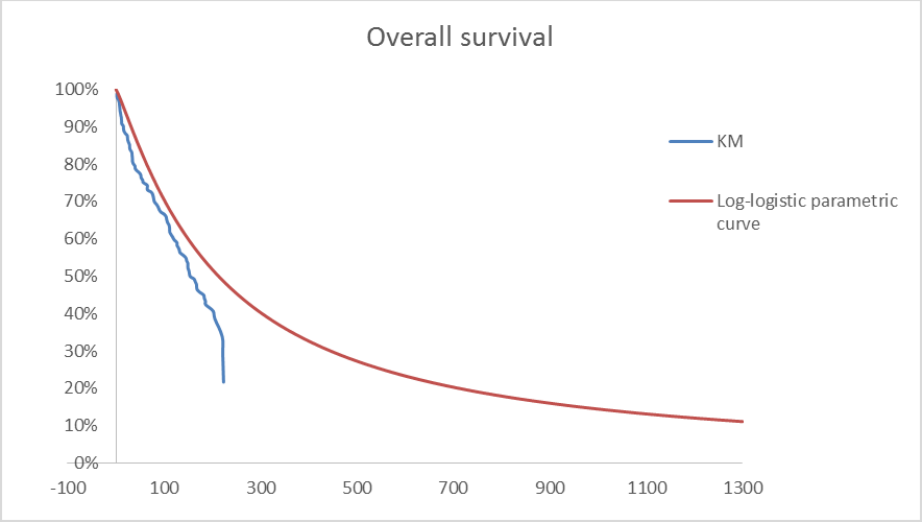
6.27 The ERG commented on the manufacturer's updated progression free survival hazard ratio for bortezomib, which had changed from 1.15 (favouring lenalidomide, in the original analyses) to 0.9 (favouring bortezomib in base case B (see section 6.12)). The ERG noted that despite this favouring bortezomib, following this change, lenalidomide dominated bortezomib (from the original base case ICER of approximately £14,500). The ERGs clinical experts advised that this progression free survival hazard ratio in favour of bortezomib was not likely to be clinically plausible, as in clinical practice patients receiving bortezomib retreatment would be expected to progress more quickly than those receiving lenalidomide.

Curves crossing

6.28 The ERG considered the manufacturer's approach to crossing curves. The manufacturer had used the 'min' function in Excel in the initial base case analyses to ensure the curves did not cross. However, the ERG commented that this does not solve the fundamental issue that the survival curves informing the Markov transition probabilities crossed. The ERG noted that the manufacturer had changed the choice of extrapolation for overall survival from exponential to log-logistic for base case B. However, the ERG commented that curve fit should be selected based on the best fit to the actual survival data and the long term natural history of the disease, rather than to prevent curves crossing. Figure 9 shows the ERG reproduced Kaplan-Meier plot and fitted log-logistic curve for overall

over 25 years, which showed a poor fit. The ERG also noted that the curves still cross in the comparator arm of the model in base case B.

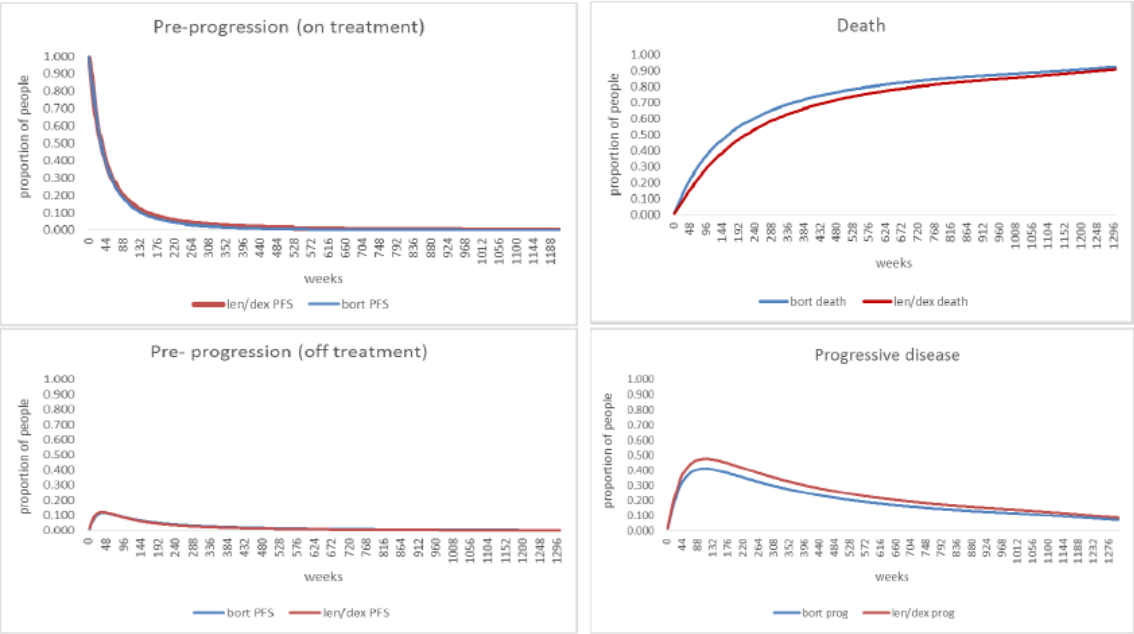
Figure 7 Kaplan-Meier and fitted log-logistic survival curve for overall survival



Cohort distribution

6.29 The ERG found conceptual and mathematical mistakes in the manufacturer's model. For example, the manufacturer's hazard ratio for the relative effectiveness of bortezomib was 0.9 (favouring bortezomib), however, the Markov traces show that in the model people receiving lenalidomide remain in the pre-progression health state for longer than those who received bortezomib (Figure 10).

Figure 8 Markov traces from manufacturer's original submission



Drug costs:

6.30 The ERG noted several issues related to cost inputs:

- Concomitant dexamethasone was not included in the initial base case, base case A or base case B
- The ERG could not trace back the calculations used to estimate the costs of bortezomib per cycle.
- The manufacturer's model assumed that patients remain on bortezomib retreatment until progression or treatment failure. However, the ERGs clinical experts suggested that bortezomib is given for a fixed number of cycles (usually 8). Fixing bortezomib retreatment duration to only 8 cycles significantly increased the ICER of lenalidomide compared with bortezomib (see section 6.30).
- The manufacturer assumed transport costs for the administration of bortezomib for 50% of patients, however, the ERGs clinical expert suggested that this would be significantly lower than 50% and the frequency would be less than that assumed in the model.

- The ERG noted the disease monitoring cost calculation for lenalidomide was not clear, particularly which costs were attributed to which state (that is, progression or progression free).

Health related quality of life

6.31 The ERG noted that patients in the progression-free survival state have a utility value of 0.81, which is higher than would be expected for a healthy member for the UK population at the same age (expected to be 0.8). The ERG also noted mathematical mistakes in the estimation of the pre-progressive state QALYs.

6.32 The ERG noted that while on 3rd and 4th line treatment, patients are assumed to always be in the progressive disease state and incur the associated utility (0.64). Patients cannot benefit from treatment in that they cannot move into progression free survival and incur a higher utility value.

Critique of results and sensitivity analysis

6.33 The ERG noted fundamental methodological issues with the economic model, including issues with the model structure (including asymmetry of the intervention and comparator arms), data extrapolation (including crossing curves), clinical plausibility of several of the inputs, issues with cost data and issues with the values for health related quality of life. The ERG presented updated analyses for lenalidomide plus dexamethasone compared with bortezomib plus dexamethasone in second line patients only (Table 15), that is, the costs and effectiveness of subsequent treatments were not included in the analysis. It was assumed that 65% of people receiving bortezomib also received dexamethasone. However, given the structural and methodological concerns raised, the ERG stated that these results should be interpreted with caution. In the ERG's analysis for second line therapy only (that is, third and fourth line treatments are not modelled), lenalidomide plus dexamethasone dominated bortezomib plus dexamethasone. The ERG presented some further scenarios (based on the manufacturer's base case B model) in

which an error in the manufacturers model regarding the allocation of patients to the different health states was amended, the bortezomib treatment duration was fixed to 8 cycles, and an adverse events disutility mistake was corrected. The ICER that incorporated all these changes was £54,369 per QALY gained for lenalidomide plus dexamethasone compared with bortezomib.

Table 15 Results of the ERG analyses using corrections to the model

Cost-effectiveness results per patient	Len/Dex	Bort	Incremental value (1-2)
Base Case – second-line only			
Total costs £	£85,546	£86,432	£-885
QALYs	3.98	2.49	1.48
ICER			Len dominates
Allocation of patients to model cycles correction			
Total costs £	£120,268	£158,420	£-3,8152
QALYs	4.09	2.66	1.42
ICER (compared with ERG base case)			Len dominates
ICER with all changes incorporated (cumulative)			Len dominates
Duration of Bort treatment correction			
Total costs £	£85,546	£42,839	£42,707
QALYs	3.98	2.50	1.48
ICER (compared with ERG base case)			£28,789
ICER with all changes incorporated (cumulative)			£54,535
AE disutility correction			
Total costs £	£85,546	£86,432	£-885
QALYs	3.98	2.49	1.48
ICER (compared with ERG base case)			Len dominates
ICER with all changes incorporated (cumulative)			£54,369

7 Equality issues

7.1 No potential equality issues have been identified

8 Innovation

8.1 No innovation statements have been provided.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Improving outcomes in Haematological Cancer. NICE Cancer Service Guidance (2003).
- Bortezomib monotherapy for relapsed multiple myeloma. NICE technology appraisal guidance 129 (2007).
- Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. NICE technology appraisal guidance 171 (2009)
- Bortezomib and thalidomide for the first-line treatment of multiple myeloma. NICE technology appraisal guidance 228 (2011).

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Multiple myeloma. NICE clinical guideline. Publication date to be confirmed.

Appendix B: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000717/WC500056018.pdf