Response to Evidence Review Group assessment

Note: This document is a response to ERG correspondence received 11 December 2013 titled “Additional clarification_lenalidomide in MM_FINAL”

Estimation of the OS and PFS curves in the model

The ERG highlighted several concerns regarding the application of OS, PFS and TTF in the economic model submitted by Celgene. These are addressed in turn below.

Possible overestimation of OS

The ERG feel that the piecewise exponential model used to characterise OS may be providing an overestimate of survival. The Markov trace for OS provided in the submission document (appendix O) shows level of survival in excess of the Kaplan-Meier (KM) plot in Figure 28 of the submission.

This concern has been addressed in a recent response to the interim request for clarifications received from the ERG. Figure 28 in the submission document shows OS for the entire Intent-to-Treat (ITT) population. This was provided as analysis was conducted using the full (ITT) population, with the curve fit for second-line patients then analysed by including the line of treatment (second or third or more) as a covariate within the regression analysis.

The relevant KM curves were provided in response to the interim request for clarifications.

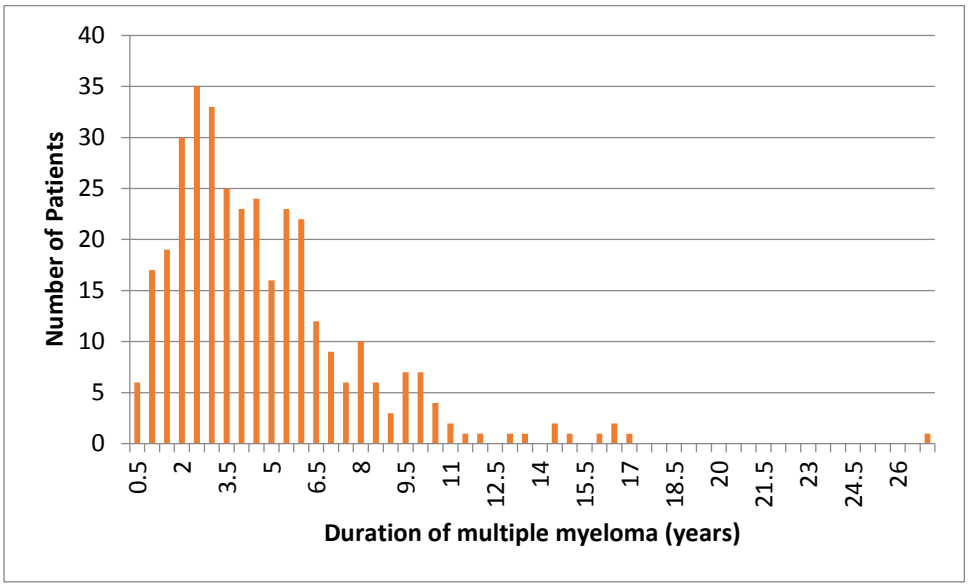
Use of mean covariates method to adjust OS

The ERG have raised concerns regarding the use of the mean covariates method to adjust overall survival. This method has been used as the information pooled across the trial arms (for baseline demographics) is the best available information on the likely demographics of a UK second line population. As presented in Section 7.8 of the submission the demographics of patients within the trial are similar to available UK population information, additionally the model predictions for lenalidomide and bortezomib retreatment OS lie within the range of estimates predicted within the SHTAC model in TA228 indicating that there is no systematic over-prediction of OS.

Figure 1 shows the distribution of patients by duration of multiple myeloma, whilst some skewing away from the mean appears to be present it is unlikely that such skewing will have a large effect within the model presented as the adjustment made for this parameter is small in all models presented (coefficient approx. -0.07 for each year of multiple myeloma away

from the mean compared to coefficient approx. -0.6 for being second line compared to third line treatment).

Figure 1 Distribution of Multiple Myeloma Population (MM010)



Possible overestimation of PFS

The ERG noted that the estimate of the comparative PFS of bortezomib relative to lenalidomide was not adjusted for baseline characteristics available in the Taverna study.

This concern has been addressed in Celgene's response to the interim request for clarifications received from the ERG. Unfortunately, failure to adjust comparative PFS estimates for the MM duration information available in Taverna et al (2012) was an oversight. This analysis has now been performed. The resulting adjusted median PFS for Len/Dex is 12.48 months. The hazard ratio of bortezomib retreatment relative to Len/Dex is 0.90.

This has now been incorporated into the base case analysis. A full set of results were provided in response to the interim request for clarifications received from the ERG. However given the additional issues raised in final request, updated results are provided at the end of this response.

Crossing of OS, PFS and TTF curves

The ERG noted that the OS curve used in the model crosses the PFS and TTF curves, such that at later time points PFS and TTF estimates exceed OS. As highlighted by the ERG, it is clearly implausible for this to be the case: thus the use of a markov structure in the original model submitted to prevent the curves crossing in the patient flow sheet.

Concern with the crossing of parametric curves was addressed in the response to the ERG's interim request for clarifications. Crossing of parametric curves is possible when different parametric models are selected for different clinical outcomes. In the base case model a piecewise exponential curve is fitted to OS, while PFS and TTF are characterised by log-logistic curves. Due to their functional form log-logistic models typically exhibit a 'long tail', with extended survival in the long term, and this is not commonly observed in exponential models (Latimer, 2013).

Importantly the KM plots for PFS and OS do not cross at any point; crossing is the result of different fitted parametric models with different long-term characteristics. KM curves were provided in Celgene's response to the interim request for clarifications.

The base case parametric models were chosen based upon their strength of fits as measured by the goodness of fit statistics presented (AIC & BIC). A full set of model results are presented at the end of this report with parametric curves selected to ensure that they do not cross (i.e. same type of parametric curve selected for all outcomes). The scenarios provided are:

- OS: Gompertz, PFS & TTF: Gompertz
- OS: log-logistic, PFS & TTF: log-logistic
- OS: gamma, PFS & TTF: gamma
- OS: Weibull, PFS & TTF: Weibull
- OS: lognormal, PFS & TTF: lognormal
- OS: piecewise exponential, PFS & TTF: exponential

On the basis of the goodness of fit statistics for all 3 outcomes (Table 1) 3 curve pairings stand out as suitable: gamma, Gompertz and log-logistic. All 3 of these curves provide a good visual fit. On the basis of the lowest combined scores across all 3 outcomes for AIC and BIC, the log-logistic curve has been selected for the revised base case analysis. Results based upon this comparison are presented at the end of this report.

Table 1 Goodness of Fit Statistics for OS, PFS and TTF

	OS		**PFS**		**TTF**	
Model	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	979.62	**987.34**	985.31	993.03	1212.52	1220.24
Weibull	**978.12**	993.57	980.90	996.34	1196.99	1212.43
Gompertz	980.50	995.95	944.59	960.03	1174.56	1190.01
Log-normal	989.30	1004.75	930.56	946.00	1237.53	1252.97
Log-logistic	984.05	999.49	**924.49**	**939.93**	**1158.20**	**1173.64**
Gamma	981.19	1004.35	931.07	954.24	1174.20	1197.37

The ERG requested information regarding the censoring of patients, suggesting that this might be causing the fitted parametric curves to cross over when extrapolated. The KM charts with censor points displayed are provided in the Appendix. Most of the OS censoring is found towards the end of the KM chart (Figure 4), while censoring of PFS is spread more evenly over time (Figure 6).

It is unlikely that the curve crossing seen in the model for certain curve selections is caused by the pattern of censoring within the trial with the most likely cause being instead the different functional forms of the curves selected.

Issues in the Excel model

The ERG raised potential issues with the patient flow calculations in the economic model submitted by Celgene. These are addressed below.

Use of the “minimum” formula and estimation of OS & PFS

Due to the issues with the curves crossing when certain functions are selected minimum formulas were used to ensure PFS was never greater than OS. These functions appear in columns M and O of the patient flow sheet for lenalidomide. Adjustment was not required for the comparator treatment flow sheet as a Markov process was used (rather than standard area under the curve) to allow for more accurate capture of movement through treatment lines to take into account the impact of use of lenalidomide at third line.

When curves which do not cross are selected the minimum function is not required (note, however, in some cases it is still activated at the very end of the time horizon due to the OS transition value rising above the PFS transition at the very end of the survival curves).

For the new base case presented below the minimum function has been removed where possible. The model now relies on the user selecting curve functions for OS, PFS and TTF which may cross.

Modelling third and fourth-line treatment

The ERG raised concerns regarding the modelling of third and fourth line treatment. The calculations to estimate the proportion of patients receiving subsequent therapies were investigated and some minor amendments were performed. This was also the case for calculations used to apply duration of third and fourth line treatment; these were investigated and some changes were applied.

The reason that summing second, third and fourth line patients with dead patients does not give a value of 100% is because of potentially unhelpful labelling within the model. The columns titled “Patients Off Therapy” in these calculations should have been labelled “New Patients Off Therapy”, as these represent patients entering the treatment line of interest in that cycle. As this does not represent the total number of patients on that line of therapy, summing these columns will not add up to 100%. The columns containing the relevant health states sum to 100%, namely columns AD to AG and AJ to AL (half-cycle corrected). Alternatively, columns AM, AR and AS will sum to 100%. These contain patients who have died, patients who are on second-line therapy, and patients who have discontinued second-line therapy, respectively.

In the comparator patient flow sheet, columns DF and DS sum to the total number of patients alive and off therapy (column AS), splitting them by whether they are receiving third-line lenalidomide or have discontinued third-line lenalidomide.

Inconsistency in patient flow sheets

The ERG requested clarification on why the comparator patient flow show differs in structure to the intervention patient flow sheet. This is primarily because the comparator sheet requires an additional level of complexity, since patients are able to receive lenalidomide as a third-line therapy. These patients assume the OS profile of a lenalidomide patient, and so two estimations of OS must be applied (requiring knowledge of the time at which patients change therapies).

The patient flow sheets in the revised model have been made consistent. Both now follow the structure of the comparator patient flow sheet. Since patients on the intervention arm do not receive lenalidomide as a third-line treatment, some of the columns in the structure of PF.Comparator become redundant and have been left blank for the intervention.

Comparator cost of dexamethasone

The ERG highlighted that the cost of dexamethasone is not being incorporated in the base case analysis, and suggested the application of dexamethasone use by the proportion of bortezomib patients presented by Taverna et al (2012). This has been implemented into the base case analysis; 64.3% of bortezomib patients receive concomitant dexamethasone. Results presented at the end of this response include this assumption.

Model sensitivity to third and fourth-line treatment

The ERG requested an additional sensitivity analysis in the final request for clarifications. This is in relation to subsequent therapies (third and fourth line treatment). The ERG have requested a scenario whereby these are stripped from the model. Model results using this scenario are provided in the updated scenario analysis results at the end of this response. Beyond second-line therapy no costs are attributed to treatment beyond second-line, and no survival benefit or adverse events associated with lenalidomide at third-line are applied.

Parameters used in the model

The ERG requested a table containing details of all parameters used in the model. Parameters used to estimate comparative efficacy, including their sources, are presented below. These estimates are used in the Comparative Efficacy worksheet to calculate hazard ratios for OS and PFS of the comparator compared to Len/Dex, having adjusted the Len/Dex estimate to match the study of interest in prognostic characteristics where possible. A complete table of remaining parameters is provided in the Appendix.

Table 2 Parameters used for Comparative Efficacy

Parameter	Estimate (months)	Source
Len/Dex median OS: unadjusted observed	37.19	MM-010 (extended follow-up)
Len/Dex median OS: adjusted to Taverna (2012)	34.58	Estimated following adjusting MM-010 for baseline characteristics.
Len/Dex median OS: adjusted to White (2013)	34.06	Estimated following adjusting MM-010 for baseline characteristics.
Bortezomib median OS (base case)	20.40	Median OS following bortezomib retreatment: 1.7 years. Taverna C, et al. (2012). Effective response with bortezomib retreatment in relapsed multiple myeloma: a multicentre retrospective survey in Switzerland. *Swiss Med Weekly,* 142.
Bortezomib median OS (scenario)	24.00	Median OS reported to be 24.0 months. White D, et al. (2013). Results from AMBER, a randomized phase 2 study of bevacizumab and bortezomib versus bortezomib in relapsed or refractory multiple myeloma. *Cancer,* 119: 339-47.

Bendamustine median OS (also used for other chemotherapy agents)	12.40	Median OS reported: 12.4 months. Damaj G, et al. (2012). Efficacy of bendamustine in relapsed/refractory myeloma patients: results from the French compassionate use program. *Leukemia & Lymphoma,* 53(4): 632-4.
Len/Dex median TTP: unadjusted observed	12.05	MM-010 (extended follow-up)
Len/Dex median PFS: unadjusted observed	10.12	MM-010 (extended follow-up)
Len/Dex TTP: adjusted to Taverna (2012)	8.02	Estimated following adjusting MM-010 for baseline characteristics.
Len/Dex TTP: adjusted to Petrucci (2013)	8.93	Estimated following adjusting MM-010 for baseline characteristics.
Len/Dex PFS: adjusted to White (2013)	9.00	Estimated following adjusting MM-010 for baseline characteristics.
Bortezomib median TTP (base case)	10.50	Median OS following bortezomib retreatment: 10.5 months. Taverna C, et al. (2012).
Bortezomib median TTP (scenario)	8.38	Median TTP reported for patients who achieved at least a partial response: 8.38 months. Petrucci MT, et al. (2013). A prospective, international phase 2 study of bortezomib retreatment in patients with relapsed multiple myeloma. *Br J Haematol,* 160(5): 649-59.
Bortezomib median TTP* (scenario)	9.30*	Median TTP reported: 9.3 months. Hrusovsky I, et al. (2010). Bortezomib retreatment in relapsed multiple myeloma – results from a retrospective multicentre survey in Germany and Switzerland. *Oncology,* 79: 247-54.
Bortezomib median PFS (scenario)	7.90	Median PFS reported to be 7.9 months. Dispenzieri A, et al. (2010). Primary therapy with single agent bortezomin as induction, maintenance and re-induction in patients with high risk myeloma: results of the ECOG E2A02 trial. *Leukemia,* 24(8): 1406-11.
Bortezomib median PFS (scenario)	5.10	Median PFS reported: 5.1 months. White D, et al. (2013).

Bendamustine median PFS (also used for other chemotherapy agents)	9.30	Median PFS reported: 9.3 months. Damaj G, et al. (2012).

*The estimate for PFS obtained from Hrusovsky et al. (2010) should have been presented as TTP, which is used as a proxy for PFS, as is also the case with the Taverna (2012) and Petrucci (2013) estimates.

Revised model results

Updated model results are provided below based upon actions taken in light of comments from the ERG. Results were also provided in Celgene's response to interim clarifications, however the results provided in the present response supersede those in the previous response. As part of the interim request for clarifications, the ERG requested model results using clinical inputs from the MM-009 study and for a subgroup of second-line patients. These are provided under the scenario analysis heading of this section.

Revised base case results

Table 3 Model outputs by clinical outcomes – lenalidomide

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
Progression-free survival	1.66	1.22	£74,337
Post-progression survival	5.91	2.76	£18,438
Total	7.56	3.98	£92,774
LY, life years; QALY, quality-adjusted life year.			

Table 4 Model outputs by clinical outcomes – bortezomib

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
Progression-free survival	1.51	1.12	£80,490
Post-progression survival	4.98	2.33	£50,621
Total	6.50	3.45	£131,111
LY, life years; QALY, quality-adjusted life year.			

Table 5 Summary of QALY gain by health state

Health state	QALY intervention (lenalidomide)	QALY comparator (bortezomib)	Increment	Absolute increment	% absolute increment
Pre-progression	1.22	1.12	0.10	0.10	18.1%
Post-progression	2.76	2.33	0.43	0.43	81.9%
Total	3.98	3.45	0.53	0.53	100%
QALY, quality-adjusted life year.					

Table 6 Summary of costs by health state

Health state	Cost intervention (lenalidomide)	Cost comparator (bortezomib)	Increment	Absolute increment	% absolute increment
Pre-progression	£74,337	£80,490	-£6,154	£6,154	16.1%
Post-progression	£18,438	£50,621	-£32,183	£32,183	83.9%
Total	£92,774	£131,111	-£38,337	£38,337	100%

Table 7 Summary of predicted resource use by category of cost

Item	Cost intervention (lenalidomide)	Cost comparator (bortezomib)	Increment	Absolute increment	% absolute increment
Technology cost	£69,473	£60,756	£8,717	£8,717	12.2%
Administration & transport cost	£168	£16,165	-£15,996	£15,996	22.4%
Monitoring & test costs	£14,649	£11,524	£3,124	£3,124	4.4%
3rd line therapy cost (inc. admin and transport)	£428	£38,895	-£38,467	£38,467	53.8%

4th line therapy cost (inc. admin and transport)	£6,822	£2,070	£4,752	£4,752	6.6%
Adverse event costs	£280	£705	-£425	£425	0.6%
Terminal care costs	£955	£997	-£42	£42	0.1%
Total	£92,774	£131,111	-£38,337	£38,337	100%

Table 8 Base-case results

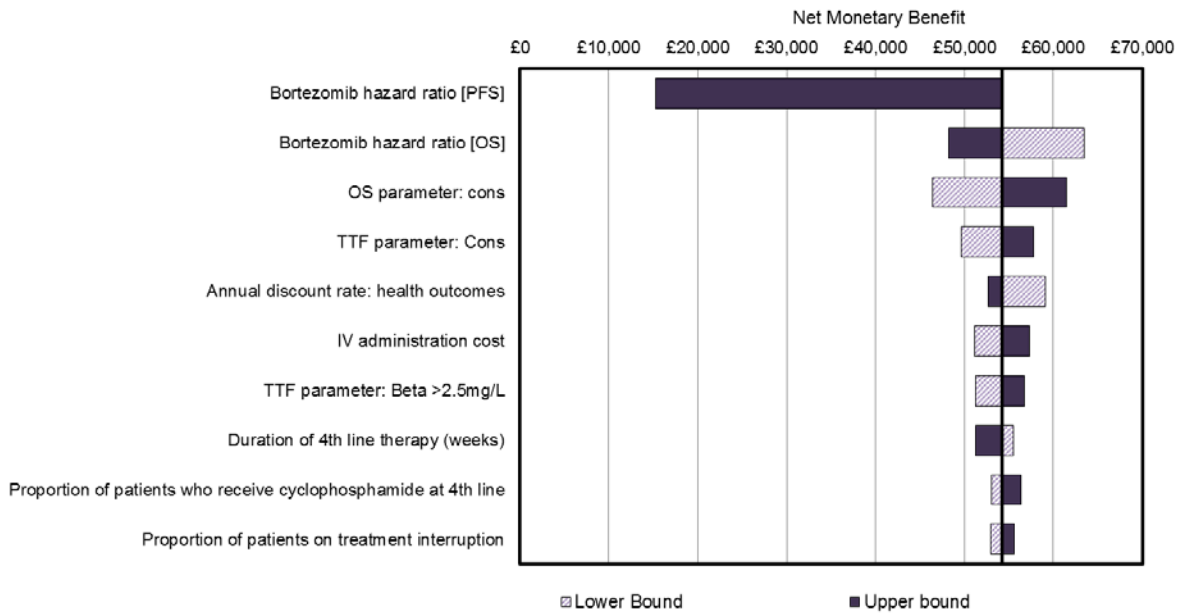
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Bortezomib	131,111	6.50	3.45	-	-	-	-
Lenalidomide	92,774	7.56	3.98	-38,337	1.07	0.53	Lenalidomide dominates
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Sensitivity analysis

One-way sensitivity analysis was performed and the results are presented below as a tornado diagram (Figure 2). The figure shows the sensitivity of Net Monetary Benefit (NMB) rather than the ICER, because negative ICERs have a distortionary effect of this type of chart (Stinet, 1998).

NMB has been calculated as the difference between the monetary value of the incremental QALYs minus the incremental costs, with a QALY valued at £30,000. The base case NMB is £54,205.

Figure 2 Tornado diagram – top 10 parameters in terms of NMB sensitivity (threshold value £30,000 per QALY)



The tornado diagram shows that Len/Dex is associated with a positive NMB in all scenarios. Results are most sensitive to comparative efficacy estimates used in the model. For OS and PFS, the “Upper bound” estimate is obtained by simultaneously setting the Len/Dex adjusted median survival estimate to its upper bound, and the bortezomib survival estimate from Taverna (2012) to its lower bound. The survival difference is increased, making this an upper bound to Len/Dex’s comparative efficacy. The effect is an increase in incremental QALYs from Len/Dex, and negative incremental costs fall – that is, the cost saving is reduced. Len/Dex remains dominant but NMB is lower, closer to zero than the base case NMB.

The “Lower bound” estimate is obtained by simultaneously setting the Len/Dex adjusted median survival estimate to its lower bound, and the bortezomib survival estimate from Taverna (2012) to its upper bound. The survival difference is reduced, making this a lower bound to the comparative efficacy of Len/Dex. The resulting ICER is very large but would be placed in the south-west quadrant of a standard cost-effectiveness plane; this would distort a tornado diagram showing ICERs, but is presented as a NMB increase in the diagram shown above.

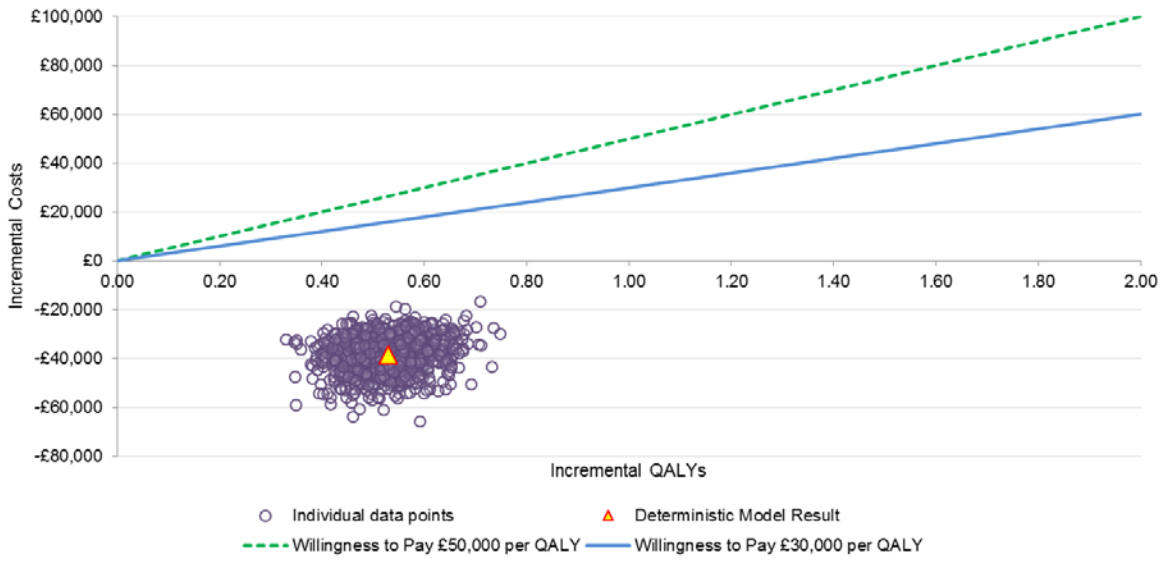
The sensitivity of model results to the PFS hazard ratio was calculated similarly. The “Upper bound” estimate of Len/Dex’s comparative PFS reduces both the cost-saving of Len/Dex and the positive incremental QALY; it means bortezomib patients progress faster, discontinuing bortezomib to receive the OS benefit from lenalidomide and third-line. This

reduces the NMB of Len/Dex. The “Lower bound” estimate gives a very similar hazard ratio to that used in the base case model, giving an almost identical NMB to the base case.

Table 9 Results from 1,000 PSA simulations

Model outcome	PSA result
Mean incremental costs (SD)	-£37,584 (7,160)
Mean incremental QALYs (SD)	0.53 (0.06)
Mean ICER	Lenalidomide dominates
Observations cost-effective at £20,000 threshold	100.0%
Observations cost-effective at £30,000 threshold	100.0%
ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; SD, standard deviation; QALY, quality-adjusted life year.	

Figure 3 Cost-effectiveness scatter plot



Scenario analysis

- **Table 10 Model results using clinical inputs for the second-line population**

Model Arm	Total Costs	Total LYG	Total QALYs	Incremental Costs	Incremental LYG	Incremental QALYs	ICER
Bortezomib	£141,359	8.25	4.11	-	-	-	-
Len/Dex	£107,708	9.96	4.92	-£33,651	1.71	0.81	Lenalidomide dominates

- **Table 11 Base case model results using MM-009 inputs**

Model Arm	Total Costs	Total LYG	Total QALYs	Incremental Costs	Incremental LYG	Incremental QALYs	ICER
Bortezomib	£125,576	6.09	3.34	-	-	-	-
Len/Dex	£96,013	6.60	3.67	-£29,563	0.50	0.33	Lenalidomide dominates

- **Table 12 Results using MM-009 clinical inputs for the second-line population**

Model Arm	Total Costs	Total LYG	Total QALYs	Incremental Costs	Incremental LYG	Incremental QALYs	ICER
Bortezomib	£131,387	6.56	3.53	-	-	-	-
Len/Dex	£102,333	7.21	3.94	-£29,054	0.65	0.41	Lenalidomide dominates

- **Results with non-crossing parametric curve fits (revised base case = log-logistic multivariable for OS, PFS and TTF)**

Table 13 Gompertz curves applied

Model Arm	Total Costs	Total LYG	Total QALYs	Incremental Costs	Incremental LYG	Incremental QALYs	ICER
Bortezomib	£125,404	4.29	2.65	-	-	-	-
Len/Dex	£84,419	4.86	2.99	-£40,984	0.57	0.34	Lenalidomide dominates

Table 14 Gamma curves applied

Model Arm	Total Costs	Total LYG	Total QALYs	Incremental Costs	Incremental LYG	Incremental QALYs	ICER
Bortezomib	£126,406	5.72	3.21	-	-	-	-
Len/Dex	£85,327	6.56	3.66	-£41,080	0.84	0.45	Lenalidomide dominates

- **Table 15 Model results with third and fourth-line therapies removed from the model**

Model Arm	Total Costs	Total LYG	Total QALYs	Incremental Costs	Incremental LYG	Incremental QALYs	ICER
Bortezomib	£86,411	4.24	2.50	-	-	-	-

Len/Dex	£85,524	7.56	3.98	-£887	3.32	1.48	Lenalidomide dominates

- **Table 16 Other scenario analyses**

Parameter	Base Case Setting	Scenario Setting	ICER
Base case	N/A	N/A	Lenalidomide Dominates
Varying the time horizon			
Time horizon	25 years	5 years	Lenalidomide Dominates
		10 years	Lenalidomide Dominates
		15 years	Lenalidomide Dominates
		20 years	Lenalidomide Dominates
Type of comparison			
Use of 3rd line lenalidomide	As per NICE recommendations i.e. earlier use of lenalidomide	As per historical BSC	£26,665
Choice of comparator	Bortezomib retreatment	Bortezomib retreatment + dexamethasone	Lenalidomide 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	Lenalidomide Dominates
Varying modelling of lenalidomide efficacy			
Parameter used to model treatment failure	Time to treatment failure	Progression-free survival	Lenalidomide dominates
Varying treatment efficacy assumptions			
Comparative efficacy of bortezomib	Overall survival from Taverna 2012	White 2013	Lenalidomide Dominates
	Progression free survival from Taverna 2012	Petrucci 2013	Lenalidomide Dominates
		Hrusovsky 2010	Lenalidomide Dominates
		Dispenzieri 2010	Lenalidomide Dominates

		White 2013	Lenalidomide Dominates
Varying cost assumptions			
Bortezomib PAS	Not included	15% discount received by all patients	Lenalidomide Dominates
		15% discount received by 55% of patients	Lenalidomide Dominates

References

Latimer N 2013. NICE DSU Technical Support Document 14: Survival Analysis for Economic Evaluations Alongside Clinical Trials – Extrapolation with Patient-level Data, report by the Decision Support Unit. http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis.updated%20March%202013.pdf

Stinet A 1998. Net Health Benefits: A New Framework for the Analysis of Uncertainty in Cost-Effectiveness Analysis. Medical Decision Making. Vol 18 No 2 Apr-Jun Suppl. S68-S80

Appendix

Table 17 Parameters used in the model

A table of parameters included in the model and their sources is provided below. This does not include comparator efficacy estimates, which are given earlier in this response.

Parameter	Estimate	Source
Model controls		
Model cycle length (weeks)	4	Model setting
Model time horizon (years)	25	Model setting
Proportion of bortezomib patients receiving dexamethasone	0.643	Taverna (2012) at ERG's recommendation
Cohort age (years)	62.55	MM-010
Proportion of cohort male	59.0%	MM-010
Proportion of cohort in β2-microglobulin <=2.5mg/L	28.2%	MM-010
Proportion of cohort with ECOG 1	43.0%	MM-010
Proportion of cohort with ECOG 2 or 3	14.5%	MM-010
Proportion of cohort with ECOG Unknown	1.7%	MM-010
Proportion of cohort with bone lesions present	78.6%	MM-010
Annual discount rate: costs	3.5%	NICE Methods Guide 2013
Annual discount rate: health outcomes	3.5%	NICE Methods Guide 2013
Annual discount rate: life years	0.0%	Model setting
PFS, OS and TTF parameters		
OS parameter: Beta >2.5mg/L	-0.824	MM-010 patient level data analysis
OS parameter: ECOG score I	-0.183	MM-010 patient level data analysis
OS parameter: ECOG score II	-0.898	MM-010 patient level data analysis
OS parameter: ECOG score unknown	-0.014	MM-010 patient level data analysis
OS parameter: Bone lesions present	-0.549	MM-010 patient level data analysis
OS parameter: Constant term	5.124	MM-010 patient level data analysis
OS parameter: Ln(Gamma_Constant)	-0.138	MM-010 patient level data analysis
OS parameter: Ln(Kappa)	0.000	MM-010 patient level data analysis
PFS parameter: Beta >2.5mg/L	-0.779	MM-010 patient level data analysis
PFS parameter: Constant term	3.116	MM-010 patient level data analysis
PFS parameter: Ln(Gamma)	-0.218	MM-010 patient level data analysis
PFS parameter: Ln(Kappa)	0.000	MM-010 patient level data analysis
TTF parameter: Beta >2.5mg/L	-0.731	MM-010 patient level data analysis
TTF parameter: Constant term	2.678	MM-010 patient level data analysis
TTF parameter: Ln(Gamma)	-0.153	MM-010 patient level data analysis
TTF parameter: Ln(Kappa)	0.000	MM-010 patient level data analysis
Comparative efficacy (OS and PFS esimates used are presented earlier in this response)		

Bortezomib hazard ratio [PFS]	0.895	MM-010 & Taverna (2012)
Bortezomib hazard ratio [OS]	1.695	MM-010 & Taverna (2012)
Bendamustine hazard ratio [PFS]	1.088	MM-010 & Damaj (2012)
Bendamustine hazard ratio [OS]	2.999	MM-010 & Damaj (2012)
Dosing		
Proportion of patients receiving lenalidomide 25mg	70.0%	MM-010
Proportion of patients receiving lenalidomide 15mg	10.5%	MM-010
Proportion of patients receiving lenalidomide 10mg	5.0%	MM-010
Proportion of patients receiving lenalidomide 5mg	3.1%	MM-010
Proportion of patients on treatment interruption	11.4%	MM-010
Proportion of lenalidomide patients receiving GCSF	26.8%	MM-010
Dexamethasone dose per day in combination with lenalidomide (mg)	38.6	MM-010
Medical resource use		
Monitoring visits per week during initial period of lenalidomide treatment	1.0	Lenalidomide SPC
Duration of increased lenalidomide monitoring (weeks)	8.0	Lenalidomide SPC
Haematology consultant visits per year: pre-progression	12.0	NICE TA171
Full blood counts per year: pre-progression	10.7	NICE TA171
Biochemistry per year: pre-progression	9.7	NICE TA171
Protein electrophoresis per year: pre-progression	6.7	NICE TA171
Immunoglobin per year: pre-progression	6.4	NICE TA171
Urinary light chain excretions per year: pre-progression	2.7	NICE TA171
Haematology consultant visits per year: progressive disease	12.0	NICE TA171
Full blood counts per year: progressive disease	20.1	NICE TA171
Biochemistry per year: progressive disease	17.3	NICE TA171
Protein electrophoresis per year: progressive disease	9.6	NICE TA171
Immunoglobin per year: progressive disease	9.7	NICE TA171
Urinary light chain excretions per year: progressive disease	4.9	NICE TA171
Costs		
Dexamethasone 500x2mg unit cost	£12.00	eMit June 2013 (NPC Code DFN019)
Dexamethasone 100x2mg unit cost	£3.14	eMit June 2013 (NPC Code DFN019)
Dexamethasone 50x2mg unit cost	£1.72	eMit June 2013 (NPC Code DFN019)
Dexamethasone proportion: 500 tablet packs	2.4%	eMit June 2013 (NPC Code DFN019)
Dexamethasone proportion: 100 tablet packs	21.8%	eMit June 2013 (NPC Code DFN019)
Dexamethasone proportion: 50 tablet packs	75.8%	eMit June 2013 (NPC Code DFN019)
Cyclophosphamide 50x100mg unit cost	£20.20	BNF65
Cyclophosphamide 1x1000mg unit cost	£17.60	BNF65
Cyclophosphamide 1x500mg unit cost	£9.20	BNF65
Lenalidomide weighted average cycle cost	£3,773	BNF65, incorporating dose reductions and interruptions.
Thalidomide 28x50mg unit cost	£298.48	BNF65
Melphalan 25x2mg unit cost	£42.88	BNF65
Melphalan 1x50mg unit cost	£129.81	BNF65
Prednisone 100x5mg unit cost	£89.00	BNF65
Bortezomib 1x3.5mg unit cost	£762.38	BNF65
Bendamustine 1x25mg unit cost	£69.45	BNF65
Bendamustine 1x100mg unit cost	£275.81	BNF65
Etoposide 1x100mg unit cost	£22.38	eMit June 2013 (NPC Code DFN019)

Etoposide 1x500mg unit cost	£73.29	eMit June 2013 (NPC Code DFN019)
Doxorubicin 1x10mg unit cost	£1.73	BNF65
Doxorubicin 1x50mg unit cost	£4.87	BNF65
Doxorubicin 1x200mg unit cost	£32.38	BNF65
Cisplatin 1x50mg unit cost	£7.16	eMit June 2013 (NPC Code DFN019)
Cisplatin 1x100mg unit cost	£14.10	eMit June 2013 (NPC Code DFN019)
Vincristine 1x1mg unit cost	£3.42	eMit June 2013 (NPC Code DFN019)
Vincristine 1x2mg unit cost	£8.49	eMit June 2013 (NPC Code DFN019)
Prednisolone acetate 5x25mg unit cost	£0.30	eMit June 2013 (NPC Code DFN019)
IV/SC administration cost	£199.83	NHS Reference Costs
Oral administration cost	£161.85	NHS Reference Costs
Haematology consultant appointment cost	£123.71	SHTAC 2009 (NICE TA228)
Full blood count cost	£3.21	SHTAC 2009 (NICE TA228)
Biochemistry cost	£5.48	SHTAC 2009 (NICE TA228)
Protein electrophoresis cost	£14.73	SHTAC 2009 (NICE TA228)
Immunoglobin cost	£44.20	SHTAC 2009 (NICE TA228)
Urinary light chain excretion cost	£14.73	SHTAC 2009 (NICE TA228)
Terminal care per 8 weeks cost	£6,177.20	King's Fund (2008)
Proportion of MM patients who require terminal care	20.0%	Multiple myeloma advisory board 2013
Transportation cost per administration appointment	£12.78	NHS Reference Costs
Proportion of patients requiring transport for administration	50.0%	Monofer SMC submission
Subsequent treatment lines		
Duration of 3rd line therapy (weeks)	17.2	HMRN Data (York)
Proportion of patients who receive lenalidomide 3rd line after comparator	100.0%	Model setting (Controls sheet)
Duration of 4th line therapy (weeks)	16.8	HMRN Data (York)
Proportion of patients who receive dexamethasone at 3rd line after lenalidomide	56.3%	HMRN Data (York)
Proportion of patients who receive prednisolone at 3rd line after lenalidomide	6.3%	HMRN Data (York)
Proportion of patients who receive Prednisone at 3rd line after lenalidomide	6.3%	HMRN Data (York)
Proportion of patients who receive Cisplatin at 3rd line after lenalidomide	12.5%	HMRN Data (York)
Proportion of patients who receive Cyclophosphamide at 3rd line after lenalidomide	62.5%	HMRN Data (York)
Proportion of patients who receive Doxorubicin at 3rd line after lenalidomide	12.5%	HMRN Data (York)
Proportion of patients who receive Etoposide at 3rd line after lenalidomide	31.3%	HMRN Data (York)
Proportion of patients who receive Melphalan at 3rd line after lenalidomide	18.8%	HMRN Data (York)
Proportion of patients who receive Vincristine at 3rd line after lenalidomide	0.0%	HMRN Data (York)
Proportion of patients who receive Bortezomib at 3rd line after lenalidomide	0.0%	HMRN Data (York)
Proportion of patients who receive Lenalidomide at 3rd line after lenalidomide	0.0%	HMRN Data (York)
Proportion of patients who receive dexamethasone at 3rd line after comparator	31.3%	HMRN Data (York)
Proportion of patients who receive prednisolone at 3rd line after comparator	3.5%	HMRN Data (York)
Proportion of patients who receive Prednisone at 3rd line after comparator	3.5%	HMRN Data (York)
Proportion of patients who receive Cisplatin at 3rd line after comparator	6.9%	HMRN Data (York)

Proportion of patients who receive Cyclophosphamide at 3rd line after comparator	34.7%	HMRN Data (York)
Proportion of patients who receive Doxorubicin at 3rd line after comparator	6.9%	HMRN Data (York)
Proportion of patients who receive Etoposide at 3rd line after comparator	17.4%	HMRN Data (York)
Proportion of patients who receive Melphalan at 3rd line after comparator	10.4%	HMRN Data (York)
Proportion of patients who receive Vincristine at 3rd line after comparator	0.0%	HMRN Data (York)
Proportion of patients who receive Bortezomib at 3rd line after comparator	0.0%	HMRN Data (York)
Proportion of patients who receive lenalidomide at 3rd line after comparator	44.4%	HMRN Data (York)
Proportion of patients who receive cyclophosphamide at 4th line	14.3%	HMRN Data (York)
Proportion of patients who receive thalidomide at 4th line	28.6%	HMRN Data (York)
Proportion of patients who receive melphalan at 4th line	14.3%	HMRN Data (York)
Proportion of patients who receive lenalidomide at 4th line	42.9%	HMRN Data (York)
Utility values		
Utility: pre-progression	0.81	van Agthoven et al. (2004)
Utility: pre-progression after 2 years	0.77	van Agthoven et al. (2004)
Utility: post-progression	0.64	van Agthoven et al. (2004)
Adverse events		
Len/dex: Cycle rate of Grade 3 Anaemia	0.006	MM-010 patient level data analysis
Len/dex: Cycle rate of Grade 3 Hypercalcemia	0.000	MM-010 patient level data analysis
Len/dex: Cycle rate of Grade 3 Pneumonia	0.004	MM-010 patient level data analysis
Len/dex: Cycle rate of Grade 3 Thrombocytopenia	0.008	MM-010 patient level data analysis
Len/dex: Cycle rate of Grade 3 Neutropenia	0.044	MM-010 patient level data analysis
Len/dex: Cycle rate of Grade 3 Diarrhoea	0.002	MM-010 patient level data analysis
Len/dex: Cycle rate of Grade 3 Constipation	0.001	MM-010 patient level data analysis
Len/dex: Cycle rate of Grade 3 Peripheral neuropathy	0.001	MM-010 patient level data analysis
Len/dex: Cycle rate of Grade 3 DVT	0.002	MM-010 patient level data analysis
Len/dex: Cycle rate of Grade 4 Anaemia	0.000	MM-010 patient level data analysis
Len/dex: Cycle rate of Grade 4 Hypercalcemia	0.000	MM-010 patient level data analysis
Len/dex: Cycle rate of Grade 4 Pneumonia	0.000	MM-010 patient level data analysis
Len/dex: Cycle rate of Grade 4 Thrombocytopenia	0.001	MM-010 patient level data analysis
Len/dex: Cycle rate of Grade 4 Neutropenia	0.004	MM-010 patient level data analysis
Len/dex: Cycle rate of Grade 4 Diarrhoea	0.000	MM-010 patient level data analysis
Len/dex: Cycle rate of Grade 4 Constipation	0.000	MM-010 patient level data analysis
Len/dex: Cycle rate of Grade 4 Peripheral neuropathy	0.000	MM-010 patient level data analysis
Len/dex: Cycle rate of Grade 4 DVT	0.000	MM-010 patient level data analysis
Bort: Cycle rate of Grade 3 Anaemia	0.013	VISTA study, via Picot et al 2010
Bort: Cycle rate of Grade 3 Hypercalcemia	0.000	MM-010
Bort: Cycle rate of Grade 3 Pneumonia	0.004	VISTA study, via Picot et al 2010
Bort: Cycle rate of Grade 3 Thrombocytopenia	0.017	VISTA study, via Picot et al 2010

Bort: Cycle rate of Grade 3 Neutropenia	0.026	VISTA study, via Picot et al 2010
Bort: Cycle rate of Grade 3 Diarrhoea	0.006	VISTA study, via Picot et al 2010
Bort: Cycle rate of Grade 3 Constipation	0.001	VISTA study, via Picot et al 2010
Bort: Cycle rate of Grade 3 Peripheral neuropathy	0.011	VISTA study, via Picot et al 2010
Bort: Cycle rate of Grade 3 DVT	0.001	VISTA study, via Picot et al 2010
Bort: Cycle rate of Grade 4 Anaemia	0.002	VISTA study, via Picot et al 2010
Bort: Cycle rate of Grade 4 Hypercalcemia	0.000	Assumption
Bort: Cycle rate of Grade 4 Pneumonia	0.002	VISTA study, via Picot et al 2010
Bort: Cycle rate of Grade 4 Thrombocytopenia	0.015	VISTA study, via Picot et al 2010
Bort: Cycle rate of Grade 4 Neutropenia	0.009	VISTA study, via Picot et al 2010
Bort: Cycle rate of Grade 4 Diarrhoea	0.001	VISTA study, via Picot et al 2010
Bort: Cycle rate of Grade 4 Constipation	0.000	VISTA study, via Picot et al 2010
Bort: Cycle rate of Grade 4 Peripheral neuropathy	0.000	VISTA study, via Picot et al 2010
Bort: Cycle rate of Grade 4 DVT	0.000	VISTA study, via Picot et al 2010
Other comparator: Cycle rate of Grade 3 Anaemia	0.020	VISTA study, via Picot et al 2010
Other comparator: Cycle rate of Grade 3 Hypercalcemia	0.000	Assumption
Other comparator: Cycle rate of Grade 3 Pneumonia	0.004	VISTA study, via Picot et al 2010
Other comparator: Cycle rate of Grade 3 Thrombocytopenia	0.017	VISTA study, via Picot et al 2010
Other comparator: Cycle rate of Grade 3 Neutropenia	0.024	VISTA study, via Picot et al 2010
Other comparator: Cycle rate of Grade 3 Diarrhoea	0.001	VISTA study, via Picot et al 2010
Other comparator: Cycle rate of Grade 3 Constipation	0.000	VISTA study, via Picot et al 2010
Other comparator: Cycle rate of Grade 3 Peripheral neuropathy	0.000	VISTA study, via Picot et al 2010
Other comparator: Cycle rate of Grade 3 DVT	0.001	VISTA study, via Picot et al 2010
Other comparator: Cycle rate of Grade 4 Anaemia	0.008	VISTA study, via Picot et al 2010
Other comparator: Cycle rate of Grade 4 Hypercalcemia	0.000	Assumption
Other comparator: Cycle rate of Grade 4 Pneumonia	0.001	VISTA study, via Picot et al 2010
Other comparator: Cycle rate of Grade 4 Thrombocytopenia	0.014	VISTA study, via Picot et al 2010
Other comparator: Cycle rate of Grade 4 Neutropenia	0.015	VISTA study, via Picot et al 2024
Other comparator: Cycle rate of Grade 4 Diarrhoea	0.000	VISTA study, via Picot et al 2025
Other comparator: Cycle rate of Grade 4 Constipation	0.000	VISTA study, via Picot et al 2026
Other comparator: Cycle rate of Grade 4 Peripheral neuropathy	0.000	VISTA study, via Picot et al 2027
Other comparator: Cycle rate of Grade 4 DVT	0.000	VISTA study, via Picot et al 2028
Events actively treated: Grade 3 Anaemia	0.919	NICE TA171
Events actively treated: Grade 3 Hypercalcemia	1.000	NICE TA171
Events actively treated: Grade 3 Pneumonia	1.000	NICE TA171
Events actively treated: Grade 3 Thrombocytopenia	0.289	NICE TA171

Events actively treated: Grade 3 Neutropenia	0.441	NICE TA171
Events actively treated: Grade 3 Diarrhoea	0.957	NICE TA171
Events actively treated: Grade 3 Constipation	1.000	NICE TA171
Events actively treated: Grade 3 Peripheral neuropathy	0.793	NICE TA171
Events actively treated: Grade 3 DVT	1.000	NICE TA171
Events actively treated: Grade 4 Anaemia	1.000	NICE TA171
Events actively treated: Grade 4 Hypercalcemia	1.000	NICE TA171
Events actively treated: Grade 4 Pneumonia	1.000	NICE TA171
Events actively treated: Grade 4 Thrombocytopenia	0.964	NICE TA171
Events actively treated: Grade 4 Neutropenia	0.707	NICE TA171
Events actively treated: Grade 4 Diarrhoea	1.000	NICE TA171
Events actively treated: Grade 4 Constipation	1.000	NICE TA171
Events actively treated: Grade 4 Peripheral neuropathy	0.839	NICE TA171
Events actively treated: Grade 4 DVT	1.000	NICE TA171
Cost of treated event: Grade 3 Anaemia	£326.95	NHS reference costs / Curtis (2012)
Cost of treated event: Grade 3 Hypercalcemia	£446.68	NHS reference costs / Curtis (2012)
Cost of treated event: Grade 3 Pneumonia	£1,263.16	NHS reference costs / Curtis (2012)
Cost of treated event: Grade 3 Thrombocytopenia	£379.08	NHS reference costs / Curtis (2012)
Cost of treated event: Grade 3 Neutropenia	£315.28	NHS reference costs / Curtis (2012)
Cost of treated event: Grade 3 Diarrhoea	£369.16	NHS reference costs / Curtis (2012)
Cost of treated event: Grade 3 Constipation	£313.68	NHS reference costs / Curtis (2012)
Cost of treated event: Grade 3 Peripheral neuropathy	£155.12	NHS reference costs / Curtis (2012)
Cost of treated event: Grade 3 DVT	£185.14	NHS reference costs / Curtis (2012)
Cost of treated event: Grade 4 Anaemia	£365.57	NHS reference costs / Curtis (2012)
Cost of treated event: Grade 4 Hypercalcemia	£527.89	NHS reference costs / Curtis (2012)
Cost of treated event: Grade 4 Pneumonia	£1,274.51	NHS reference costs / Curtis (2012)
Cost of treated event: Grade 4 Thrombocytopenia	£416.14	NHS reference costs / Curtis (2012)
Cost of treated event: Grade 4 Neutropenia	£306.04	NHS reference costs / Curtis (2012)
Cost of treated event: Grade 4 Diarrhoea	£496.00	NHS reference costs / Curtis (2012)
Cost of treated event: Grade 4 Constipation	£496.00	NHS reference costs / Curtis (2012)
Cost of treated event: Grade 4 Peripheral neuropathy	£201.95	NHS reference costs / Curtis (2012)
Cost of treated event: Grade 4 DVT	£403.41	NHS reference costs / Curtis (2012)
Utility decrement associated with: Grade 3 Anaemia	0.310	Brown et al (2013)
Utility decrement associated with: Grade 3 Hypercalcemia	0.000	Brown et al (2013)
Utility decrement associated with: Grade 3 Pneumonia	0.190	Brown et al (2013)
Utility decrement associated with: Grade 3 Thrombocytopenia	0.310	Brown et al (2013)
Utility decrement associated with: Grade 3 Neutropenia	0.145	Brown et al (2013)
Utility decrement associated with: Grade 3 Diarrhoea	0.000	Brown et al (2013)
Utility decrement associated with: Grade 3 Constipation	0.000	Brown et al (2013)
Utility decrement associated with: Grade 3 Peripheral neuropathy	0.065	Coffey (2002)
Utility decrement associated with: Grade 3 DVT	0.150	Brown et al (2013)
Utility decrement associated with: Grade 4 Anaemia	0.310	Brown et al (2013)

Utility decrement associated with: Grade 4 Hypercalcemia	0.000	Brown et al (2013)
Utility decrement associated with: Grade 4 Pneumonia	0.190	Brown et al (2013)
Utility decrement associated with: Grade 4 Thrombocytopenia	0.310	Brown et al (2013)
Utility decrement associated with: Grade 4 Neutropenia	0.145	Brown et al (2013)
Utility decrement associated with: Grade 4 Diarrhoea	0.000	Brown et al (2013)
Utility decrement associated with: Grade 4 Constipation	0.000	Brown et al (2013)
Utility decrement associated with: Grade 4 Peripheral neuropathy	0.065	Coffey (2002)
Utility decrement associated with: Grade 4 DVT	0.150	Brown et al (2013)

Figure 4 OS (ITT population) with 95% confidence interval

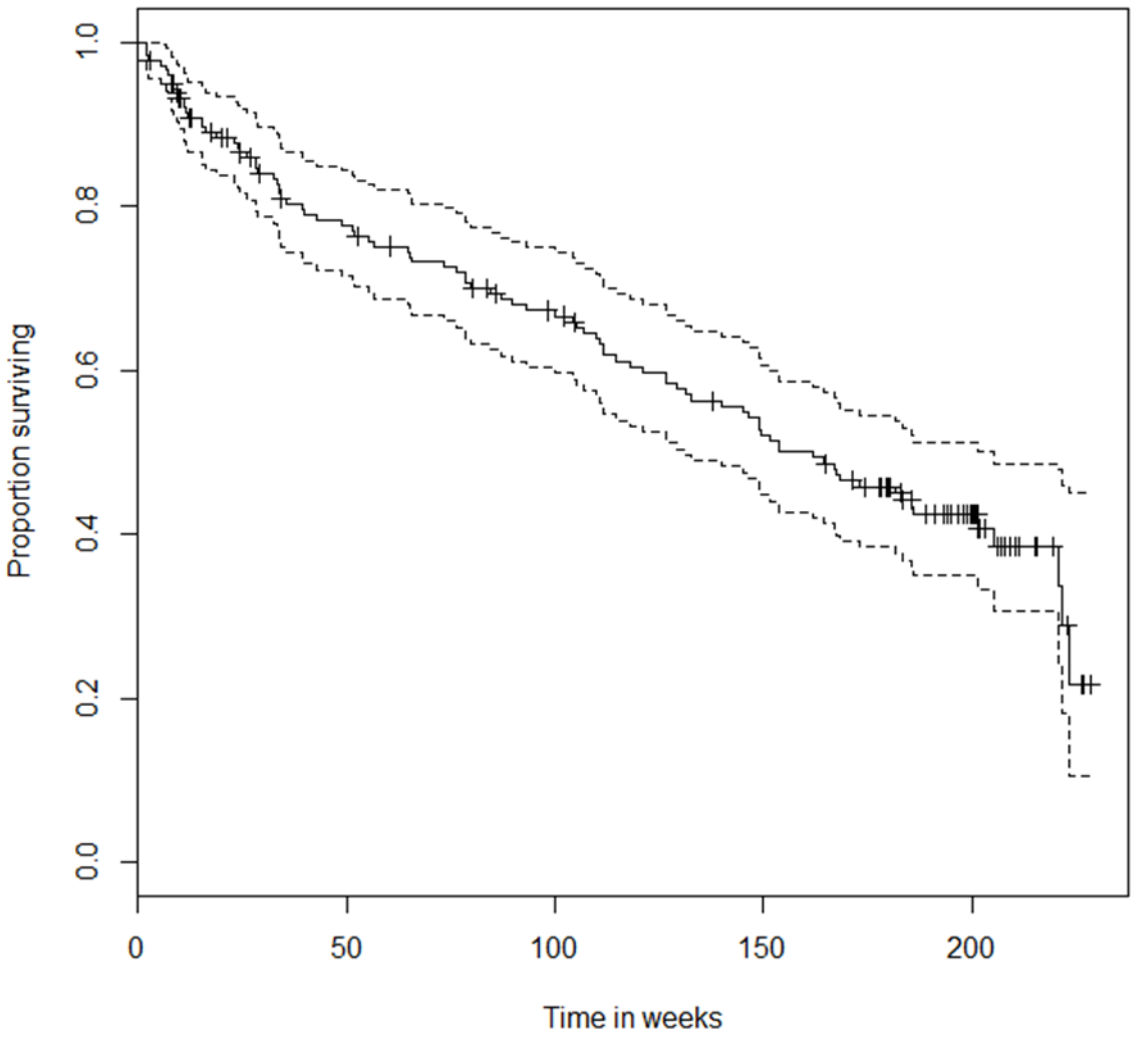


Figure 5 OS separated by number of prior treatments

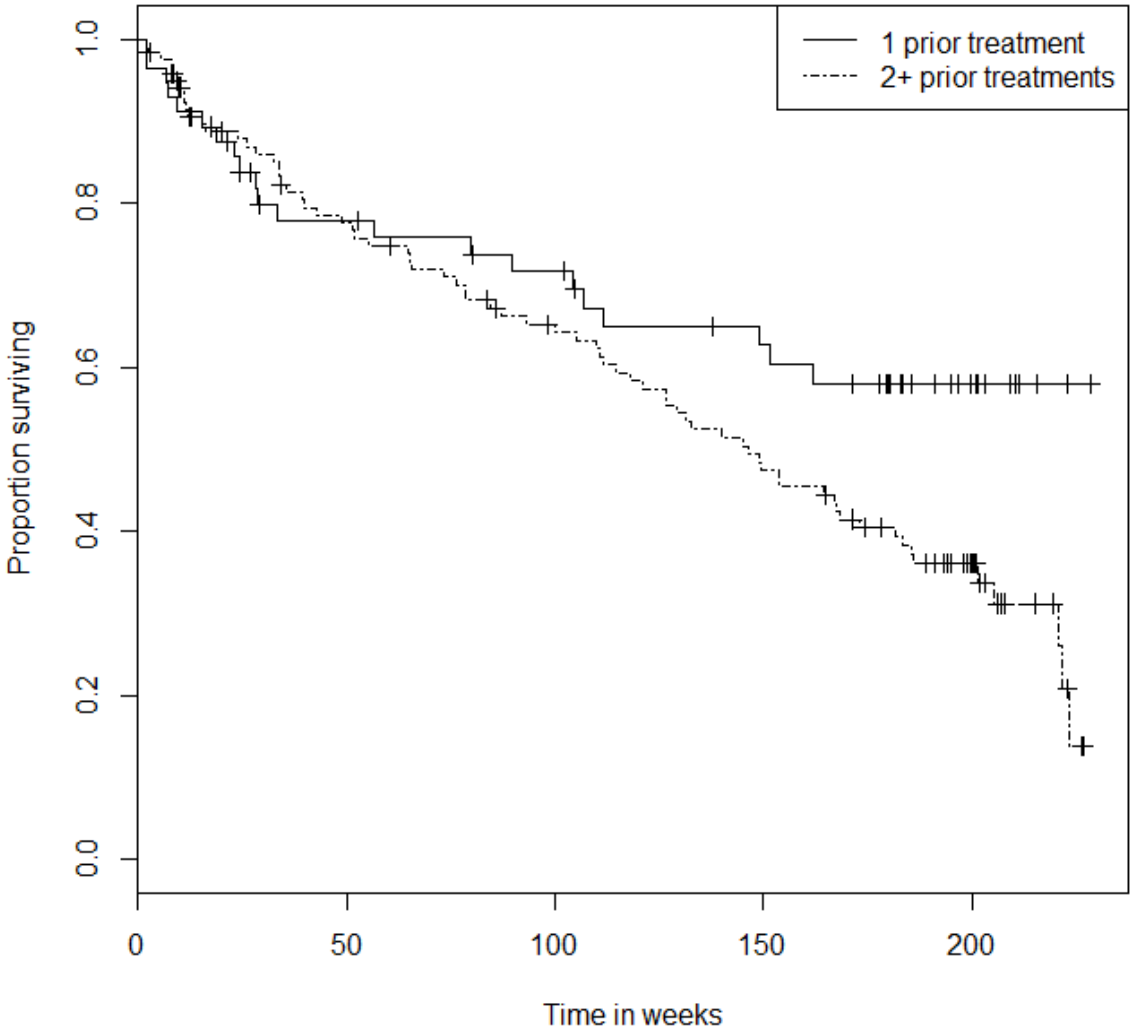


Figure 6 PFS (ITT population) with 95% confidence intervals

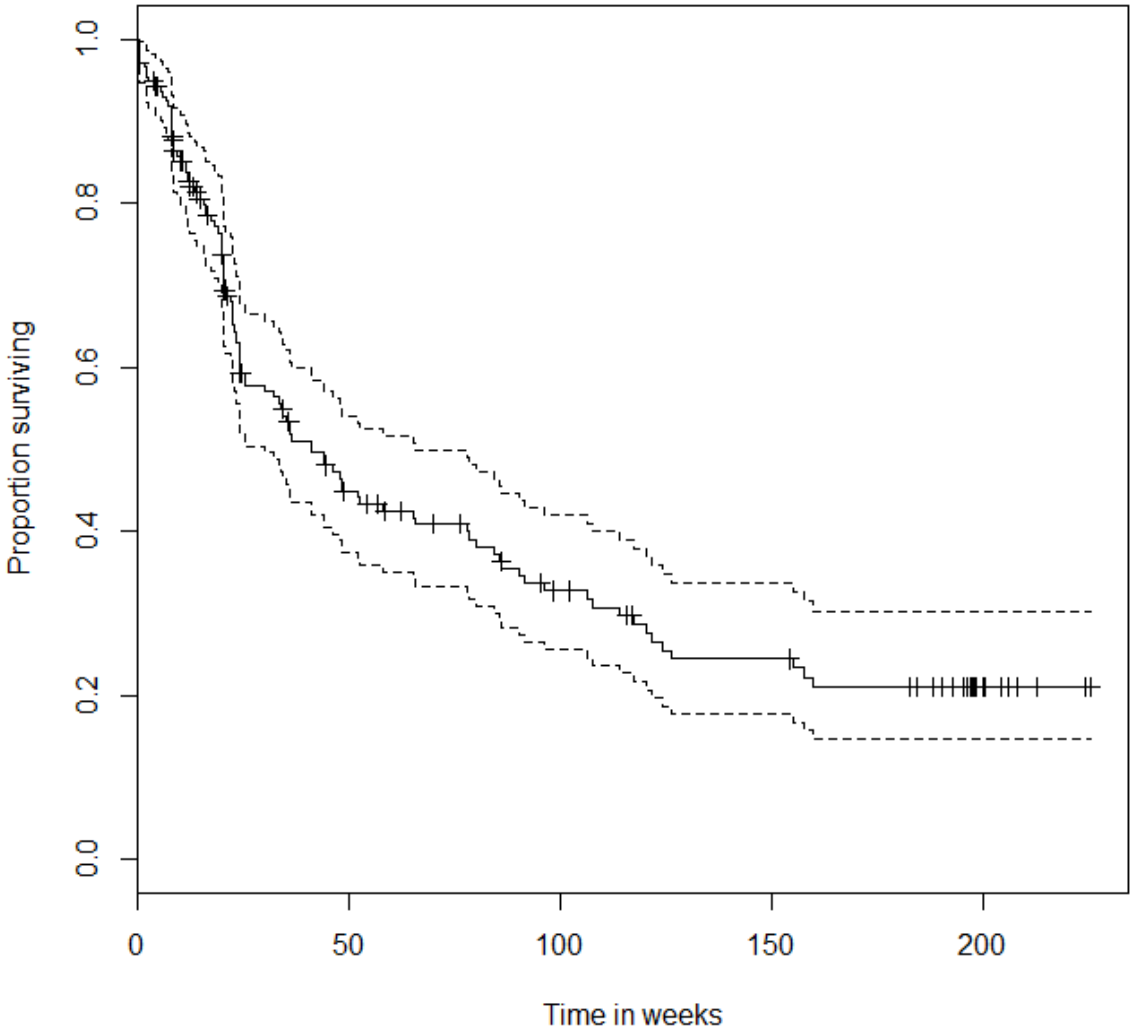


Figure 7 PFS separated by number of prior treatments

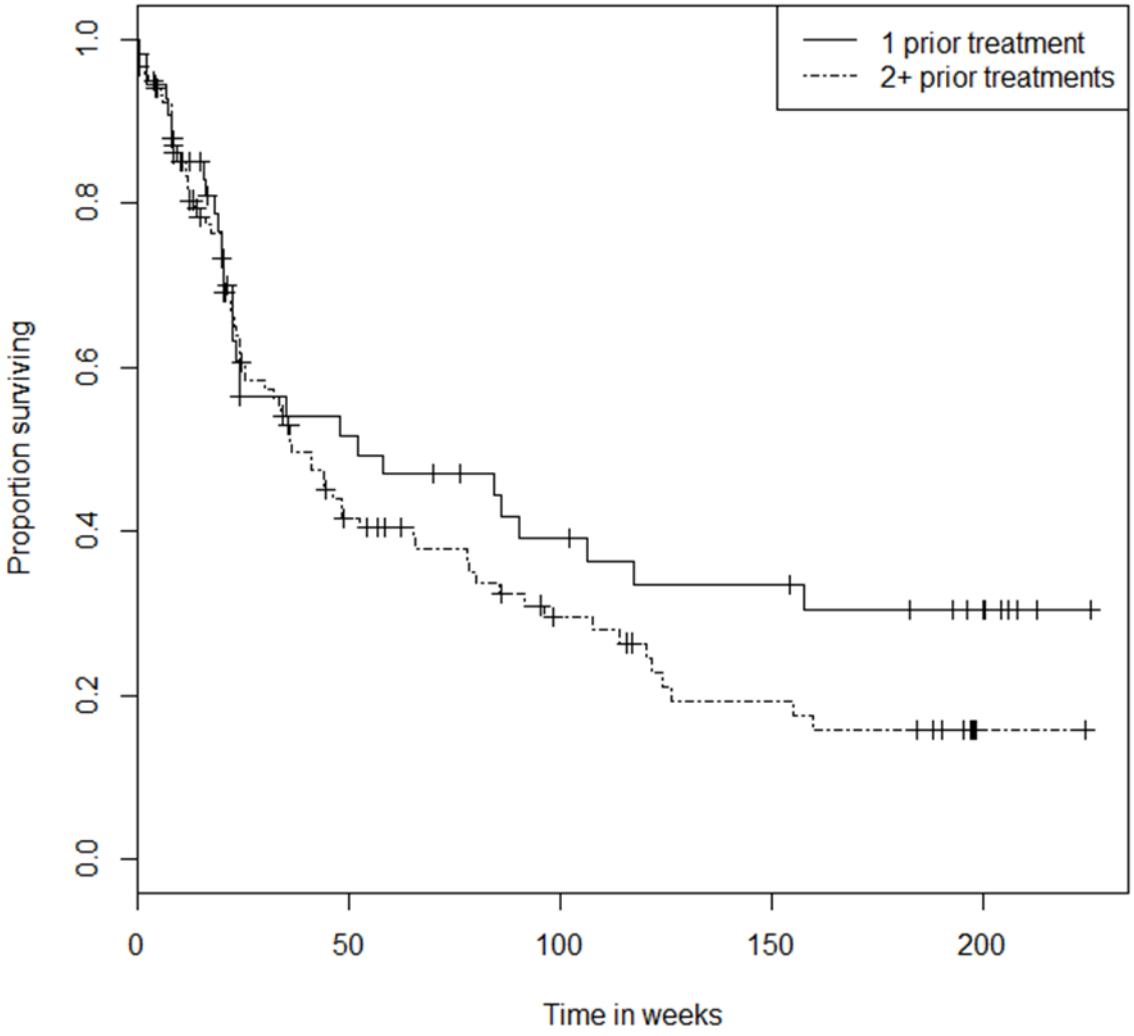


Figure 8 TTF (ITT population) with 95% confidence intervals

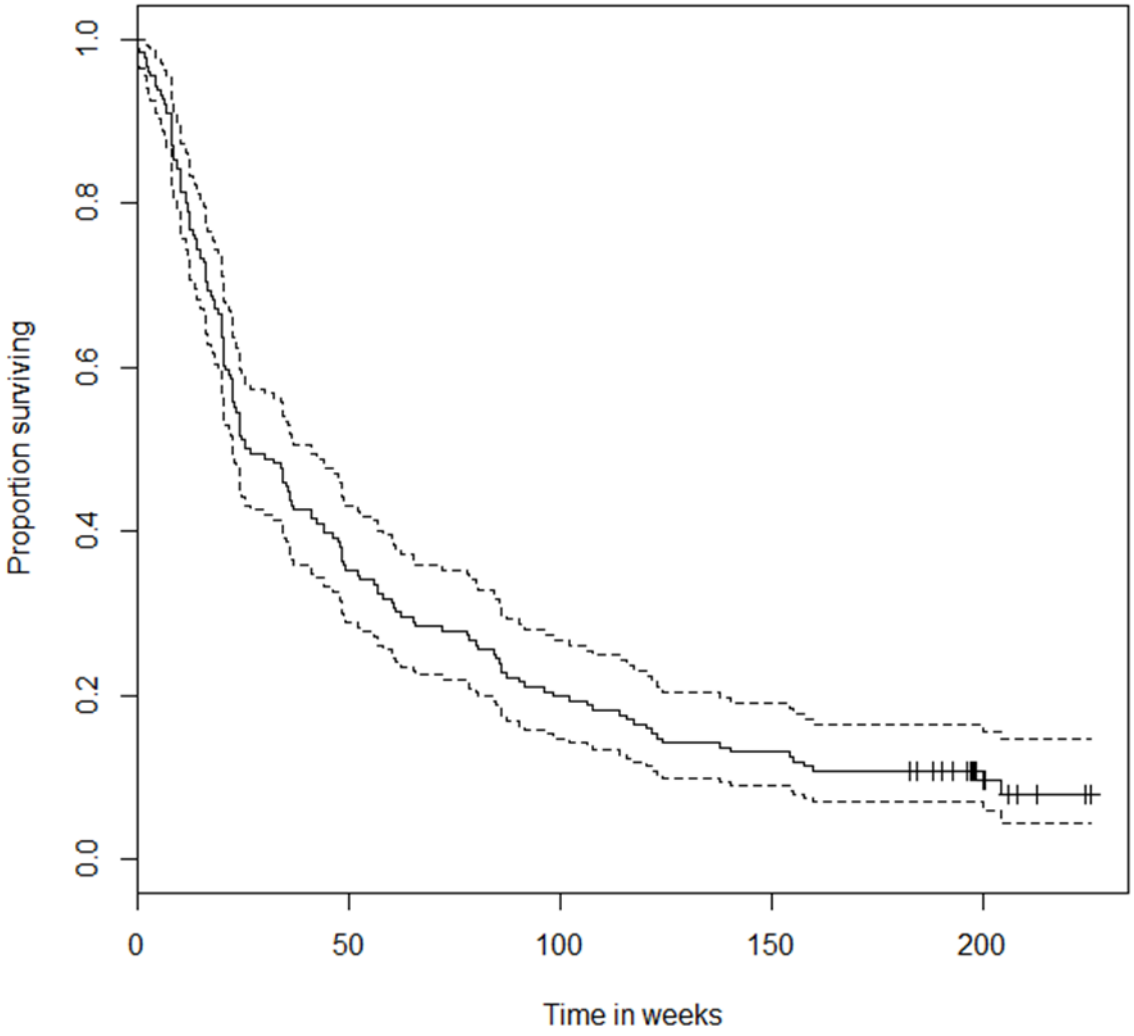
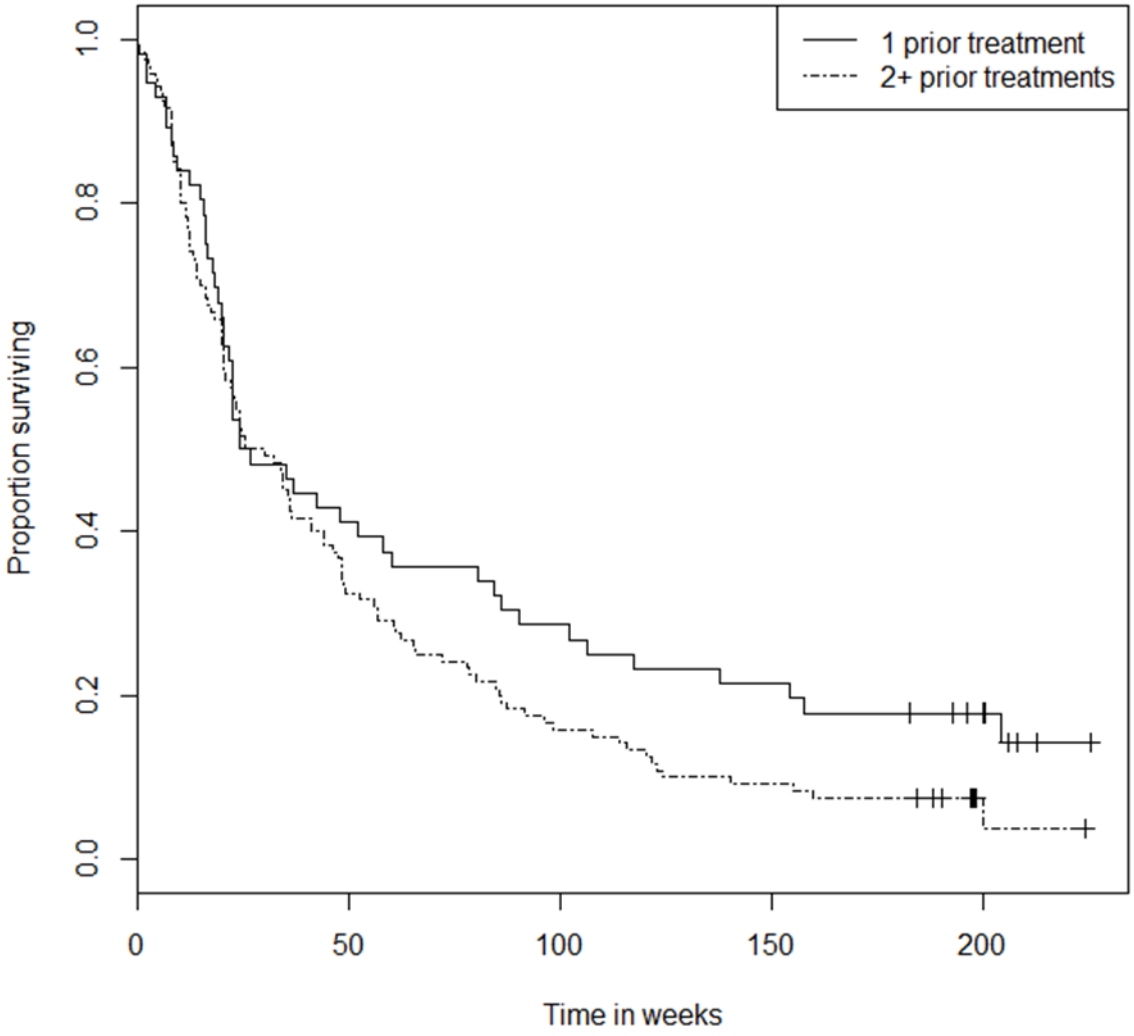



Figure 9 TTF separated by number of prior treatments