Single technology appraisal (STA)

Lenalidomide for multiple myeloma in people who have received at least one prior therapy

Celgene Comments on the Appraisal Consultation Document (ACD)

As invited in the letter dated 21 October 2008, we are pleased to offer these comments on the above appraisal consultation document (ACD). As requested, our comments will be organized under the four general headings and our comments on the issues raised in the Evaluation Report are attached as an appendix to this response.

Referring to paragraph 4.2 of the ACD and highlighting the appraisal committee's note of the importance that patients, their carers and physicians place on having effective options to treat multiple myeloma, we have focused our responses to the ACD on patients who have ***received at least two prior therapies*** as there are more limited treatment options available to patients and physicians at this stage of the disease. Thus, we are not responding to comments regarding lenalidomide treatment in patients with only one prior therapy. Thus we are not responding to the suggestion that bortezomib is frequently used in combination with dexamethasone and this combination should be examined (page 15 in the Evaluation Report and page 13 (4.3) of the ACD). We are not including a comparison with this combination because it is not a licensed use of either drug, there is insufficient evidence on its efficacy, and it is not recommended by NICE.

Thank you for the opportunity to respond to the ACD. Herewith are our remarks.

i) Do you consider that all of the relevant evidence has been taken into account?

We believe that the appraisal considered all of the relevant evidence for the use of lenalidomide in previously treated multiple myeloma that was available at the time of the appraisal. We pointed out in our original submission that the MM-009/010 trials are ongoing and continue to mature. Most importantly, we highlighted in our original submission that the median overall survival (OS) with lenalidomide/dexamethasone (Len/dex) had not yet been reached, as <50% of patients in the Len/dex arm had died at the time of the most recent data analysis and that as the data mature it is possible that the median OS with Len/dex will increase further.

We will be adding a number of additional references in support of our comments below, but these do not constitute new evidence.

ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?

We agree with the summarisation of the clinical evidence and are pleased that the committee recognises the clinical value of lenalidomide in managing patients with previously treated multiple myeloma. We thank the committee for commenting that the general structure of the submitted model was reasonable. However, we do not agree with the committee's determination that the use of lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy is not cost effective use of NHS resources and we present our views below. As noted above, we will focus on multiple myeloma patients who have received two prior therapies and encourage the committee to recommend lenalidomide for patients who have received at least two prior therapies because there are few effective treatment options at this stage of the disease and lenalidomide offers a significant and cost-effective extension in patients survival beyond that offered by the current treatment options.

iii) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

As indicated in response to item 2 above, we do not agree with the committee's findings on the economic value of lenalidomide. The Evidence Review Groups (ERG) Evaluation Report recommended changes in the cost effectiveness (CE) model. The ERGs key recommendations and comments include (from section 4.9 of the ACD) those listed below. We respond to each of the issues as presented in the ACD.

1. Recalibration of the Len/dex survival to more closely reflect the publication (we accept this suggested change) – thus, decreasing Len/dex survival. The new analysis below uses the ERGs recommended recalibration in the Len/dex group.
2. Recalibration of the Dex survival using the mean MRC data (4.9 and 3.16). We do not agree with this approach (see details in the attached supporting response to ERG) because the resulting curve is less representative of the published curves (Dimopoulos et al. 2007; Weber et al. 2007) than our calculation. Figure 6 in the ERG report illustrates the problem of calibrating to the mean. It departs more from the target curve in the publication than the analyses we submitted using the median. Thus we have not accepted this recalibration in our reanalyses. We believe that using the mean places more emphasis on the tail of distribution where there are fewer patients and greater uncertainty. We point out in our response to the ERG report that the calibration is to help adjust for the cross-over effect and we believe that using the mean delays that correction and in doing so results in a less robust correction.

3. The submitted model results in higher overall survival with lenalidomide compared to the publications (Dimopoulos et al. 2007 and Weber et al. 2007). We investigated our model and can report the following details possibly contributing to the differences:
    a. Exclusion of non-evaluable patients from the model – we do not have sufficient data on these patients for response or TTP. The publications reported only overall survival (not post progression survival) and the non evaluable patients were included. Overall survival is the only efficacy data we have for these patients. Thus, it is problematic to include them in the model. The trial publications do not include these patients in the TTP calculations.

    b. Pooling all patients to ensure similar populations for each treatment. To ensure that identical patients were simulated on each treatment, the model selects individual patients from a population composed of all the evaluable patients from both trials, regardless of treatment to which they were randomised. Each patient is then modeled under each treatment option. This variance reduction technique not only reduces the sample size required to achieve stable results, it also removes any residual confounding present in the trial data. Randomization in clinical trials reduces differences across the groups and makes it possible to carry out unbiased comparisons of the average results. The inevitable differences between the groups, however, can become a problem when individuals are simulated over longer periods of time and the full extent of their course is used in computing the consequences of treatment. The pooling removes this problem but means that predictions will differ somewhat from the raw observed trial data.

    c. Data cuts differ from the published trials. The model includes data available at the time of its design (2005). The trials have continued to report findings and the publications used data from 2006. Since then more data have been reported. More patients have died, but the median overall survival has still not been reached for the Len/dex arm. The published plotted KM curves represent censoring and underestimate survival, particularly in the later portions of the curve.
4. The ERG CE results for the subgroups with two prior therapies were greater than £40,000/QALY (section 4.11). A reanalysis of these subgroups (new base case) is presented below incorporating the ERG recommended change in Len/dex survival, but not the use of mean instead of median (see details in our ERG response document and point 2 above). The cross-over impact observed in the clinical trials on the Dex survival was addressed by adjusting the post-progression survival of this group based on the median overall survival derived from the MRC data, rather than using the mean. (See point 2 above.)
5. Other identified issues (4.12) with the model base case are examined in sensitivity analyses presented below.

a. Adverse event (AE) costs not fully included. The submitted model included costs of grade 3 and 4 adverse events according to location of care (hospital/physician surgery etc) and long term management. Included were anaemia, thrombocytopenia, neutropenia, hypercalcaemia, pneumonia, neuropathy, and deep vein thrombosis (DVT). Prophylaxis for DVT (comment from 3.17) was not included, but is included in a sensitivity analysis shown below. G-CSF (comment from 3.17) use was included in our resubmission in August (we agree with the reviewers that it was not included in our original submission) based upon the July comments from the reviewers. Details are shown in our response to the ERG report.
b. Disutility for AEs not included (4.12 and 3.13). We did not find published values for the AEs in relevant oncology patients for the original submission. We have included disutilities for long term AEs obtained from patients with other disease (such as diabetes and breast cancer) in a sensitivity analyses shown below. A table in our response to ERG report shows the decrements applied and the sources of the values.
c. Pre-progression utility value (0.81) for multiple myeloma patients used in our submission was considered too high, given the age of the trial population (4.12 and 3.12). This comment is surprising for two reasons. First, it is the value suggested by the ERG in the NICE appraisal of bortezomib (6.3.4.3 page 36; Green et al. Bortezomib in treatment of multiple myeloma) and appears to be the most relevant value available in the published literature, although the current reviewers sited 3 additional references (page 94 in Evaluation Report) which we have discussed in our response to ERG report attached as an appendix. Also the 0.81 value indicates these patients would accept a 19% chance of death to change from the asymptomatic pre-progression state to normal health – a hefty penalty. Second, the ERG report and the ACD comment implies that a lower utility is more appropriate for patients in the pre-progression state. This is tantamount to saying that keeping them alive for each additional year is less worthwhile than keeping a younger patient population alive. We do not believe that the appraisal committee wished to imply this age specific inequality message in the ACD. Despite our concerns about this utility value, we included sensitivity analyses around the utility values ($\pm$ 10%) in our original submission and provide these again with the new base case analysis. We did not adopt the values in the publications suggested by the reviewers (section 5.3.3.6 in the Evaluation Report).
d. The costs for routine management of myeloma and administration of the therapies used in our submission were questioned (4.12 and 3.17) and the comment made that they were not inflated to 2008. We agree that the costs should be inflated and we have done so in the reanalyses included below.

To clarify the resources included, our model had one outpatient physician visit every other month before progression and one outpatient physician visit every month after progression, plus regular lab tests at frequencies based on whether the patient had progressed (page 131, Table 45 of our original submission). However, we agree that inadvertently the model left out the costs for outpatient visits. These are now included in the new analyses below.

Examining the costs used in the bortezomib appraisal by NICE and the source document (Bruce et al. 1999) indicates that the value includes costs that are considered separately in our model. Thus the costs are not comparable. In addition, we are no longer comparing lenalidomide to bortezomib (thus the cost of this drug and its administration is no longer relevant) since we are focusing on patients who have already received at least two prior therapies for multiple myeloma.

6. Cost effectiveness reanalyses for Len/dex therapy in the patient populations with 2 or more prior therapies for multiple myeloma, including those with prior thalidomide, compared to dexamethasone monotherapy findings are reported below. The results use the model adapted to reflect the ERG recommended recalibrated survival for Len/dex (point 1 above), inclusion of the outpatient visits, costs inflated to 2008 and the recommended sensitivity analyses all of which have been discussed above (Tables 2 to 7 and Figures 1 to 4 below). We have provided a fully executable copy of our adapted model with this response.

7. Furthermore, we would like to draw the appraisal committee's attention to the unique nature of lenalidomide as a treatment for multiple myeloma in that it is an oral therapy and is associated with a more favourable adverse effect profile (as noted in the ACD 4.6). It is the combination of these factors that enables patients to remain on long-term treatment and continue to benefit from lenalidomide until their disease progresses. It is the ability for patients to remain on treatment and continue to receive long-term benefits that is the key cost driver in the cost-effectiveness of lenalidomide because costs continue to accrue as patients continue to benefit from treatment. Following the publication of the ACD there has been significant media coverage, which has included a coalition of patients groups (including Myeloma UK, MacMillan Cancer Support and Leukaemia CARE) calling on the Department of Health, NICE and Celgene to work in partnership to overturn the preliminary negative recommendation for those seriously ill patients who could benefit from lenalidomide through improvements in their life-expectancy and quality of life. In response to the call from the coalition of patient groups we have proposed a price capping scheme to the Department of Health that will enable patients who have received at least two prior therapies to continue to enjoy the benefits of

long-term treatment with lenalidomide. Specifically, we have proposed a scheme that will cap the maximum cost to the NHS for an individual patient at two years of treatment (26 cycles each of 28 days). The cost of lenalidomide for those patients who remain on treatment beyond two years will be met by Celgene. We propose to implement the scheme through the existing Pregnancy Prevention Programme and in doing so believe that the scheme would have neutral burden or arguably reduce NHS burden. The scheme improves the cost-effectiveness of lenalidomide and importantly removes the uncertainty over the long-term costs to the NHS. The scheme reduces the ICERs using the new updated base case as discussed above to £30,350/QALY for patients with 2 prior therapies and £28,941/QALY for patients with 2 prior therapies, including thalidomide. These ICERs are within the range of those for other medicines for serious life-limiting diseases which have received positive NICE recommendations. We include, as an appendix, a copy of a letter that we have sent to the Department of Health outlining our proposed scheme and have been asked by the Department of Health to inform you that we are in discussions with them regarding this scheme.

Table 1: New base case and proposed capping scheme Discounted ICERs per QALY

Subgroup	New update Base Case Cost/QALY	Proposed Capping Scheme Cost/QALY
2+ Prior Therapies	£34,108	£30,350
2+ Prior Therapies (incl Thal)	£30,939	£28,941

ICERs per QALY from sensitivity analyses including the proposed capping scheme range between £27,700 and £36,800 for two + prior therapies and between £23,300 and £34,100 when varying the same parameters shown below.

NEW BASE CASE RESULTS

The following tables and figures show the results for the new model comparing Len/dex to Dex alone and incorporating the Len/dex survival calibration change recommended by the ERG, outpatient visits, and costs inflated to 2008. The findings are separated for the two subgroups: 2 or more prior therapies and 2 or more prior therapies including thalidomide. We have provided a fully executable copy of our adapted model with this response.

Table 2: New base case - Len/dex vs Dex monotherapy: Patients with Two or More Prior Therapies

	Undiscounted		Discounted	
	Len/dex	**Dex**	**Len/dex**	**Dex**
Summary of Clinical Outcomes				
Achieved Best Response (%)				
Complete Response	14%	2%	14%	2%
Partial Response	49%	20%	49%	20%
Stable Disease	35%	62%	35%	62%
Progressive Disease	1%	16%	1%	16%
Patients Progressed (%)	100%	100%	100%	100%
Median Time to Progression (months)	9.57	4.63	9.57	4.63
Deaths (%)	100%	100%	100%	100%
Quality Adjusted Life Years (QALYs)	3.06	0.78	2.62	0.76
Life Years (median)	2.78	1.11	2.78	1.11
Total Life Years (mean)	4.49	1.07	3.81	1.04
Average Cost (per patient)	£68,414	£1,774	£65,173	£1,732
Medication	£59,946	£110	£58,015	£109
Monitoring	£7,644	£1,463	£6,345	£1,424
Adverse Event-Complication	£824	£201	£813	£199
Cost-Effectiveness Outcomes				
Incremental cost per QALY Gained	£29,228		£34,108	
Incremental cost per Life Year Gained	£19,485		£22,903	

Table 3: Additional Sensitivity Analyses: New base case - Len/dex vs Dex monotherapy: Patients with Two or More Prior Therapies

Analysis	Incremental cost (£)	Incremental life years	Incremental QALYs	Cost/ QALY	Cost/ LYG
Base Case - discounted	63,441	2.77	1.86	34,108	22,903
RU associated with AEs					
100% increase in costs	64,055	2.77	1.86	34,438	23,125
100% decrease in costs	62,827	2.77	1.86	33,778	22,681
RU associated with Disease Monitoring					
100% increase in costs	68,362	2.77	1.86	36,754	24,679
100% decrease in costs	58,520	2.77	1.86	31,462	21,126
RU associated with All Costs (except medication)					
100% increase in costs	68,956	2.78	1.86	37,073	24,804
100% decrease in costs	57,827	2.77	1.86	31,090	20,876
Lenalidomide Costs					
5% discount	60,447	2.77	1.86	32,585	21,822
Utilities					
10% increase	63,398	2.78	2.05	30,926	22,805
10% decrease	63,357	2.79	1.68	37,713	22,709
Median Comparator Survival (Base case → 1.11 years)					
1 month decrease (1.04)	64,895	3.51	2.33	27,852	18,489
1 month increase (1.17)	62,200	2.21	1.50	41,598	28,126
Disutilities Associated with AEs	63,261	2.77	1.82	34,759	22,838
Thrombosis Prophylaxis	64,452	2.78	1.86	34,633	23,189

Table 4: New base case - PSA Results for Len/dex versus Dex in patients with two or more prior therapies

	Incremental Cost (£)	Incremental QALY	Incremental cost per QALY
Mean	63,741	1.85	34,733
Median	63,594	1.85	34,454
Standard Deviation	2,698	0.17	3,408
Range Minimum	56,680	1.37	26,310
Range Maximum	72,319	2.33	48,083
Mean Std. Error	121	0.01	152
2.5% Percentile	58,521	1.51	28,996
97.5% Percentile	69,748	2.18	41,696

Figure 1. New base case - Cost/QALY for Len/dex versus Dex in multiple myeloma treatment for Patients with two or more prior therapies

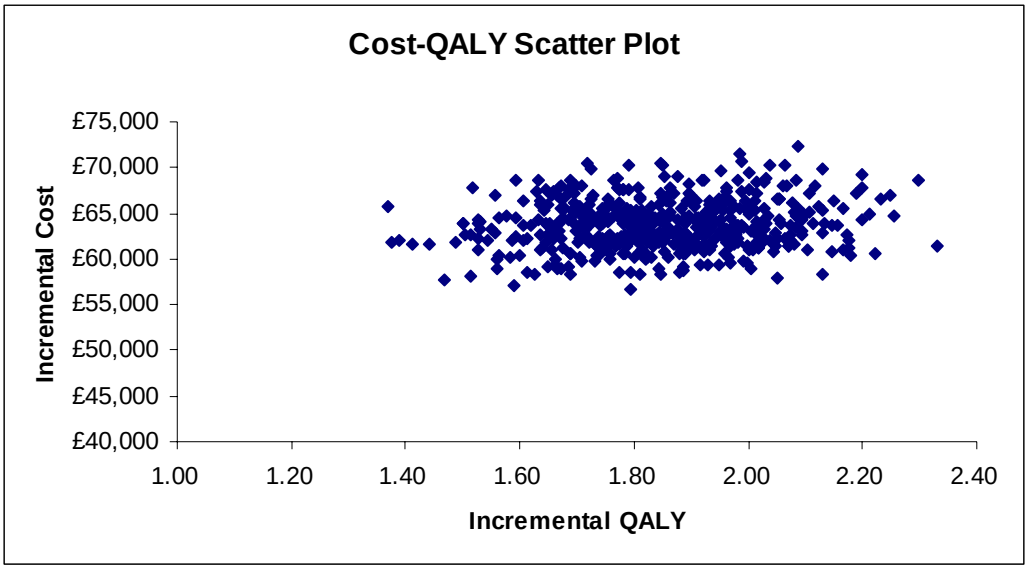


Figure 2. New base case - Acceptability Curve for Len/dex versus Dex in multiple myeloma treatment for Patients with two or more prior therapies

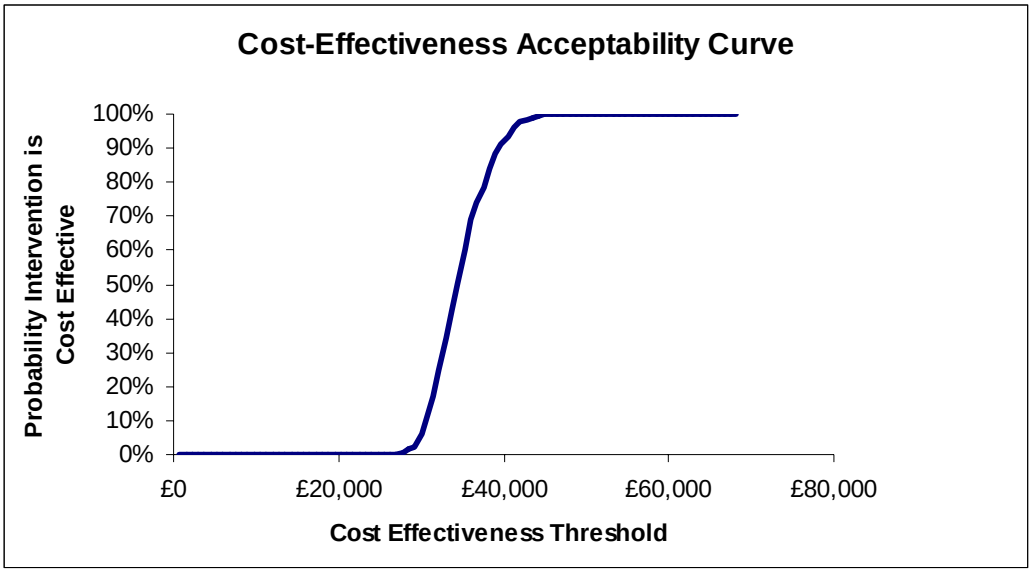


Table 5: New base case - Len/dex vs Dex monotherapy: Two or More Prior Therapies (Including Prior Thalidomide treatment)

	Undiscounted		Discounted	
	Len/dex	**Dex**	**Len/dex**	**Dex**
Summary of Clinical Outcomes				
Achieved Best Response (%)				
Complete Response	8%	1%	8%	1%
Partial Response	48%	14%	48%	14%
Stable Disease	43%	67%	43%	67%
Progressive Disease	1%	18%	1%	18%
Patients Progressed (%)	100%	100%	100%	100%
Median Time to Progression (months)	7.39	3.71	7.39	3.71
Deaths (%)	100%	100%	100%	100%
Quality Adjusted Life Years (QALYs)	2.76	0.70	2.38	0.68
Life Years (median)	2.61	1.05	2.61	1.05
Total Life Years (mean)	4.11	1.00	3.54	0.97
Average Cost (per patient)	£56,789	£1,769	£54,323	£1,726
Medication	£48,822	£102	£47,485	£101
Monitoring	£7,141	£1,467	£6,024	£1,428
Adverse Event-Complication	£826	£200	£814	£197
Cost-Effectiveness Outcomes				
Incremental cost per QALY Gained	£26,709		£30,939	
Incremental cost per Life Year Gained	£17,691		£20,466	

Table 6: Additional Sensitivity Analyses: New base case - Len/dex vs Dex monotherapy: Patients with Two or More Prior Therapies (Including Prior Thalidomide treatment)

Analysis	Incremental cost (£)	Incremental life years	Incremental QALYs	Cost/ QALY	Cost/ LYG
Base Case - discounted	52,597	2.57	1.70	30,939	20,466
RU associated with AEs					
100% increase in costs	53,214	2.57	1.70	31,302	20,706
100% decrease in costs	51,980	2.57	1.70	30,576	20,226
RU associated with Disease Monitoring					
100% increase in costs	57,193	2.57	1.70	33,643	22,524
100% decrease in costs	48,001	2.57	1.70	28,236	18,677
RU associated with All Costs (except medication)					
100% increase in costs	57,875	2.57	1.71	33,845	2,519
100% decrease in costs	47,491	2.56	1.70	27,936	18,551
Lenalidomide Costs					
5% discount	50,276	2.57	1.71	29,489	19,597
Utilities					
10% increase	52,599	2.57	1.88	27,978	20,467
10% decrease	52,687	2.57	1.54	34,212	20,501
Mean Comparator Survival (Base case → (1.05 years)					
1 month decrease (1.01)	54,129	3.31	2.18	24,827	16,385
1 month increase (1.11)	51,620	2.12	1.42	36,407	24,349
Disutilities Associated with AEs	52,644	2.56	1.67	31,523	20,564
Thrombosis Prophylaxis	53,721	2.56	1.70	31,583	20,989

Table 7: New base case - PSA Results for Len/dex versus Dex in Patients with Two or More Prior Therapies (Including Prior Thalidomide treatment)

	Incremental Cost (£)	Incremental QALY	Incremental cost per QALY
Mean	53,093	1.71	31,733
Median	53,071	1.69	31,497
Standard Deviation	2,442	0.28	4,948
Range Minimum	46,257	0.96	20,190
Range Maximum	60,365	1.70	52,278
Mean Std. Error	109	0.01	221
2.5% Percentile	48,746	1.20	22,997
97.5% Percentile	58,251	2.30	43,227

Figure 3. New base case - Cost/QALY for Len/dex versus Dex in patients with two or more prior therapies (Including prior thalidomide treatment)

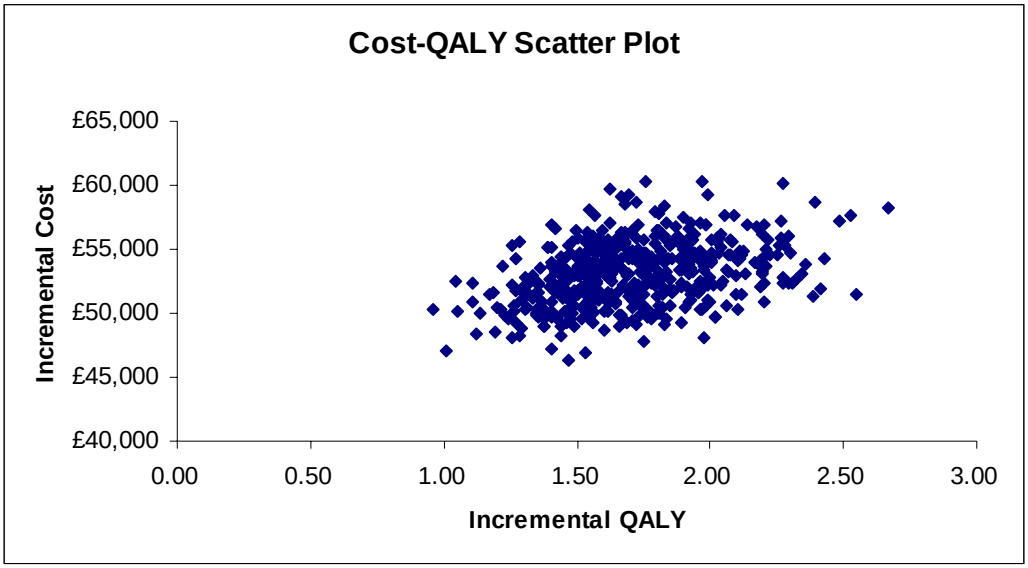
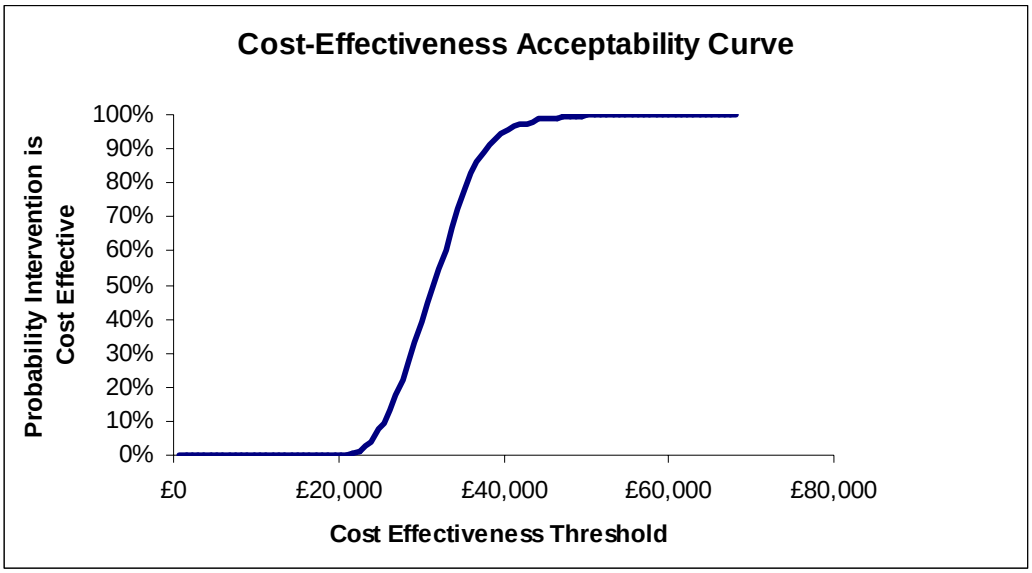


Figure 4. New base case - Acceptability Curve for patients with two or more prior therapies (including prior thalidomide treatment)



iv) Are there any equality related issues that need special consideration that are not covered in the ACD?

The equity issue we have raised above in 5c. The ACD comments that the quality of life for the older pre-progression patients should be lower implying it is less worthwhile than keeping a younger patient population alive. We suggest that this be modified to avoid the inequality message. As further indication of the value to use in this population, the ERG comments (Bortezomib in treatment of multiple myeloma, Green et al, 2006) indicate that 'a health state value between 0.644 and 0.789 may be appropriate for patient groups with MM. However, Kind et al (1998) have reported health state values in the UK general population by age group, valued using the EQ-5D, with those aged between 60-69 years ranging between 0.829-0.806.' Thus, a health state value near 0.80 is likely appropriate for the population in pre-progression.

References

Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007; 357:2123-2132.

Green C, Bryant J, Takeda A, et al. Bortezomib for the treatment of multiple myeloma. ERG report April 2006. (not attached)

Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007; 357:2133-2142.