Response to:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy with bortezomib (part-review of TA171) [ID667]

Prepared by:

Celgene Limited

16 April 2014

Response to the Appraisal Consultation Document: Lenalidomide for treating multiple myeloma after one prior treatment with bortezomib (part-review of TA171) [ID667]

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Approved Name of Medicinal Product:	lenalidomide
Brand Name:	Revlimid®
Company:	Celgene Ltd
Submitted by:	Sujith Dhanasiri
Position:	Senior Manager, Market Access, UK & Ireland
Date:	16th April 2014

Dear Dr George,

Celgene is grateful for the opportunity to respond to the Appraisal Consultation Document (ACD) developed by the Appraisal Committee (the Committee) following its meeting on 18 February 2014. We are of course disappointed that the Committee was unable to recommend lenalidomide for as a second-line treatment option for a small cohort of multiple myeloma patients. However, we are hopeful that following consultation on a number of key issues, the Committee will review its preliminary recommendations and produce final guidance to the NHS that supports the use of lenalidomide as a clinically and cost-effective treatment for this group.

The Committee concluded that the most plausible ICER (incremental cost-effectiveness ratio) presented at the first meeting was at least £22,000, but that the actual value was subject to uncertainty. To address the specific concerns raised by the Committee, and reduce this uncertainty, we have included in our response a set of important additional analyses. These relate to:

1. Comparative efficacy versus bortezomib retreatment

The lack of strong comparative evidence for bortezomib retreatment versus lenalidomide is identified as an issue in this review. However, there is clear evidence and therefore a compelling clinical rationale that supports the fact that retreating with bortezomib is unlikely to deliver comparable treatment outcomes to those achieved with a first course of lenalidomide. Numerous studies have demonstrated that bortezomib retreatment is less efficacious compared to initial treatment (with bortezomib) and additional evidence submitted within this ACD response (including an update of an MTC with bortezomib presented in TA171) demonstrates that lenalidomide is superior to initial treatment with bortezomib; and by extension it is therefore superior to bortezomib retreatment. Available evidence and clinical opinion from real-world practice also indicate that lenalidomide is superior in terms of treatment outcomes compared to retreatment with bortezomib. We hope the MTC analyses included in this response help to further clarify any remaining uncertainty on this aspect of the appraisal.

It is noted that the Committee had some concerns regarding a number of the assumptions incorporated in the cost-effectiveness model developed by Celgene. In particular, the methods used to estimate overall survival were questioned, leading the Committee to conclude that the available data had not been appropriately adjusted to allow for differences in patient characteristics between the studies, and therefore that comparative efficacy had not been established. Analysis of efficacy for lenalidomide and comparator treatments has therefore been fully repeated, with the methodology presented in a fully transparent manner (as agreed in email correspondence from NICE on 20 March 2014). This additional analysis feeds through to an updated cost-effectiveness analyses that show

lenalidomide to remain cost-effective regardless of the methodology used for comparison, the source of information selected for bortezomib retreatment or the curve fit used to model survival.

2. Comparative efficacy versus chemotherapy

As originally stated in Celgene's response to the draft scope produced by NICE the treatment pathway for multiple myeloma has evolved with the advent of proteasome inhibitors and immunomodulatory agents plus more recent label extensions of existing agents within the pathway. Chemotherapy is now rarely used (<10% of patients), as where patients who do not receive retreatment with bortezomib, they invariably receive lenalidomide second line through the Cancer Drugs Fund.

In section 4.13 of the ACD, the Committee presents what it considers to be the most plausible ICERs as a basis for making recommendations (£60,000/QALY for the comparison between lenalidomide and melphalan plus prednisolone and £68,000/QALY for the comparison between lenalidomide high-dose cyclophosphamide plus dexamethasone). In clinical reality, these analyses are not likely to be relevant in terms of choice of comparator. This was also confirmed by the clinical advisor at the Committee meeting.

However, since the Committee wants to consider chemotherapy as an option for a small group of patients, Celgene have widened the original systematic review in an attempt to find more evidence for chemotherapy. Two additional papers were found which indicate substantially worse outcomes than those presented in the original submission (where bendamustine efficacy was used as a proxy). We hope the additional published evidence identified help to further clarify the limited clinical value of chemotherapy in this indication.

3. Evidence on health-related quality of life

Scenarios are presented to address Committee uncertainty around long-term quality of life, which demonstrate and confirm that lenalidomide remains cost-effective compared to bortezomib retreatment, even without accounting for this underlying uncertainty.

4. Evidence on costs

Scenarios are presented to address expressed uncertainty around costs and the use of subsequent therapies. Evidence is presented on the use of bortezomib retreatment (in relation to the maximum duration of treatment and likely link between duration of treatment and efficacy). The clinical specialist at the first Appraisal Committee meeting highlighted the variation in UK practice in relation to retreatment, with some physicians treating until progression (as is the case for the key evidence sources) and some limiting treatment to a maximum of 8 cycles. The SPC is also unclear on the maximum treatment duration for either retreatment or monotherapy, and the key trial appraised for bortezomib in TA129 includes treatment beyond 8 cycles.

In response to AC comments both bortezomib and lenalidomide third line costs are presented including the relevant patient access schemes. It should be noted that the existing patient access scheme for lenalidomide at third line was in fact included in the original modelling work submitted by Celgene.

5. Updated cost-effectiveness analysis

Updated cost-effectiveness analyses are presented incorporating the additional analyses detailed in Sections 1 to 5 and suggested changes noted by the ERG at the initial Committee meeting. These analyses continue to demonstrate lenalidomide to be a cost-effective use of NHS resources.

In the updated base case analysis lenalidomide is dominant when compared to bortezomib retreatment. Deterministic model results show a cost saving of £13,634 per patient over a lifetime, and a QALY gain of 0.81 (probabilistic results show a 100% chance of cost-effectiveness at a threshold of £20,000/QALY).

Compared to melphalan plus prednisolone, a representative chemotherapy agent, the base case analysis provides an ICER of £54,898 for lenalidomide plus dexamethasone. This is achieved through a cost increase of £54,414 and 0.99 incremental QALYs. However there is evidence that chemotherapy agents are rarely used in practice, which was the main reason the Committee decided that bendamustine was not a relevant comparator.

Scenario analysis shows that lenalidomide remains cost-effective compared with bortezomib retreatment regardless of the assumptions made around (1) sequencing, (2) the curve fits selected, the source of comparator efficacy evidence used for retreatment, (3) the inclusion of the bortezomib price discount, and (4) the time horizon used and (5) the source of utilities.

Two key scenarios have the potential to impact the cost-effectiveness of lenalidomide compared to bortezomib retreatment:

- The number of cycles of bortezomib retreatment given to patients – in a highly conservative scenario where patients are limited to 8 cycles of bortezomib (when given in combination with dexamethasone), and assuming bortezomib efficacy to be constant, the ICER for lenalidomide is £31,999. When a maximum of 19 cycles is assumed (the maximum observed within the Taverna data used for efficacy, where patients still remained on treatment at the time of analysis) lenalidomide is cost-effective with an ICER of £15,409.
- Using the updated MTC to inform the efficacy of bortezomib retreatment increases the ICER to £8,120, with lenalidomide remaining cost-effective but no longer dominant. This is a highly conservative scenario however, as it assumes bortezomib retreatment is equally as effective as initial bortezomib.

Thank you once again for the opportunity to respond to the ACD and we hope that these additional analyses and clarifications will adequately inform the AC.

Yours sincerely

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Section 1: Update of comparative efficacy analysis versus bortezomib retreatment

Summary:

- Committee members raised concerns that the evidence presented was not sufficient to show that lenalidomide was more effective than retreatment with bortezomib. One key area of concern regarding this comparison was the methods used to adjust available data for lenalidomide to compare it to bortezomib retreatment, which was originally undertaken due to a lack of sufficient comparative efficacy data for bortezomib retreatment.
- Celgene have therefore conducted additional analyses to resolve the uncertainty surrounding the decision problem that stems from this issue.
- The additional analyses have four components:
  - Comparative efficacy evidence is presented from a mixed treatment comparison (MTC), which demonstrates that lenalidomide is more effective than bortezomib at second line, even if bortezomib is given for the first time.
  - Comparative efficacy evidence is presented from the only published RCT evidence for bortezomib retreatment versus lenalidomide, which shows that patients receiving lenalidomide had a higher rate of response to treatment.
  - All available data for bortezomib retreatment are analysed versus pooled MM-010 and MM-009 trial data, which allows a greater sample size and reduces uncertainty around the effectiveness of lenalidomide. Results are presented using a transparent model selection process based upon factors previously shown/accepted to significantly affect overall survival (OS), progression-free survival (PFS) or time to treatment failure (TTF).
  - Comparative efficacy is presented using both the mean of covariates method previously submitted and the Evidence Review Group (ERG) preferred methodology.
- All available evidence is conclusive and shows that lenalidomide is more effective at second line than bortezomib, regardless of whether the latter is given for the first time or as retreatment.

Context

In the ACD the Committee concluded that, when offered second line, lenalidomide was likely to be more effective than placebo and standard chemotherapy, but that it was unclear whether lenalidomide was clinically more effective than retreatment with bortezomib (Section 4.4). The Committee heard from the clinical experts that lenalidomide would be expected to be more effective than bortezomib retreatment. However, the Committee noted that there was currently no robust evidence to support this view given the concerns relating to the modelling methodology used to carry out comparisons.

Within the initial submission, comparison to bortezomib retreatment was made using available published evidence. The study by Taverna *et al*[1] was selected as the primary source of evidence for bortezomib retreatment as this was the largest study containing OS evidence. None of the bortezomib retreatment studies contained comparative evidence, and

as such it was not possible to conduct formal MTCs or indirect comparisons. Therefore, the mean of covariates method was used to simulate lenalidomide efficacy in a comparative population to each individual study available and median OS and PFS results from the bortezomib retreatment studies were used to produce comparative efficacy estimates.

Whilst the above method applied is a standard and known approach in situations where comparative published evidence is scarce, four key concerns with comparative efficacy estimates were raised, leading the Committee to believe that the methods used to estimate the efficacy of lenalidomide compared with bortezomib were not fully robust (Section 4.8 and 4.9). The following specific issues were raised:

- The selection criteria used to determine which covariates were adjusted for to make comparisons as fair as possible were not transparent and did not appear to match published evidence
- The equations used produced a surprising result for comparative PFS when using the Taverna *et al*[1] paper, which did not match clinical expectation
- Not all evidence had been taken into account when making comparisons: the Hrusovsky *et al*[2] paper was omitted for bortezomib retreatment and only the MM-010 study was used for lenalidomide

The ERG had an additional concern that use of the mean of covariates method might introduce bias to the analysis and therefore suggested use of an alternative method (corrected group prognosis) to produce comparative efficacy estimates.

The Committee concluded that the most plausible ICER presented at the first meeting was at least £22,000, and that the actual value was dependent on uncertainties. Additional analyses have therefore been conducted to resolve the uncertainty surrounding the decision problem that stems from the above issues. The additional analyses performed had four components:

1. Comparative efficacy evidence is presented from an MTC which demonstrates that lenalidomide is more effective than bortezomib at second line even if bortezomib is given for the first time.
2. Comparative efficacy evidence is presented from the only published source of comparative evidence for bortezomib retreatment vs lenalidomide which shows that patients receiving lenalidomide had a higher rate of response to treatment.
3. All available data for bortezomib retreatment are analysed versus pooled MM-009 and MM-010 trial data, which allows a greater sample size and reduces uncertainty around the effectiveness of lenalidomide. Results are presented using a transparent model selection process based upon factors previously shown/accepted to significantly affect OS, PFS or TTF.
4. Comparative efficacy is presented using both the ERG preferred methodology and the mean of covariates method previously submitted.

1. Comparative efficacy for lenalidomide vs initial bortezomib in relapsed or refractory multiple myeloma

An MTC of bortezomib as an initial treatment and lenalidomide plus dexamethasone in relapsed/refractory multiple myeloma was previously undertaken by Celgene. This was an update of the MTC submitted with TA 171[3], replicating its methodology and identifying an additional relevant study. This updated MTC is currently in publication development.[4, 5] This was not submitted initially because Celgene felt it was not relevant to the patient population of interest in the appraisal. However, following the discussions at the Committee meeting, Celgene is including this piece of evidence to allay concerns around the confidence of lenalidomide efficacy.

A systematic literature search was carried out between December 2010 and January 2011 to identify relevant clinical studies. No head-to-head trial between bortezomib and lenalidomide plus dexamethasone exists, a finding confirmed by a re-filtered update of the search for the present NICE submission, which extended the search period to August 2013 (no additional relevant evidence was identified). However the common comparator dexamethasone allowed for a connected network of pair-wise treatment comparisons with bortezomib as an initial treatment. Four studies were included in the MTC MM-009[6], MM-010[7], APEX [8] and DOXIL[9]. The inclusion of the DOXIL study provided greater power to the analysis than was possible in the original indirect comparison conducted for TA171.

Indirect comparisons were derived with the Bucher method and with Bayesian methods (random effect and fixed effect MTC). Hazard ratios (HRs) were employed for time to progression (TTP) (the primary endpoint in the studies) and for OS.

With respect to the primary endpoint, TTP, the updated indirect treatment comparison significantly favoured the lenalidomide plus dexamethasone regimen over bortezomib (Bucher: HR 0.63, 95% confidence interval (CI) [0.42, 0.92]; MTC: HR 0.64, 95% CI [0.41; 0.95]). With respect to the secondary endpoint OS, a 28% higher chance of survival with lenalidomide plus dexamethasone therapy was observed (Bucher: HR 0.68, 95% CI [0.41, 1.10][a]; MTC: HR 0.72, 95% CI [0.49; 1.01]). The other MTC-derived parameters (response and safety) showed no statistically significant differences, though numerical advantages for lenalidomide plus dexamethasone compared with bortezomib were seen in the thrombocytopenia and peripheral neuropathy analyses.

The APEX study was a randomised, multicentre phase 3 study across Europe, North America and Israel designed to compare bortezomib plus high-dose dexamethasone with monotherapy dexamethasone for the treatment of multiple myeloma following relapse on 1-3 prior therapies. Study patients had not received bortezomib prior to study entry, and so there was no bortezomib retreatment as per the present decision problem.

All patients in the DOXIL study were also bortezomib-naïve. However, given the clinical expectation of better response to initial exposure to a therapy, compared to retreatment with the same therapy, the impact of bortezomib retreatment may be inferred from the results of the study. The DOXIL study was a randomised, multicentre study, designed to compare bortezomib and pegylated liposomal doxorubicin with bortezomib monotherapy. Patients

[a] Calculation based upon the log standard error presented in the MTC appendices

had progressed following response to at least 1 prior therapy, or were refractory to initial treatment.

The APEX, DOXIL and MM studies are reasonably comparable in terms of patient characteristics, and the superior clinical performance of lenalidomide compared to bortezomib is evident from the data presented in Table 1, which shows summary outcomes from the studies.

The HR results from the indirect comparison are consistent with the comparative efficacy estimates for bortezomib retreatment, presented in point 4 below. The MTC HRs have been used to inform the comparative efficacy of bortezomib retreatment in a scenario analysis. This scenario utilises RCT evidence and is a highly conservative assumption since the MTC results relate to initial treatment with bortezomib, rather than retreatment which would be clinically expected to result in worse outcomes.

Table 1: Summary of clinical outcomes from APEX, DOXIL MM-010/MM-009 studies

Outcome	APEX[8]	DOXIL[9]	MM-010[7]	MM-009[6]
Patient characteristics (intervention arm)	Patients had progressed after 1-3 prior therapies. No patients had received prior BOR. 67% received prior SCT/HDT. Median patient age = 62 years. Median time since diagnosis = 3.5 years.	Patients had progressed following response to 1 or more prior therapy, or were refractory to prior therapy. 34% of patients had received 1 prior therapy (66% had received >1). 54% of patients received prior SCT. Median patient age = 62 years. Median time since diagnosis = 3.8 years.	Patients had progressed after at least 2 cycles of anti-myeloma therapies 4.5% of patients had received prior BOR.55.1% received prior SCT/HDT. Median patient age = 63 years. Median time since diagnosis = 4.2 years.	Patients had progressed after at least 2 cycles of anti-myeloma therapies 10.7% of patients had received prior BOR.61.1% received prior SCT/HDT. Median patient age = 64 years. Median time since diagnosis = 3.1 years.
Median cycles of study drug received	6[10]	5	11	12
Median OS	29.8 months[10]	NR	37.2 months	39.1 months
Median TTP	6.2 months	6.5 months	18.8 months	17.7 months
CR	6%	2%	15.3%	13.0%
PR	32%	39%	43.8%	47.5%
Progressive disease	7%	NR	2.8%	2.8%
Not evaluable	3%	NR	9.1%	8.5%
Patients experiencing ≥1 grade 3 / 4 AE	61% / 14%	64% (grade 3 or 4)	75.6% / 25.0%	80.2% / 27.7%
Thrombocytopenia, grade 3 / 4	26% / 4%	8% / 8%	8.5% / 1.7%	13.0% / 1.1%
Peripheral neuropathy, grade 3 / 4	7% / 1%	9% (grade 3 or 4)	1.1% / 0.0%	1.7% / 0.0%

2. Available evidence for lenalidomide after bortezomib

Whilst the number of patients receiving lenalidomide after bortezomib is limited in the MM-009 and MM-010 trials, there is evidence available for the efficacy of lenalidomide following bortezomib from analysis of subsequent treatments given in the VISTA trial.[11]

Lenalidomide had a demonstrably better response rate at second line following bortezomib than either retreatment with bortezomib or thalidomide: 73% compared to 41% and 37%, respectively.

Data for bortezomib retreatment show that response rates are substantially lower than response rates with initial treatment, even when only patients showing previous response are assessed.[1, 2, 12] Response rates are even lower in patients who have not previously achieved partial response.[13, 14] Given that lenalidomide plus dexamethasone is more effective than bortezomib as an initial treatment it follows logically that lenalidomide plus dexamethasone is even more effective when compared to bortezomib as retreatment. This was accepted as a valid clinical argument subsequent to the ACD through clinical expert feedback.

Also when previously a total of 15 leading haematologists were surveyed and asked whether a prior treatment with VMP (bortezomib, melphalan and prednisone) would impact the treatment effect for lenalidomide at second line relative to what was observed in the MM-009 and MM-010 trials, there was a 100% response to the survey and all responses reported that the treatment effect of lenalidomide following VMP can be expected to be similar if not better relative to the response rates/ TTP observed in the MM-009 and 010 trials.[15]

The same cannot be said for repeat treatment with bortezomib where all available literature indicates efficacy is reduced with retreatment.[1, 2, 12]

3. Updated survival analysis

Survival analysis was re-run to provide the Committee with greater clarity regarding the methods used to conduct comparative efficacy analysis and also to make use of the maximum amount of data available for lenalidomide to increase certainty in outcomes.

Parametric survival models were developed that included coefficients to allow adjustment for clinically important factors. Models for OS, TTP, PFS and TTF were produced using pooled MM-010 and MM-009 trial data according to the following process:

- Step 1: Unadjusted models were run to determine the parametric survival models that provide the best fit to the data with no covariate adjustment.
- Step 2: Relevant covariates were identified to test for prognostic significance in the survival models using the publications, CSRs and clinician feedback.
- Step 3: Stepwise regression analysis was performed to inform the selection of covariates into the final models. This showed which of the variables identified in Step 2 are important within, and across, the different models.
- Step 4: Covariate-adjusted parametric survival models were estimated to produce the final survival models which were adjusted for the most relevant variables, as determined in Step 3.

3.1 Unadjusted models

Parametric models were fitted to the pooled OS, PFS, TTF and TTP data to determine which were most likely to characterise the data for each variable. OS, PFS and TTF are used within the model to estimate comparative cost-effectiveness. TTP was included within the analysis as TTP Kaplan–Meier data were available from three publications for the efficacy of bortezomib retreatment, which in turn allowed validation of the methodology used to estimate comparative OS, PFS and TTF.

The following distributions were evaluated:

- Exponential
- Gompertz
- Log-logistic
- Weibull
- Log-normal
- Gamma
- Piecewise exponential
- Piecewise Gompertz

<u>Overall survival</u>

The Gompertz and gamma distributions offered the best visual fits to the Kaplan–Meier data for OS (see Appendix A for all parametric curve fits with no covariate adjustment). These also provided among the lowest Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics (see Table 2). The exponential model provided the next-best fit to the data, while the Weibull model offered a moderate fit. The log-logistic and log-normal curves did not fit the data well, either visually or by AIC and BIC statistics.

The clinical validity of the long-term extrapolation of these models was also evaluated. All models predict relatively similar 5-year OS (29.4% to 37.7%), but substantial variation is present at 10 years. The gamma and Gompertz models predict 10-year survival of 2.1% and 4.2%, respectively, while the log-logistic and log-normal models appear to overestimate survival (19.1% and 21.9%, respectively). At 20 years, the gamma and Gompertz models predict less than 0.01% survival, while the log-logistic and log-normal models continue to predict much higher survival (9.2% and 11.0%, respectively). The exponential and Weibull models results are consistently in between these extremes.

<u>Piecewise overall survival</u>

The original submission to NICE included a piecewise exponential model to characterise OS. Based upon visual inspection of the Kaplan–Meier plot for the pooled MM-010 and MM-009 trial data, a piecewise approach does not appear to be obviously necessary for this updated analysis. For completeness, we have however included the piecewise models in this updated analysis as scenario analyses, since a piecewise model was included in the original submission.

For the piecewise scenario analysis, parametric models were fitted to the survival data after 100 weeks (at which point there appears to be a slight change in gradient of the Kaplan–

Meier plot). Survival during the initial 100 weeks, preceding the parametric curve, were informed by the observed Kaplan–Meier data, given the large number of observations informing early survival. This therefore provides a piecewise approach scenario analysis, with OS split into observed and extrapolated sections.

The exponential curve was the best for characterising OS beyond 100 weeks in terms of AIC and BIC and visual goodness of fit. The Gompertz and Weibull curves also performed well visually. The gamma distribution was a weak predictor in terms of AIC and BIC, while the log-logistic and log-normal were omitted because both predicted unrealistically long 'tails' of extended survival. As this was a scenario analysis, only the exponential and Gompertz models have been used to include a piecewise approach.

Progression-free survival

The gamma model provided the best fit to the pooled PFS data, both visually and by AIC. It also had the second-lowest BIC statistic. The log-logistic and log-normal models provided reasonable fits to the data visually, while the exponential and Weibull models were weak models. Despite relatively high AIC and BIC statistics, the Gompertz model appeared to visually fit the Kaplan–Meier data well.

Time to treatment failure

Only the exponential and Weibull models offered poor visual fits to the pooled TTF data, and these also produced the highest AIC and BIC statistics. All other models appeared visually strong fits to the data, particularly the gamma and Gompertz distributions despite not possessing the lowest AIC or BIC statistics.

Time to progression

The parametric models were, overall, slightly weaker fits to TTP data; the log-normal and log-logistic did not characterise these data as well as the TTF data. The Gompertz and gamma were strong visual fits, and the gamma had the lowest AIC and BIC statistics (see Appendix B).

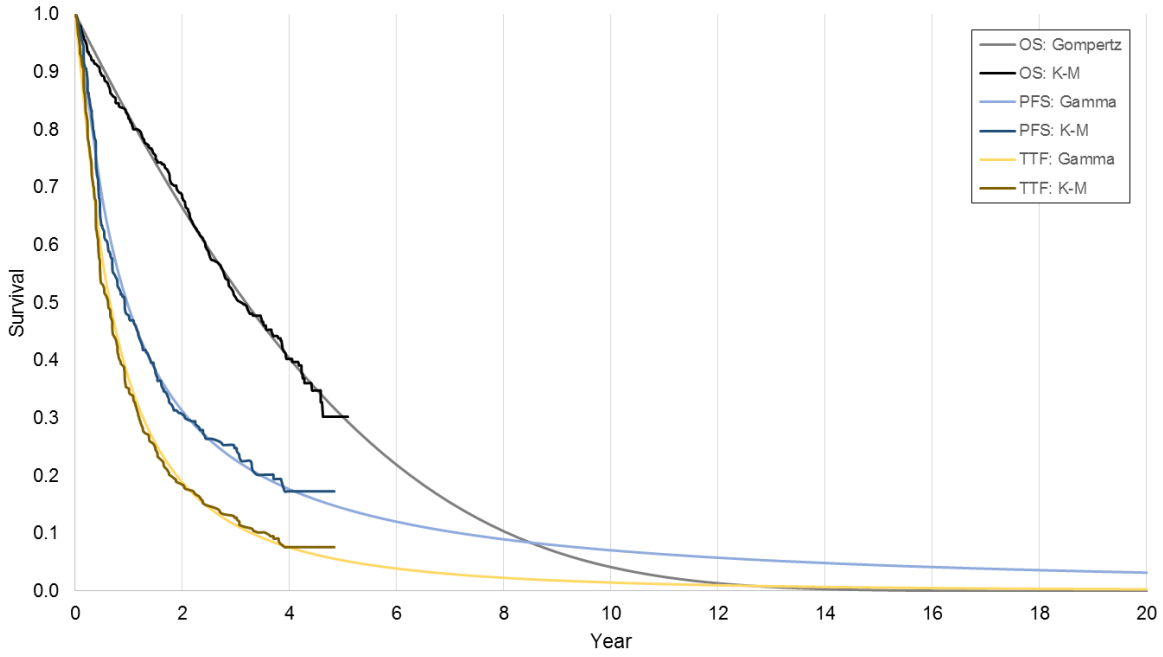
Table 2: Goodness of fit statistics (AIC and BIC) for unadjusted parametric survival models

Measure of goodness of fit	Parametric model	AIC, BIC statistics			
		OS (full)	OS (post-100 weeks, scenario)	PFS	TTF
AIC statistic	Gompertz	911.2 *	514.1	893.8	1068.4
	Gamma	912.2	515.3	876.9 *	1059.9
	Exponential	912.0	512.1 *	919.8	1102.2
	Weibull	913.2	514.1	915.4	1092.9
	Log-normal	937.1	514.2	878.5	1058.0
	Log-logistic	923.3	514.3	884.0	1054.1 *

BIC statistic	Gompertz	918.9	520.9	901.5	1075.9
	Gamma	923.8	525.5	888.5	1071.2
	Exponential	915.9 *	515.5 *	923.6	1105.9
	Weibull	920.9	520.9	923.1	1100.4
	Log-normal	944.9	521.0	886.2 *	1065.6
	Log-logistic	931.1	521.1	891.8	1061.7 *

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.
* denotes lowest AIC or BIC statistic
Note: TTP goodness of fit statistics are not shown as TTP is not used in the cost-effectiveness analysis.

Figure 1: Best-fitting unadjusted OS, PFS and TTF models, with respective Kaplan–Meier plots



Key: OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.

Based upon these assessments, the curve choices to be selected for the base case cost-effectiveness analysis and scenario analyses for each clinical outcome are provided in Table 3. Full, updated cost-effectiveness results are provided in Section 5.

Table 3: Parametric model selection for cost-effectiveness analysis

Outcome	Base case model	Scenario analyses	Justification
OS	Gompertz	Gamma, exponential, Weibull, piecewise exponential, piecewise Gompertz	Best visual fit and low AIC/BIC statistic. Log-normal and log-logistic do not fit the data well. Piecewise models (split by KM and parametric) scenario analyses.
PFS	Gamma	Gompertz, log-normal, log-logistic	Best visual fit and low AIC/BIC statistic. Exponential and Weibull do not fit the data well.
TTF	Gamma	Gompertz, log-normal, log-logistic	Consistent with PFS and TTP

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure; TTP, time to progression.
Note: TTP curve fits not presented as TTP is not used in the cost-effectiveness analysis.

3.2 Identification of relevant covariates

The variables identified as potentially relevant determinants of clinical outcomes, based upon analysis presented in the clinical study reports (CSRs) for MM-010 and MM-009 and associated publications, are presented in Table 4. The CSRs were searched first and additional variables were added from relevant publications. Clinical experts were also consulted via personal communications to inform the relevant covariates, and all variables highlighted by clinicians were included.

Table 4: Variables identified for testing as potentially relevant prognostic factors

Source for inclusion	Variable	Definition
MM-010 CSR[7]	Prior thalidomide	Yes or no
	Prior doxorubicin	Yes or no
	Prior bortezomib	Yes or no
	Worsening extramedullary plasmacytoma disease	Yes or no
	Baseline bone marrow cellularity-aspirate/biopsy	Normal, hyperplasia, hypoplasia or missing
MM-009 CSR[6]	Prior melphalan	Yes or no
	Baseline plasma cell %	High or low
Dimopoulos *et al*[16]	Baseline beta-2 microglobulin	>2.5 or ≤2.5 mg/L
	Duration of multiple myeloma	Years
	Lytic bone lesions present at baseline	Yes or no
	Prior high-dose therapy or stem cell transplant	Yes or no
	Prior dexamethasone	Yes or no

Source for inclusion	Variable	Definition
	Baseline ISS score	1, 2 or 3
	Baseline plasma cell %	High or low
Stadtmauer *et al*[17]	Number of prior anti-myeloma therapies	1 or 2+ Note: required to produce estimates for the population of interested (1 prior therapy)
	Age	Years
Clinical advice	Sex	Male or female

Key: CSR, clinical study report; ISS, International Staging System.

3.3 Stepwise regression to inform selection of covariates

Stepwise regression analysis was performed for the full ITT population data, using all covariates identified as being potential prognostic factors (listed in Table 4). Variables with non-significant p-values were omitted in turn. The criterion for omitting a variable was if the p-value was less than 0.05. The proportion of patients who had received one or two or more prior therapies was forcibly kept in the stepwise process, as this covariate is required to present outcomes for a second-line population. The results of the stepwise regression analyses are provided in in Appendix C (results for TTP in Appendix B).

Myeloma duration, beta-2 microglobulin, the number of prior therapies (one or two or more) and worsening extramedullary plasmacytoma disease were found to be consistently significant prognostic factors for OS, PFS, TTF and TTP, as would be expected in clinical practice, and therefore these covariates were selected for inclusion in the final adjusted survival models.

3.4 Adjusted survival models

The stepwise regression results were assessed to inform the final, covariate-adjusted models. Any variable was included if it was significant ($p<0.05$) in influencing OS and one or both of the other outcomes to be included in the cost-effectiveness model (PFS and TTF). OS was afforded preference as it is the most important clinical outcome and the driver of cost-effectiveness results. This selection rule prevented the inclusion of variables that statistically appear to affect only one variable, avoiding clinical inconsistencies whereby only one of two related variables is adjusted. An example of this is the presence of hyperplasia as a determinant of PFS, which is not a statistically significant covariate for OS in any of the preferred models (only the poor-fitting log-logistic and log-normal models).

The results of these regression analyses to determine the final models are provided in Table 5 to Table 8 (results for TTP are provided in Appendix B). The final models selected are presented in Figure 2 as they are used in the cost-effectiveness analysis. The final models are consistent with the observed Kaplan-Meier data from second-line patients in the trial therefore providing validation of the model.

Although the curves for different clinical outcomes cross over, the Committee noted that this is not itself an issue and that curves should be selected based upon how well they fit the data. In the cost-effectiveness analysis, the OS curves takes precedence if it falls below any other curve.

Table 5: Final models – full OS

Parameter	Coefficients			
	Exponential	Gamma	Gompertz	Weibull
Myeloma duration (years)	-0.081	0.063	-0.086	-0.084
Beta-2 microglobulin >2.5mg/L	0.745	-0.609	0.791	0.767
2+ prior therapies	0.583	-0.517	0.610	0.598
Worsening Ex PD	0.902	-0.722	0.966	0.943
Intercept	-6.119	6.148	-6.445	-6.711
Gamma			0.003	
Rho				1.113
Sigma		0.651		
Kappa		1.658		
Key: Ex PD, extramedullary plasmacytoma disease; OS overall survival.				

Table 6: Final models – OS beyond week 100 (for piecewise, Kaplan–Meier and curve scenario analysis)

Parameter	Coefficients			
	Exponential	Gamma	Gompertz	Weibull
Myeloma duration (years)	-0.099	0.099	-0.099	-0.100
Beta-2 microglobulin >2.5mg/L	0.726	-0.700	0.740	0.738
2+ prior therapies	0.789	-0.755	0.794	0.794
Worsening Ex PD	1.011	-0.997	1.014	1.015
Intercept	-5.949	5.834	-6.055	-6.260
Gamma			0.002	
Rho				1.066
Sigma		1.010		
Kappa		0.862		
Key: Ex PD, extramedullary plasmacytoma disease; OS overall survival.				

Table 7: Final models – PFS

Parameter	Coefficients			
	Gamma	Gompertz	Log-logistic	Log-normal
Myeloma duration (years)	0.060	-0.051	0.056	0.058
Beta-2 microglobulin >2.5mg/L	-0.647	0.524	-0.679	-0.653
2+ prior therapies	-0.405	0.476	-0.510	-0.452
Worsening Ex PD	-0.880	1.041	-0.911	-0.951
Intercept	4.349	-4.716	4.569	4.523
Gamma			0.743	
Rho				
Sigma	1.308			1.277
Kappa	-0.236			

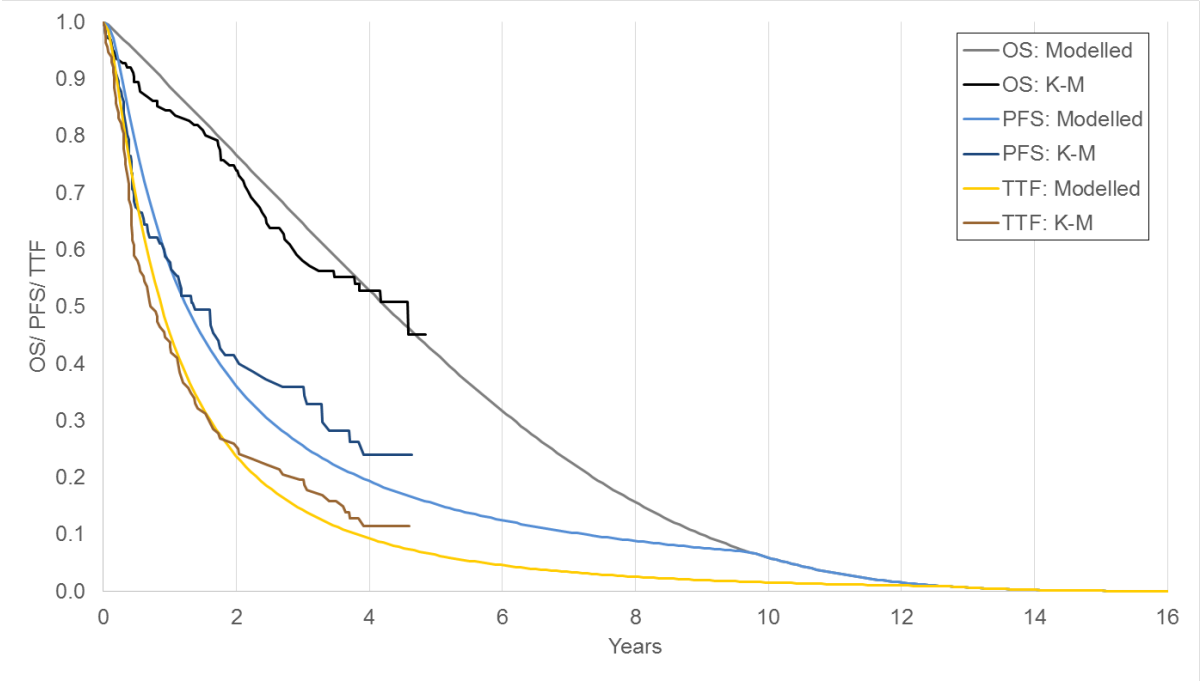
Key: Ex PD, extramedullary plasmacytoma disease; PFS, progression-free survival.

Table 8: Final models – TTF

Parameter	Coefficients			
	Gamma	Gompertz	Log-logistic	Log-normal
Myeloma duration (years)	0.043	-0.029	0.041	0.047
Beta-2 microglobulin >2.5mg/L	-0.618	0.533	-0.616	-0.603
2+ prior therapies	-0.409	0.353	-0.390	-0.403
Worsening Ex PD	-0.665	0.727	-0.564	-0.614
Intercept	4.161	-4.319	4.055	4.032
Gamma			0.704	
Rho				
Sigma	1.216			1.237
Kappa	0.172			

Key: Ex PD, extramedullary plasmacytoma disease; TTF, time to treatment failure.

Figure 2: Base case OS, PFS and TTF models using all trial data and covariate analysis versus second-line K-M plots



Key: OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.

Two methods were employed to predict survival for each of the clinical outcomes using data for covariates included in the final model selected[18]. The mean of covariates method was used to estimate OS and PFS in the original submission, and is again included for consistency. The corrected groups prognosis method was highlighted by the Evidence Review Group as being a potentially superior method, avoiding biased results were a mean covariate comes from a skewed distribution. The results of these methods are presented in turn below.

3.5 Mean of covariates method

The following patient inputs, from the pooled MM-010 and MM-009 trial data, were used to predict the outcome of interest for the 'average' patient in the intention-to treat (ITT), second-line and third-line populations:

Table 9: Pooled MM-010 and MM-009 trial data – patient characteristics

Variable	ITT population	Second-line population	Third-line population
1 prior therapy (vs 2+ prior therapies)	64.9%	100%	0.0%
Myeloma duration	3.9 years	2.7 years	4.6 years
Beta-2 microglobulin level >2.5 mg/L	70.8%	63.7%	74.7%
Worsening extramedullary plasmacytoma disease	3.4%	5.6%	2.2%
Key: ITT, intention-to-treat.			

3.6 Corrected group prognosis method

The ERG expressed concern that the mean of covariates method might provide biased results. As such a second approach to predicting survival, the corrected group prognosis method, was explored. Rather than applying a mean covariate value to all patients, this involves predicting the relevant clinical outcome for each 'possible patient' and calculated the average survival (weighted by the chance of each possible patient occurring).

For example, 70.8% of pooled MM-010 and MM-009 patients had a beta-2 microglobulin level of >2.5mg/L. Application of this value (0.708) is sufficient for a mean of covariates model, by assuming that the 'average patient' has a 70.8% likelihood of having beta-2 microglobulin of >2.5mg/L. The corrected group prognosis approach would instead estimate survival for a patient who presents with beta-2 microglobulin >2.5mg/L, and every possible combination of other covariates, and then do the same for a patient who presents with beta-2 microglobulin level ≤2.5mg/L. The resulting array of survival estimates are then weighted by the likelihood of each type of patient presenting and summed to give a corrected group prognosis survival estimate.

The same method that was used to adjust the pooled dataset is also used to estimate the comparative efficacy of bortezomib. However, as no patient-level data were available for bortezomib, the following simplifying assumptions had to be made:

- The likelihood of a patient presenting in one particular clinical group has no bearing on the likelihood that the patient falls within any other group. For example, the likelihood of having worsening extramedullary plasmacytoma disease is independent of having a beta-2 microglobulin level >2.5mg/L.
- Patients were distributed into myeloma duration groups of 0–1 year, 1–2 years, 2–3 years and so on, up to 15+ years. The actual duration within each group was assumed to be the midpoint of that group (for example, a patient in the '3–4 years' was assumed to have been diagnosed 3.5 years ago).

Plotted survival curves are presented in Appendix D for all fitted models included in the updated cost-effectiveness model. In general, the mean of covariates method predicts slightly higher short-term survival but lower long-term survival compared to the corrected group prognosis method. Results are very similar, however, using the two methods and in all cases the Kaplan–Meier data available lies between the two methods tested. As such the mean of covariates method is presented in the cost-effectiveness analysis base case as it is a more conservative estimate of long-term survival, and the corrected group prognosis method is presented as scenario analysis.

4. Statistical analysis of the comparative efficacy of bortezomib retreatment

The available evidence for bortezomib retreatment was used to estimate the comparative efficacy of lenalidomide plus dexamethasone relative to bortezomib retreatment. Where possible, the available evidence was used to adjust the pooled MM-010 and MM-009 dataset (ITT patients) to more closely match each comparative study.

Details of patient characteristics for the covariates included in the final models were extracted from the literature identified (presented in Table 10). These values were used in the final models, with the associated coefficient, to provide an estimate of the lenalidomide results if the MM-010 and MM-009 populations had matched patients in the study of interest in these covariates. With survival estimated using the mean of covariates method, these

comparative point estimates simply replaced the original estimates from the MM-010 and MM-009 pooled studies.

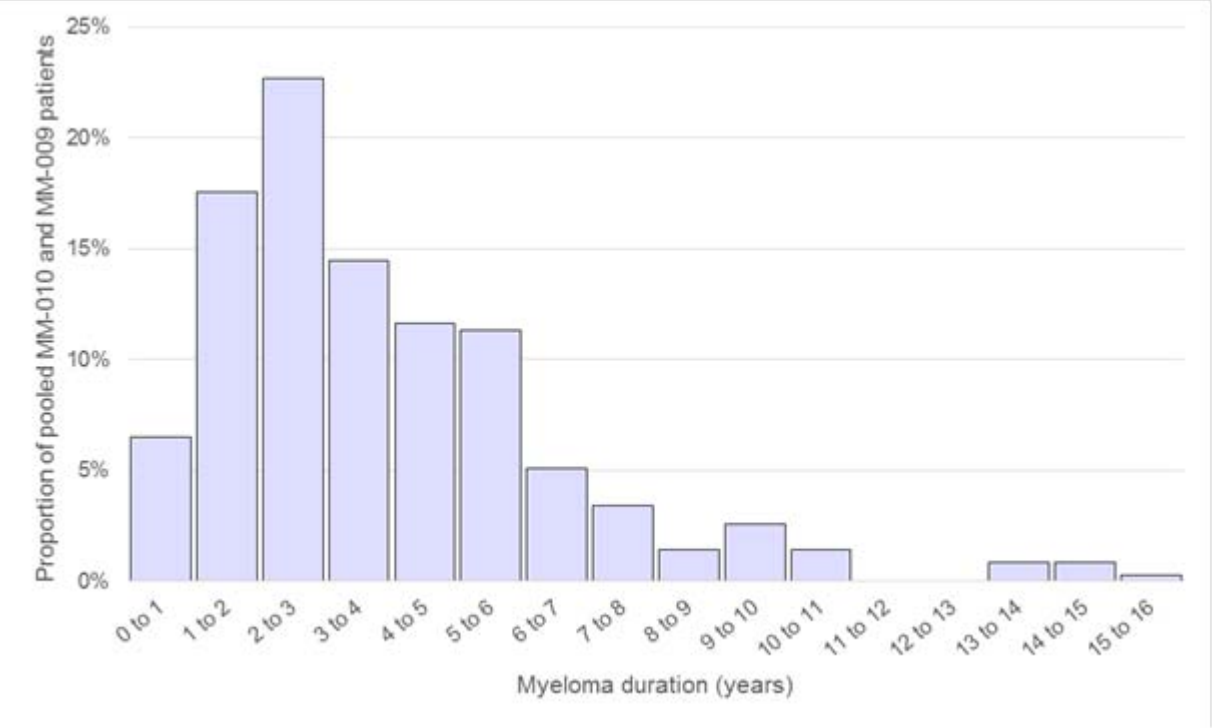
Table 10: Patient characteristics from the literature identified – BOR retreatment

Source	Characteristic	Value
Taverna *et al*[1]	Myeloma duration	Median = 2.8 years
Hrusovsky *et al*[2]	Myeloma duration	Mean = 4.3 years
Sood *et al*[19]	Myeloma duration	Median = 3.7 years
Petrucci *et al*[12]	Myeloma duration 1 prior therapy (vs 2+ prior therapies)	Median = 4.5 years 11.5%
Dispenzieri *et al*[14]	Beta-2 microglobulin level >2.5 mg/L	100.0%
MM-009 and MM-010 ITT population[6, 7]	Myeloma duration 1 prior therapy (vs 2+ prior therapies) Beta-2 microglobulin level >2.5 mg/L Worsening extramedullary plasmacytoma disease	Median = 3.9 years 35.1% 70.8% 3.4%
Key: ITT, intention-to-treat.		

The predicted median outcome was used alongside the observed bortezomib median outcome to calculate a comparable HR for bortezomib relative to lenalidomide. This was possible for OS, PFS and TTP, as these were represented by at least one source of bortezomib evidence. Additionally, 'unadjusted' HRs were calculated that used outcomes from the pooled MM-010 and MM-009 studies with no adjustment for patient characteristics.

Estimating comparative efficacy based upon estimates from the corrected group prognosis method was limited by the lack of patient level data for comparator studies. Without this, the distribution of patients by multiple myeloma duration for each comparator study was unknown. As such, we assumed that the shape of the distribution of patients by myeloma duration was fixed according to the pooled MM-010 and MM-009 data, able only to shift in relation to the known mean or median input value. Similarly, where only a median value was available within a bortezomib study, it was assumed that the relationship between the mean and median was constant, meaning the distribution could be shifted according to either the difference in mean or median outcome (between the pooled study data and the comparator evidence). The distribution of pooled MM-010 and MM-009 patients by myeloma duration, which was allowed to shift to adjust for comparative myeloma duration evidence, is shown in Figure 3.

Figure 3: Distribution of pooled MM-010 and MM-009 patients by myeloma duration



The resulting HRs, including unadjusted HRs, are presented in Table 11 and Table 12. A HR >1 favours lenalidomide. For both OS and PFS for all papers using both methods lenalidomide is consistently predicted to be more effective than retreatment with bortezomib.

Table 11: OS HR estimates

Source of adjustment	Model type	HRs using mean of covariates method		HRs using corrected group prognosis method	
		LEN/DEX data adjusted	LEN/DEX data unadjusted	LEN/DEX data adjusted	LEN/DEX data unadjusted
Taverna *et al*[1]	Exponential	1.86	1.92	1.57	1.61
	Gompertz	1.89	1.94	1.63	1.67
	Weibull	1.86	1.91	1.58	1.61
	Gamma	1.92	1.96	1.62	1.67
	Piecewise exponential	1.83	1.85	1.63	1.65
	Piecewise Gompertz	1.85	1.87	1.66	1.68
Hrusovsky *et al*[2]	Exponential	2.11	2.04	1.77	1.71
	Gompertz	2.12	2.06	1.83	1.77
	Weibull	2.10	2.02	1.77	1.71
	Gamma	2.14	2.08	1.82	1.77
	Piecewise exponential	2.00	1.96	1.77	1.75
	Piecewise Gompertz	2.02	1.99	1.81	1.78
Key: HR, hazard ratio; LEN/DEX, lenalidomide plus dexamethasone; OS, overall survival.					

Table 12: PFS HR estimates

Source of adjustment	Model type	HRs using mean of covariates method		HRs using corrected group prognosis method	
		LEN/DEX data adjusted	LEN/DEX data unadjusted	LEN/DEX data adjusted	LEN/DEX data unadjusted
Taverna *et al*[1]	Exponential	1.06	0.90	1.44	1.29
	Log-logistic	1.08	0.96	1.26	1.15
	Log-normal	1.06	0.93	1.26	1.15
	Gamma	1.11	0.99	1.26	1.20
Hrusovsky *et al*[2]	Exponential	1.01	1.02	1.36	1.46
	Log-logistic	1.04	1.08	1.20	1.30
	Log-normal	1.02	1.05	1.20	1.30
	Gamma	1.06	1.12	1.20	1.36

Source of adjustment	Model type	HRs using mean of covariates method		HRs using corrected group prognosis method	
		LEN/DEX data adjusted	LEN/DEX data unadjusted	LEN/DEX data adjusted	LEN/DEX data unadjusted
Sood *et al*[19]	Exponential	1.11	1.43	1.36	2.06
	Log-logistic	1.04	1.52	1.20	1.83
	Log-normal	1.02	1.48	1.20	1.83
	Gamma	1.06	1.57	1.20	1.91
Petrucci *et al*[12]	Exponential	1.11	1.13	1.40	1.62
	Log-logistic	1.13	1.20	1.23	1.44
	Log-normal	1.08	1.16	1.26	1.44
	Gamma	1.11	1.24	1.26	1.50
Dispenzieri *et al*[14]	Exponential	1.42	1.67	1.20	1.26
	Log-logistic	1.32	1.64	1.32	1.42
	Log-normal	1.35	1.67	1.32	1.42
	Gamma	1.32	1.61	1.32	1.42
Key: HR, hazard ratio; LEN/DEX, lenalidomide plus dexamethasone; PFS, progression-free survival.					

The HRs presented above were implemented in the cost-effectiveness model alongside the other agreed changes to provide the Committee with updated cost-effectiveness results (email correspondence from NICE on 20 March 2014). The HRs estimated using the Taverna *et al* study are used in the base case analysis, this was the base case source of comparative efficacy in the original submission. This study was selected as it is the most comparable to the MM-010 and MM-009 studies, and provides information on both OS and PFS.

5. Validation of approach – bortezomib retreatment

Available TTP evidence for bortezomib retreatment was evaluated to determine how closely the methodologies used characterised the data. Kaplan-Meier TTP plots from Sood *et al* (2009)[19] and Petrucci *et al* (2013)[12] were digitised and plotted alongside the covariate-adjusted best-fitting gamma curve (see Appendix B).

The resulting figures are presented below, and show that the best available evidence may over-predict bortezomib TTP in the long-term relative to the observed data. This is because the fitted parametric models visibly fit the Kaplan-Meier plots reasonably well, particularly in the case of the Sood *et al* (2009) paper; however, the Kaplan-Meier plots fall to zero or close to zero for pre-progression survival, whereas the fitted curves predict extended TTP over time. It is therefore likely that the models overestimate long-term bortezomib retreatment efficacy and, as a result, provide a conservative estimate of the cost-effectiveness of lenalidomide.

Figure 4: Gamma models for TTP, having applied the HR to lenalidomide TTP adjusted for Sood *et al* characteristics, and TTP Kaplan-Meier plot for bortezomib retreatment from Sood *et al* (2009)

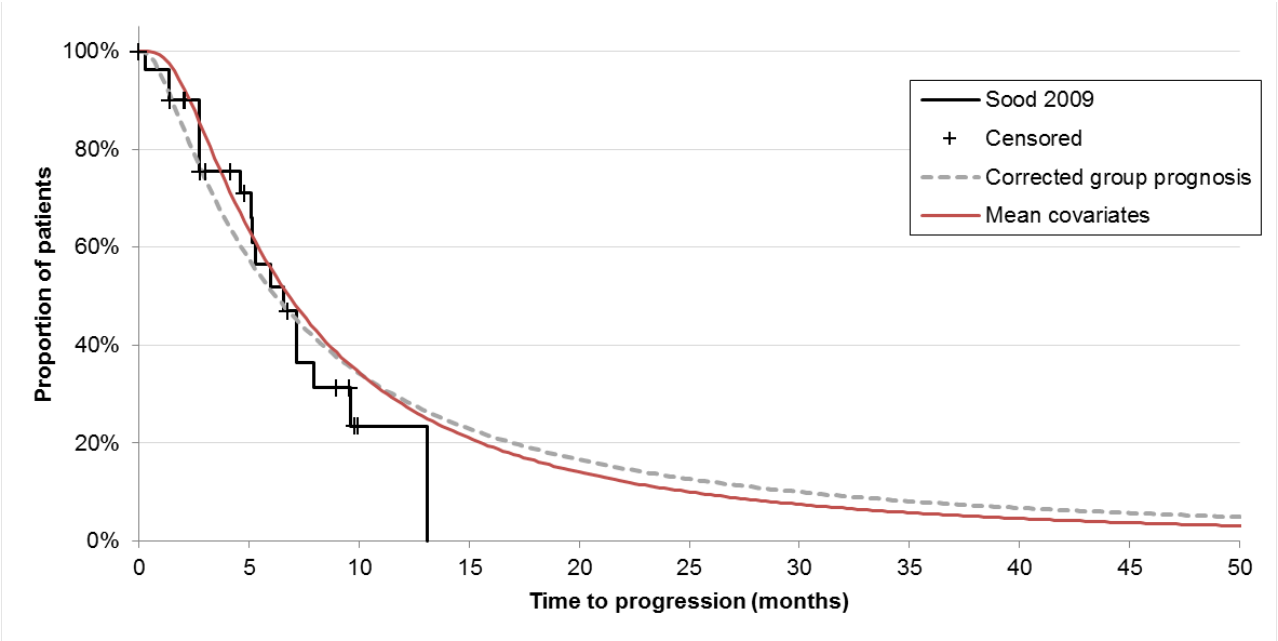
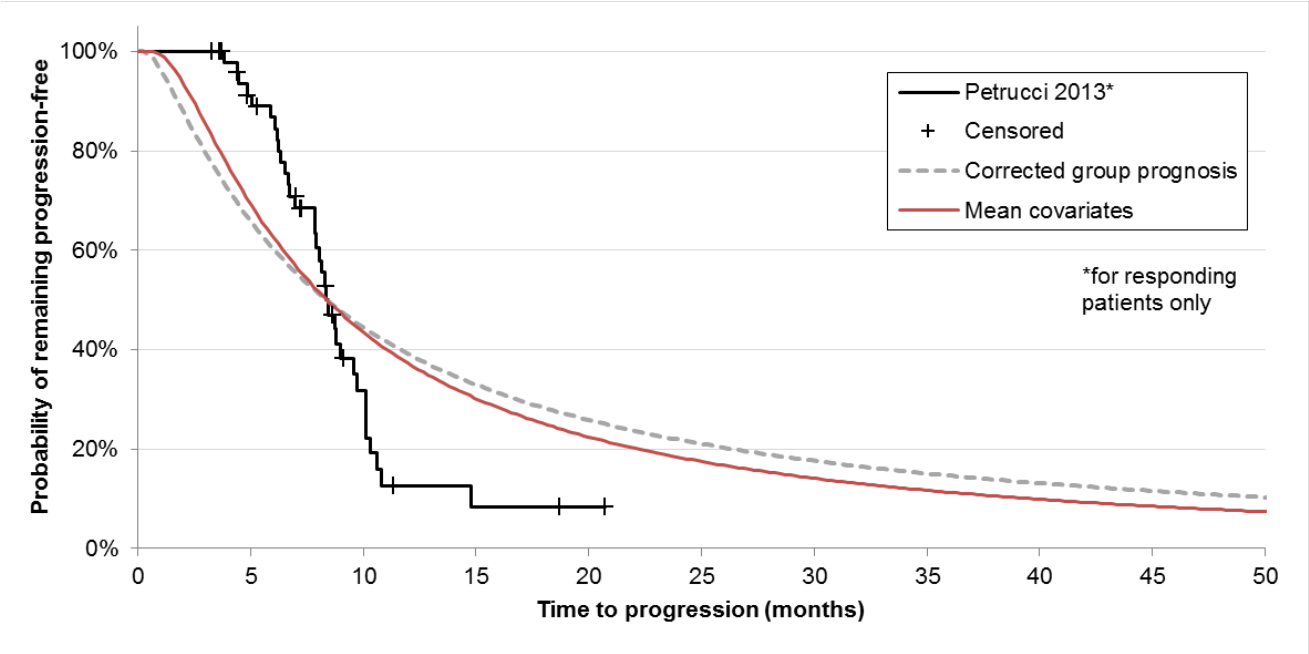


Figure 5: Gamma models for TTP, having applied the HR to lenalidomide TTP adjusted for Petrucci *et al* characteristics, and TTP Kaplan-Meier plot for bortezomib retreatment from Petrucci *et al* (2013)



Conclusion

The Committee raised concerns regarding the comparative efficacy of lenalidomide relative to bortezomib. Celgene have taken steps to reduce this uncertainty, presenting new evidence and analyses above.

The updated MTC included in this response demonstrates the effectiveness of lenalidomide compared to a first bortezomib treatment when given at second line, that is, in patients who had received one prior, non-bortezomib regimen (see page 8). To utilise the methodological strength of an MTC, its results are used to inform a scenario analysis on the comparative efficacy of bortezomib retreatment in this updated analysis. The only source of comparative evidence available, subsequent treatment data from the VISTA trial, also highlights the greater likelihood of response on lenalidomide relative to bortezomib retreatment.

The Committee noted that the MM-009 and MM-010 studies are very similar and pooling is a valid approach. Therefore, to provide more robust estimates of OS, PFS and TTF, the data were combined to create a larger dataset. Parametric survival models were assessed to determine which best characterised the data and to inform covariate-adjusted survival methods. This analysis was undertaken using the mean of covariates method, initially used in the present submission, and the ERG's preferred methodology, the corrected group prognosis approach.

Further analysis using the available bortezomib retreatment evidence provided an array of HRs demonstrating its effectiveness relative to lenalidomide. Across both methods used and all parametric curves and evidence sources, lenalidomide is estimated to provide improved clinical outcomes compared to bortezomib retreatment. This is consistent with the experience of clinical experts as shared at the first Committee meeting. Based upon the best-fitting curves and the Taverna *et al* evidence, bortezomib has an OS HR of 1.89 and a PFS HR of 1.11 relative to lenalidomide (where HR >1 favours lenalidomide). HRs associated with the Taverna *et al* study have been used in the revised base case analysis, which is consistent with the original submission. All HRs obtained through this estimation of comparative efficacy are also presented in scenario analysis.

Section 2: Update of comparative efficacy analysis versus chemotherapy

Summary:

- Market research, provided with the original submission, shows that chemotherapy agents are not typically used to treat multiple myeloma patients after one prior therapy. The survey of clinicians in England reported that, similar to bendamustine, only 5-10% of patients receive chemotherapy.
- Chemotherapy is therefore a much less clinically relevant comparator than retreatment with bortezomib.
- While concluding that lenalidomide is likely to be more effective than standard chemotherapy agents, Committee members were concerned that the evidence presented for comparison with chemotherapy was not robust. The concern stemmed from the lack of published evidence for chemotherapy in this area; none was identified, and its use in the relevant population is limited and off-label.
- To provide a complete evaluation, Celgene have conducted additional analyses aiming to resolve the uncertainty surrounding the decision problem that stems from this issue. There were three components to the additional analyses performed:
  - The papers identified within the systematic review were searched again to identify any evidence for chemotherapy in patients who had had at least one prior treatment regardless of the treatment received. Two papers were identified.
  - These two papers were analysed versus pooled data from the MM-009 and MM-010 trials, allowing a greater sample size to reduce uncertainty around the effectiveness of lenalidomide. Results are presented using a transparent model selection process based upon factors previously shown to significantly affect OS, PFS or TTF.
  - Comparative efficacy is presented using both the mean of covariates method previously submitted and the ERG preferred methodology.

Context

In the ACD the Committee concluded that, when offered at second line, lenalidomide was likely to be more effective than both placebo and standard chemotherapy (Section 4.4), based upon clinical expert opinion and based on the comparative evidence presented for lenalidomide versus dexamethasone from MM-010 and MM-009.

Within the initial submission, comparison to chemotherapy was made using published evidence for bendamustine (as no published evidence was available for chemotherapy in the correct population following treatment with bortezomib). The Committee agreed that bendamustine was not an appropriate comparator in this appraisal (Section 4.3) as it is not licensed for use in this setting and is rarely used. However, the Committee did not appear to apply the same rule for chemotherapy agents, which have also been shown to be rarely used in practice, and are used off-label.

With bendamustine no longer considered a relevant comparator, the previous approach of assuming bendamustine efficacy for chemotherapies is no longer appropriate. However, the

original literature searches did not identify relevant evidence for chemotherapy agents. To rectify this, and for completeness, the papers identified within the systematic review were subjected to a wider filter to identify any evidence for chemotherapy in patients who had had at least one prior treatment (any type of treatment). Two papers were identified and reported results were compared to the pooled MM-010 and MM-009 trial data. In the absence of alternative evidence, and without crudely assuming equivalence to bendamustine efficacy or alternatively zero efficacy, these two papers produce the best possible comparison with chemotherapy agents. Results are presented using a transparent model selection process based upon the same factors previously shown to significantly affect OS, PFS or TTF, identified in Section 1.

The key concerns regarding the methodological robustness of the comparison detailed in Section 1 of this document also applied to the comparison with chemotherapy. Comparative efficacy is therefore presented using both the mean of covariates method previously submitted and the ERG preferred methodology.

Evidence of limited chemotherapy use

As was stated in Celgene's response to the draft scope produced by NICE, chemotherapy is rarely used in UK practice. The treatment pathway for multiple myeloma has evolved with the advent of proteasome inhibitors and immunomodulatory agents plus, more recently, label extensions of existing therapies within the pathway. As a result, where patients do not receive retreatment with bortezomib, they invariably access lenalidomide as a second-line therapy through the Cancer Drugs Fund.

The Committee agreed that bendamustine is not a relevant comparator as it does not form part of typical clinical practice, informed by clinical expert advice at the Committee meeting and Celgene market research, which showed it to be used in no more than 10% of patients. The same market research, provided within the original submission document, showed that UK haematologists use standard chemotherapy agents to treat just 5-10% of patients, and it is therefore also a much less relevant comparator than bortezomib retreatment.

Available evidence for chemotherapy

The original search found no evidence for chemotherapy (with or without steroids) following treatment with bortezomib. As the Committee appears to consider chemotherapy as an option for this small group of patients, Celgene have widened the original systematic review. This provided the opportunity to find better quality evidence for chemotherapy and to search for evidence for chemotherapy following at least one prior treatment, regardless of the type. Lenalidomide is expected to be unaffected by the use of prior bortezomib (compared to other initial treatments), due to different mechanism of action, and for the same reason the efficacy of chemotherapy is also assumed to be unaffected by the type of prior therapy given. In the absence of any evidence, this assumption is potentially conservative to lenalidomide.

Two papers were found that indicate substantially worse outcomes than presented in the original submission which used evidence for bendamustine as a proxy:

- Celesti *et al* (1997)[20] – a non-randomised study comparing HD cyclophosphamide 1.2 g/m^2 + LD dexamethasone and LD cyclophosphamide 0.5 mg/m^2 + MD dexamethasone which reported ORR, DoR, OS and toxicity
- Petrucci *et al* (1989)[21] – a single arm trial of melphalan 25 mg/m^2 IV + prednisolone 60 mg/m^2 (MP) which reported ORR, DoR, OS and safety

A summary of trial outcomes and baseline characteristics from these two trials can be found in Appendix E. The trials have been used to provide a closer estimate of the effectiveness and cost-effectiveness of lenalidomide compared to previously submitted assumptions. Alternative chemotherapies (such as vincristine and doxorubicin) have not been included due to a lack of evidence and similar costs across all agents.

Celesti et al reported that "the two schedules (HD vs LD cyclophosphamide) proved to be equally effective", therefore pooled outcomes from this study are used in all analyses presented. Dosing in the updated cost-effectiveness model is in line with the dosing regimens reported in the identified evidence (see above).

Statistical analysis of the comparative efficacy of chemotherapy

The available evidence for chemotherapy agents was used in the same way as the bortezomib evidence to estimate HRs relative to lenalidomide, by adjusting the pooled MM-010 and MM-009 dataset (ITT patients) to more closely match each study. Details of patient characteristics for the covariates included in the final models were extracted from the literature identified (presented in Table 13).

Table 13: Patient characteristics from the literature identified – chemotherapy

Source	Characteristic	Value
Celesti et al (1997)	1 prior therapy (vs 2+ prior therapies)	40.0%
Petrucci et al (1989)	Myeloma duration	Median: 2.25 years
MM-009 and MM-010 ITT population	1 prior therapy (vs 2+ prior therapies) Myeloma duration	35.1% Median: 3.9 years

The predicted median outcome was used alongside the observed chemotherapy median outcome to calculate a comparable HR for chemotherapy relative to lenalidomide. This was possible for melphalan+ prednisolone and cyclophosphamide+ dexamethasone, as these were represented by at least one source of chemotherapy evidence. Additionally, 'unadjusted' HRs were calculated which used outcomes from the pooled MM-010 and MM-009 studies with no adjustment for patient characteristics.

The resulting HRs are presented in Table 14, where a HR>1 favours lenalidomide. The estimated HRs are notably higher than those obtained through the bortezomib comparison, reflecting worse efficacy outcomes with chemotherapy agents.

Table 14: OS HR estimates – chemotherapy agents compared to lenalidomide plus dexamethasone

Source of adjustment	Model type	HRs using mean of covariates method		HRs using corrected group prognosis method	
		LEN/DEX data adjusted	LEN/DEX data unadjusted	LEN/DEX data adjusted	LEN/DEX data unadjusted
Celesti *et al* (1997)[20]	Exponential	5.13	5.01	4.25	4.22

	Gompertz	5.19	5.07	4.39	4.36
	Weibull	5.10	4.98	4.28	4.22
	Gamma	5.25	5.13	4.39	4.36
	Piecewise exponential	4.89	4.84	4.28	4.30
	Piecewise Gompertz	4.98	4.89	4.33	4.39
Petrucci *et al* (1989)[21]	Exponential	4.51	4.89	3.79	4.11
	Gompertz	4.66	4.94	4.00	4.25
	Weibull	4.54	4.86	3.85	4.11
	Gamma	4.71	5.00	4.00	4.25
	Piecewise exponential	4.54	4.71	4.25	4.20
	Piecewise Gompertz	4.63	4.77	4.34	4.28
Key: HR, hazard ratio; LEN/DEX, lenalidomide plus dexamethasone; OS, overall survival.					

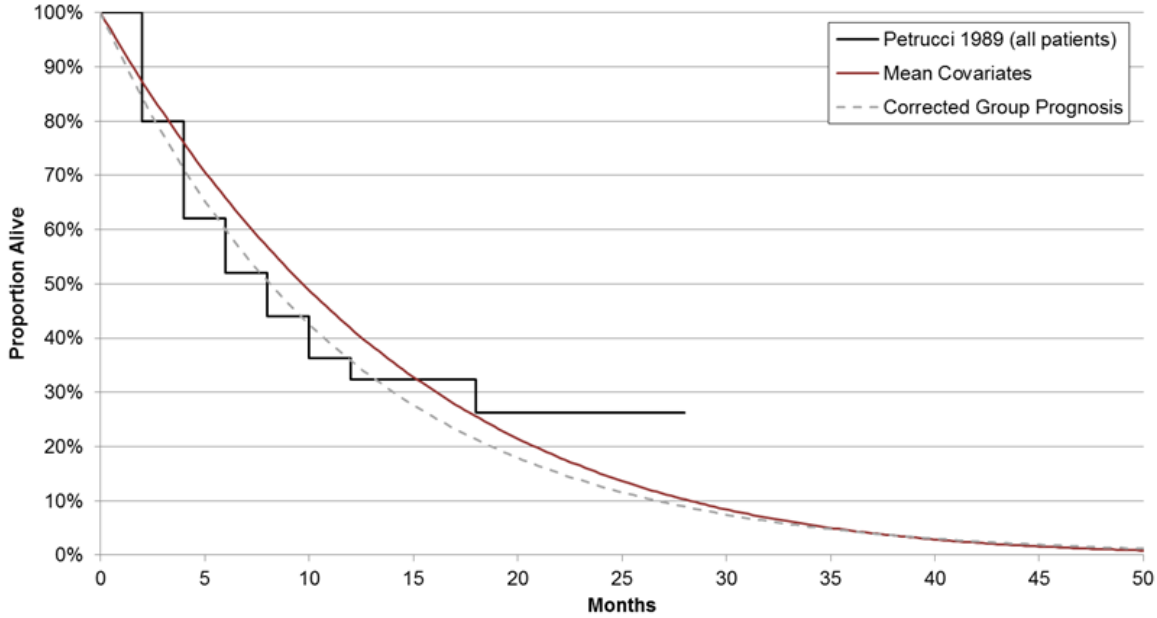
Chemotherapy evidence was only available for OS. As such, for the cost-effectiveness model, the HR for OS was applied to PFS and TTF.

While these results shows a considerable efficacy advantage of lenalidomide over standard chemotherapy agents, it should be borne in mind that such agents do not form typical clinical practice in the UK. The survey of clinicians in England, presented within the original submission, found that such regimens were used in around 5% of patients (and no more than 10%). This was comparable to the reported use of bendamustine, which the Committee have agreed is not a relevant comparator based on a clinical specialist stating that it is rarely used.

Validation of approach – chemotherapy

The OS curve presented by Petrucci *et al* (1989)[21] for chemotherapy was used alongside the best-fitting Gompertz curve to evaluate fitted and observed survival. The resulting figure (Figure 6) shows the fitted models provide a good characterisation of the observed survival data for chemotherapy.

Figure 6: Gompertz models for OS, having applied the HR to lenalidomide TTP adjusted for Petrucci *et al* characteristics, and OS Kaplan-Meier plot for chemotherapy from Petrucci *et al* 1989



Conclusion

The Committee accepted that lenalidomide is likely to be more clinically effective than standard chemotherapy agents. However, there is a lack of published evidence for chemotherapy, and so quantifying comparative efficacy is challenging. Initially, Celgene assumed that the efficacy of chemotherapy agents was equal to that of bendamustine; however, based upon clinical specialist advice at the first Appraisal Committee meeting, the Committee have confirmed that bendamustine is not a relevant comparator.

As such, papers identified by the original systematic literature review were filtered less restrictively and this highlighted two non-RCT studies providing evidence of chemotherapy efficacy. These were used and the same comparative efficacy estimation methods were employed as described earlier for bortezomib retreatment. The resulting HRs suggest that melphalan plus prednisolone and cyclophosphamide regimens are far less effective than lenalidomide in terms of their expected OS and PFS outcomes.

Section 3: Updated evidence for health-related quality of life

Summary:

- The Committee discussed the plausibility of assumptions used for health-related quality of life (HRQL) within the model. They concluded that, although the values used within the submitted model had been used in previous appraisals for multiple myeloma, there was significant uncertainty in the values of utility and disutility used in the modelling. In addition, they noted that it was not clinically plausible that, as an individual's disease progresses, the utility value remained constant despite receiving third- and fourth-line treatments.
- The forthcoming results sections present three scenario analyses designed to address Committee concerns regarding the reliance of the model on utilities from a single source and a lack of change in utility with latter line treatments. This section presents the methodology behind the utility values used.

Context

The Committee raised concerns regarding the plausibility of the utilities used within the model (Section 4.10 and 4.12). The Committee concluded that although the values used within the submitted model had been used in previous appraisals for multiple myeloma, there was significant uncertainty in the values of utility and disutility used in the modelling. In addition, they noted that it was not clinically plausible that, as an individual's disease progresses, the utility value remained constant despite receiving third- and fourth-line treatments.

During the Committee meeting discussions on 18 Feb 2014, scenario analysis using an alternative utility source identified in TA228 was suggested as a potential method to allay some of the uncertainty surrounding the utilities used within the model.

Methodology

Two scenarios are presented to address Committee concerns regarding the reliance of the model on utilities from only one source and lack of change in utility with latter line treatments:

- Utilities from the alternative scenario presented in TA228
- The inclusion of a reduced utility at fourth and later line treatments based upon a recently presented poster by Palumbo *et al* (2013)[22], which used the baseline EQ-5D HRQL results from study MM-003 where patients had received a median of five prior lines of therapy

<u>Utilities from the alternative scenario presented in TA228</u>

Utilities from the alternative scenario presented in TA228 were implemented in the model. HRQL in this scenario was dependent upon time since the start of treatment. The ERG in TA228 recommended the use of the McKenzie and van der Pol mapping, therefore these values were used in the model. Use of the Kontodimopolous values was included as a further scenario analysis. Progression status was not explicitly considered in estimating these utility weights.

When using these scenarios no additional decrements were included for adverse events as these were already included in the mapping presented in TA228 and were therefore not modelled separately.

Table 15: EQ-5D utility derived by mapping EORTC QLQ-C30 scores as presented in TA228

Algorithm used to map to EQ-5D	Time in Months					
	0	**1**	**5**	**12**	**24**	**36**
McKenzie and van der Pol	0.55	0.58	0.68	0.68	0.68	0.69
Kontodimopolous	0.52	0.58	0.69	0.69	0.69	0.71

Inclusion of a greater drop in utility for later line therapies

Based upon the Palumbo et al (2013) abstract and poster, a scenario was included where the utility of patients drops from the point at which fourth-line treatment starts within the model. The utilities used in this scenario are presented in Table 16. The baseline utility of patients within the MM-003 study (at a median of 5 prior lines of treatment) was 0.59 indicating that utility did not drop substantially from post-progression in the van Agthoven study to the start of fifth-line treatment.

Table 16: Utility by health state – lower utility from fourth-line treatment scenario

State	Utility
Pre-progression	0.81
Pre-progression after 2 years	0.77
Post-progression	0.64
4th line onwards	0.59

Conclusion

To address the Committee's concerns regarding uncertainty around HRQL estimates included in the model, Celgene have incorporated the two additional sources of health state utilities from TA228 into the cost-effectiveness analysis. Additionally, lower utility values have been included for patients who reach fourth-line treatment, based upon a recent poster describing HRQL outcomes in patients with relapsed and refractory multiple myeloma. Updated results after considering the utilities discussed above and suggested by the Committee demonstrate lenalidomide to be cost-effective, indicating that the outcome is not sensitive to the source of utility data to inform HRQL (see Section 5).

Section 4: Updated evidence for costs

Summary:

- The Committee discussed the plausibility of assumptions used to cost treatment. Four main concerns were raised:
  - The lack of inclusion of the costs of corticosteroids given with bortezomib in the original submission.
  - The cost of lenalidomide at third line – which should include the patient access scheme agreed with NICE.
  - The cost of bortezomib inclusive of a patient access scheme, which the Committee agreed should be included in the model base case.
  - The duration for which bortezomib retreatment is given.
- In response to these concerns the costs of dexamethasone have been included in the model in line with the efficacy evidence presented.
- The third-line lenalidomide patient access scheme was already included in the model, this has now been flagged with NICE as a factual error in the ACD.
- The patient access scheme for bortezomib is also included in the model base case. Scenario analyses are presented regarding the discount received via the bortezomib patient access scheme, which has been acknowledged to have a poor uptake in clinical practice.
- Scenario analyses are presented around the duration of treatment with bortezomib, although these should be viewed with caution as both papers presenting OS used within the model include treatment durations considerably greater than 8 cycles. Patients in the Taverna *et al* study had received up to 19 treatment cycles at the time of analysis.

Context

The Committee raised concerns regarding the plausibility of the costs used within the model (Section 4.10). Four main concerns were raised:

- The lack of inclusion of the costs of corticosteroids given with bortezomib in the original submission
- The cost of lenalidomide at third line, which should include the patient access scheme agreed with NICE
- The cost of bortezomib inclusive of a patient access scheme, which the Committee agreed should be included in the model base case
- The duration for which bortezomib retreatment is given, which varies in the UK between a maximum of 8 cycles up to treatment until progression

Methodology

Inclusion of dexamethasone costs

In the present, updated analysis, the cost of corticosteroids is included in the model with the proportion of patients incurring the cost of dexamethasone based on the proportion receiving dexamethasone in the relevant efficacy evidence (64.3% in the Taverna *et al* paper), as requested by the ERG.

Whilst it is a commonly held belief in clinical practice that combination with dexamethasone should be more effective[13], results from available trials show no significant difference in efficacy and, in fact, a trend towards worse outcomes with dexamethasone combination.[1, 2, 12] This is consistent with NICE having recommended bortezomib as a monotherapy in TA129, rather than explicitly recommending combination therapy with dexamethasone.

The cost of lenalidomide at third line

As clarified with NICE, the original model submitted included the patient access scheme agreed with NICE for lenalidomide at third line (page 176 of the original submission document). In fact the detailed inclusion of the patient access scheme was the cause of the differences in the methodology used to model treatments following comparator therapies versus lenalidomide. In order to simplify the model and maintain consistency between the methodology used to model lenalidomide and comparator therapies, the inclusion of the patient access scheme within the model has been simplified. The level of discount received via the patient access scheme is now derived from the mean time on treatment with lenalidomide before and after the start of the patient access scheme (7 cycles and 20 cycles, respectively), using the curves fitted to patients receiving third-line therapy in MM-009 and MM-010.

Based upon this methodology, it is estimated in the model that 15.52% of patients remain on treatment at 26 cycles. This is consistent with published evidence from the TCS database, which states that 15.69% of patients remained on treatment at 26 cycles.[23]

The cost of bortezomib retreatment

The cost of bortezomib retreatment within the model base case has been amended to include the patient access scheme. A 15% price discount is applied based upon available published evidence.[24] However, the uptake of the bortezomib patient access scheme is low in practice due to difficulties in claiming a refund. It is an outcomes-based risk sharing scheme and therefore requires close clinician monitoring and record-keeping, and a refund must be claimed within 60 days of the qualifying assessment. Published literature indicates that less than half of patients who would be eligible actually receive this discount.[25] As such, since the full potential discount is not achieved by NHS, the discount is only applied to 55% of patients in the present base case analysis, again based upon published literature. [25]

The duration of bortezomib retreatment

The clinical specialist at the first Appraisal Committee stated that UK practice is varied with regards to the duration of bortezomib retreatment, with patients potentially treated until progression, as noted in the ACD. Published evidence indicates that retreatment is given for considerably longer durations than 8 cycles: up to 19 cycles were received in both the Taverna *et al*[1] and Sood *et al*[19] studies, with patients still on treatment at the time of analysis in both (see Table 40 in Appendix F). Patients receiving retreatment are a self-selected population in that clinicians only retreat patients who have responded to initial therapy with bortezomib and are likely to tolerate it for longer duration. Patients receiving bortezomib for the first time in the APEX study, which is the pivotal study supporting the label for bortezomib in relapsed/refractory multiple myeloma, allowed patients to continue on bortezomib as maintenance after receiving an initial 8 cycles. Patients could receive up to 11 cycles; responding patients received a median of 10 cycles.[10]

NICE guidance (TA 129) recommends bortezomib use as a monotherapy rather than in combination, and the bortezomib SPC does not specify a maximum number of cycles in patients who receive monotherapy (see Table 17).[26] This is consistent with the APEX study which allowed patients to go on to receive further cycles of therapy after 8 cycles.

Table 17: Wording from the bortezomib SPC on duration of treatment

Indication / dosing regimen (not specific to retreatment)	**Wording of duration of treatment from the SPC**
Progressive multiple myeloma (patients who have received at least one prior therapy) monotherapy	"It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of VELCADE therapy."
Progressive multiple myeloma (patients who have received at least one prior therapy) combination with dexamethasone	"Patients achieving a response or a stable disease after 4 cycles of this combination therapy can continue to receive the same combination for a maximum of 4 additional cycles."
Note: There is no guidance in the SPC relating to the duration of treatment for bortezomib when used as a retreatment.	

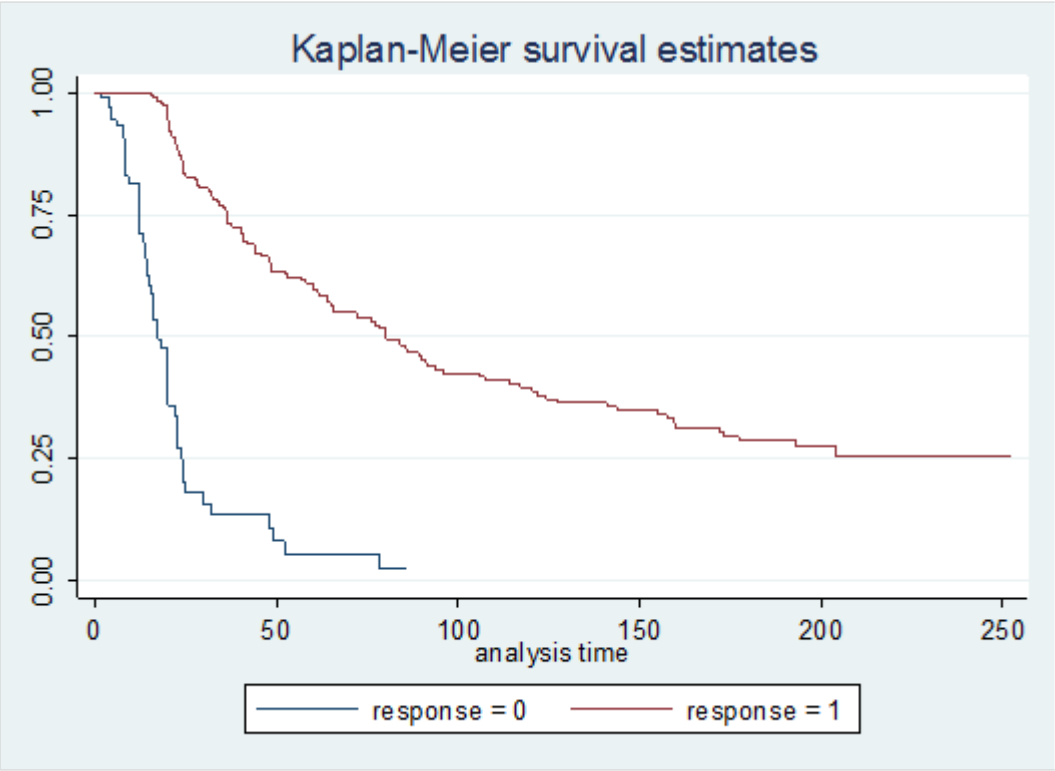
Furthermore, the bortezomib SPC does not contain specific information on posology for retreatment, which is likely to contribute to the varied practice seen within the available trials and within the UK. Some centres provide bortezomib retreatment until progression and some provide only a maximum of 8 cycles, as mentioned by a clinical specialist at the first Appraisal Committee meeting. Only the Petrucci *et al* study[12] reported a maximum of 8 cycles, however this study did not present OS, PFS or TTP for all patients, which are integral to clinical and cost-effectiveness analysis.

Market research conducted by Celgene, through a survey completed by UK haematologists, shows that a large majority (78%) of clinical experts who have experience retreating patients with bortezomib (n = 18) feel that its efficacy is directly related to the number of cycles administered. This is supported by the Petrucci *et al* study, which reports a TTP for only the 40% of patients who responded. This is still lower than that of the overall population (including non-responding patients) in the Taverna *et al* data (8.4 months vs 10.5 months).

Data from the lenalidomide trials (MM-009 and MM-010) indicate that patients who respond experience considerably longer TTP than those who don't (Figure 7; HR 0.135, 95% CI

0.094 – 0.196). As both OS and TTP/PFS are only available from the Taverna *et al* study and Hrusovsky *et al*[2] study, the most reasonable comparison with bortezomib retreatment is one which assumes that treatment continues for longer than 8 cycles, provided the patient is continuing to receive benefit.

Figure 7: Comparison of responder versus non-responder TTP in MM-009 and MM-010



Additional scenario analyses have been included exploring the impact on cost of fewer treatment cycles with bortezomib in combination with dexamethasone. However, analyses could not be performed exploring the likely associated reduction in efficacy, due to lack of evidence. These scenarios should therefore be viewed as biased towards bortezomib retreatment and at the upper limits of the lenalidomide ICER.

Conclusion

The Committee were concerned that the original cost-effectiveness model was straying from clinical practice in terms of treatment with bortezomib by allowing patients to receive therapy until progression / treatment failure. However, the clinician present at the Committee meeting confirmed that duration of bortezomib retreatment does vary in UK clinical practice. Moreover most of the studies forming the basis of comparative efficacy evidence reported that patients were treated for more than 8 bortezomib cycles on average. Nevertheless, scenario analyses for restricted bortezomib in combination with dexamethasone are included in the cost-effectiveness update. Uptake of the bortezomib price discount has also been included in the updated cost-effectiveness analysis. The results of these changes show lenalidomide to remain cost-effective (see Section 5).

Section 5: Update of cost-effectiveness analysis results

Summary:

- An updated cost-effectiveness analysis was performed based upon the ACD as discussed extensively in the preceding sections. Model results are presented in this section having taken into consideration all issues raised in Sections 1 to 4.
- In the updated base case analysis lenalidomide is dominant when compared to bortezomib retreatment. Deterministic model results show a cost saving of £13,634 per patient over a lifetime, and a QALY gain of 0.81. This puts lenalidomide in the dominant, lower-right quadrant of the cost-effectiveness plane.
- Lenalidomide has a 100% chance of cost-effectiveness at a threshold of £20,000/QALY base upon the results of probabilistic analysis. The probabilistic ICER is dominant, with a mean cost saving of £14,067 and mean gain of 0.82 QALYs.
- Compared to melphalan plus prednisolone, a representative chemotherapy agent, lenalidomide is associated with an ICER of £54,898. This is achieved through a cost increase of £54,414 and 0.99 incremental QALYs. However, chemotherapy agents are rarely used in practice, which was a major reason the Committee decided that bendamustine was not a relevant comparator.
- Scenario analysis show that lenalidomide remains cost-effective compared with bortezomib retreatment regardless of the assumptions made around sequencing, the curve fits selected, the source of comparator efficacy evidence used for retreatment, the inclusion of the bortezomib price discount, the time horizon used and the source of utilities.
- Two key scenarios have the potential to impact the cost-effectiveness of lenalidomide compared to bortezomib retreatment:
  - The number of cycles of bortezomib retreatment given to patients – in a highly conservative scenario where patients are limited to 8 cycles of bortezomib (when given in combination with dexamethasone), without any impact on efficacy, the ICER for lenalidomide is £31,999. When a maximum of 19 cycles is assumed (the maximum observed within the Taverna data used for efficacy, where patients still remained on treatment at the time of analysis) lenalidomide is cost-effective with an ICER of £15,409.
  - Using the Celgene MTC to inform the efficacy of bortezomib retreatment increases the ICER to £8,120, with lenalidomide remaining cost-effective but no longer dominant. This is a highly conservative scenario, however, as it assumes bortezomib retreatment is equally as effective as initial bortezomib.

Summary

The cost-effectiveness analysis was updated based upon feedback from the Committee. The updated survival and comparative efficacy analysis described in the sections above formed a major part of this update. The following additional changes were made to provide the updated results:

- Input data were taken from the pooled MM-010 and MM-009 trial data.
- The matrix structure that fed into patient flow sheets has been removed to ensure consistency across model arms.
- Patient flow sheets were altered to correctly implement the ERG suggested logic changes relating to the use of the OS, PFS and TTF curves for lenalidomide and to correct a small error in the calculation of adverse event utility decrements
- Scenario analyses were conducted around utilities as detailed in Section 3.
- The cost of dexamethasone has been included in the base case analysis.
- A scenario has been implemented whereby a stopping rule (maximum number of cycles) for bortezomib in combination with dexamethasone can be tested.
- The bortezomib patient access scheme is applied (15% price discount) for 55% of patients (to reflect likely actual uptake of the discount).
- A scenario analysis is provided that compares the sequence of lenalidomide followed by bortezomib with bortezomib followed by lenalidomide.
- A scenario analysis was explored in which lenalidomide is not given as a third-line therapy, departing from current NICE guidance in which lenalidomide is recommended.
- A similar scenario is also presented whereby no subsequent therapies of any kind are given.
- A scenario analysis is provided applying all comparative efficacy estimates obtained through this updated analysis, and the use of HRs from an MTC for initial bortezomib therapy.

Base case results are presented for lenalidomide plus dexamethasone compared to bortezomib retreatment. Additional results, including scenario analysis, are presented comparing to melphalan plus prednisolone (representing a standard chemotherapy agent).

Importantly, these treatments may not be relevant in clinical reality. Market research submitted for the present submission suggests that chemotherapy agents are rarely used for the treatment of second-line multiple myeloma in the UK, albeit following any prior therapy. Although this is not the treatment pathway being appraised by NICE the results indicate that only a minority of patients currently receive treatment with chemotherapy agents after first relapse. This was supported by a survey of clinicians in England, also provided within the presented submission, which stated that only up to 10% of patients are likely to receive standard chemotherapy regimens.

Updated results – Base case: Lenalidomide compared to bortezomib retreatment

Table 18: Lenalidomide model outcomes by health state

LEN/DEX	Costs	QALYs	LYs
Pre-progression	£92,740	1.83	2.56
Post-progression	£12,124	1.22	2.14
Total	£104,864	3.05	4.69
Key: LEN/DEX, lenalidomide plus dexamethasone; LYs, life years; QALYs, quality-adjusted life years.			

Table 19: Bortezomib model outcomes by health state

Bortezomib retreatment	Costs	QALYs	LYs
Pre-progression	£91,360	1.56	2.12
Post-progression	£27,138	0.68	1.16
Total	£118,498	2.24	3.28
Key: LYs, life years; QALYs, quality-adjusted life years.			

Table 20: Summary results vs bortezomib retreatment – discounted

Treatment	Costs	QALYs	LYs	ICER
LEN/DEX	£104,864	3.05	4.69	Lenalidomide dominates
Bortezomib retreatment	£118,498	2.24	3.28	
Incremental	-£13,634	0.81	1.41	
Key: LEN/DEX, lenalidomide plus dexamethasone; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.				

Table 21: Summary results vs bortezomib retreatment – undiscounted

Treatment	Costs	QALYs	LYs	ICER
LEN/DEX	£111,012	3.34	4.69	Lenalidomide dominates
Bortezomib retreatment	£123,581	2.38	3.28	
Incremental	-£12,570	0.96	1.41	
Key: LEN/DEX, lenalidomide plus dexamethasone; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.				

Table 22: Modelled costs (discounted) by cost item vs bortezomib retreatment

Cost item	LEN/DEX	Bortezomib retreatment
Cost of therapy	£86,327	£67,286
Administration of therapy +transport	£168	£19,480
Monitoring and tests	£10,452	£6,473
Terminal care	£1,076	£1,127
Lenalidomide given 3rd line	£0	£18,600
Other 3rd line therapy +admin +transport	£398	£0
4th line therapy +admin +transport	£6,235	£4,933
Adverse event costs	£207	£598
Total	£104,864	£118,498
Key: LEN/DEX, lenalidomide plus dexamethasone.		

Updated results: Lenalidomide compared to melphalan plus prednisolone

Table 23: Lenalidomide model outcomes by health state

LEN/DEX	Costs	QALYs	LYs
Pre-progression	£92,740	1.83	2.56
Post-progression	£12,124	1.22	2.14
Total	£104,864	3.05	4.69
Key: LEN/DEX, lenalidomide plus dexamethasone; LYs, life years; QALYs, quality-adjusted life years.			

Table 24: Melphalan plus prednisolone model outcomes by health state

Melphalan + prednisolone	Costs	QALYs	LYs
Pre-progression	£7,461	0.39	0.49
Post-progression	£42,989	1.67	2.86
Total	£50,450	2.06	3.35
Key: LYs, life years; QALYs, quality-adjusted life years.			

Table 25: Summary results vs MP – discounted

Treatment	Costs	QALYs	LYs	ICER
LEN/DEX	£104,864	3.05	4.69	£54,898
Melphalan + prednisolone	£50,450	2.06	3.35[a]	
Incremental	£54,414	0.99	1.34	

Key: LEN/DEX, lenalidomide plus dexamethasone; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.

Note: a Total life years with MP is less than total life years with bortezomib. This is due to the much higher hazard ratio for chemotherapy PFS, meaning patients progress more rapidly and move on to benefit from lenalidomide as a third-line therapy.

Table 26: Summary results vs MP – undiscounted

Treatment	Costs	QALYs	LYs	ICER
LEN/DEX	£111,012	3.34	4.69	£51,944
Melphalan + prednisolone	£51,741	2.20	3.35[a]	
Incremental	£59,271	1.14	1.34	

Key: LEN/DEX, lenalidomide plus dexamethasone; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.

Note: a Total life years with MP is less than total life years with bortezomib. This is due to the much higher hazard ratio for chemotherapy PFS, meaning patients progress much more rapidly and move on to benefit from lenalidomide as a third-line therapy.

Table 27: Modelled costs (discounted) by cost item vs MP

Cost item	LEN/DEX	Melphalan + prednisolone
Cost of therapy	£86,327	£936
Administration of therapy +transport	£168	£5,292
Monitoring and tests	£10,452	£7,039
Terminal care	£1,076	£1,124
Lenalidomide given 3rd line	£0	£28,319
Other 3rd line therapy +admin +transport	£398	£0
4th line therapy +admin +transport	£6,235	£7,490
Adverse event costs	£207	£250
Total	£104,864	£50,450

Key: LEN/DEX, lenalidomide plus dexamethasone.

Scenario analysis results versus bortezomib retreatment

The following scenario analyses were explored to address concerns raised by the Committee:

- Type of comparison with bortezomib retreatment
- The use of lenalidomide at third line
- Inclusion of subsequent treatment lines in the model
- Different curve fits to model lenalidomide efficacy
- Comparative efficacy assumptions, including the use of available bortezomib retreatment evidence, and use of the ERG's preferred methodology for adjusting for covariates
- Assumptions around the cost of bortezomib retreatment
- Model time horizon
- The source used to model HRQL

Lenalidomide remains cost-effective regardless of the assumptions made around the curve fits selected, the source of comparator efficacy evidence used for bortezomib, the time horizon used and the source of utilities (Table 28). A further table is presented to allow the Committee to assess the clinical validity of the curve fits selected within the model and used for scenario analysis (Table 29). Lenalidomide is cost-effective (dominant) even when the bortezomib price discount is redeemed in 100% of bortezomib patients, although this is highly unlikely given the difficulties in obtaining the discount.

Table 28 shows that two key scenarios have the potential to impact the cost-effectiveness of lenalidomide compared to bortezomib retreatment and are discussed in turn below:

- The number of cycles of bortezomib retreatment given to patients
- Use of the Celgene MTC to inform bortezomib retreatment efficacy

Three scenarios are presented around the number of cycles of bortezomib retreatment given to patients. If a maximum of 8 cycles are given to patients receiving bortezomib plus dexamethasone, the ICER compared to retreatment is £31,999. This scenario is highly conservative as noted in Section 4; the efficacy evidence used includes patients receiving considerably more than 8 cycles of retreatment (up 19 cycles in Taverna *et al*), with patients still on treatment at the time of analysis. Market research conducted by Celgene, completed by 18 UK haematologists who have retreated patients with bortezomib, shows that the vast majority (78%) feel that its efficacy is directly related to the number of cycles administered. The Petrucci *et al* study is the only source of evidence where patients were limited to 8 cycles of treatment, and indicates considerably worse outcomes: TTP, reported for only the 40% of patients who responded, is still lower than that of the overall population (including non-responding patients) in the Taverna *et al* data. TTP is highly influenced by response in data from MM-009 and MM-010 (presented in Section 4).

When a maximum of 11 cycles is assumed (observed within the APEX study for initial bortezomib treatment which lead to the recommendation of bortezomib in TA129), lenalidomide is associated with an ICER of £26,923. A maximum of 19 cycles (observed within the Taverna *et al* data used for efficacy) gives a cost-effective ICER of £15,409. It should be noted, however, that the maximum of 19 cycles is likely to be an underestimate, as patients were still receiving treatment upon assessment in the Taverna *et al* study.[1]

The results of assuming bortezomib retreatment efficacy is equal to initial bortezomib efficacy, utilising the methodological advantages of an MTC, are also presented. This scenario shows lenalidomide to remain cost-effective with an ICER of £8,120. This is not dominant and therefore reflects reduced cost-effectiveness compared to the base case analysis, however, it is a highly conservative scenario and should be viewed as an absolute extreme of the effectiveness of bortezomib retreatment.

In all cases the ICERs presented above should be viewed in light of the validation evidence presented in Section 1. Comparative efficacy evidence shows that long-term outcomes (TTP) are considerably worse on bortezomib retreatment than is predicted within the model, and patients do not achieve the same level of durable response to bortezomib retreatment as with initial lenalidomide treatment.

Table 28: Scenario analyses for lenalidomide compared to bortezomib retreatment

Type of comparison and subsequent therapy assumptions					
Parameter	**Base case assumption**	**Scenario analysis**	**Incremental**		**ICER**
			Costs	**QALYs**	
The use of LEN/DEX at third line	As per NICE recommendations (i.e. earlier use of lenalidomide)	As per historical best supportive care (i.e. sub-100% lenalidomide use at third line)	-£1,516	1.07	Lenalidomide Dominates
		No use of lenalidomide at 3rd line (i.e. a simple Markov model without sequencing)	£6,064	1.22	£4,953
Sequence	Lenalidomide followed by best supportive care vs bortezomib retreatment followed by lenalidomide	Lenalidomide followed by bortezomib retreatment vs bortezomib retreatment followed by lenalidomide	-£772	0.81	Lenalidomide Dominates
Subsequent therapies	Included	Not included	£4,767	1.22	£3,893
Modelling lenalidomide efficacy					
Parameter	**Base case assumption**	**Scenario analysis**	**Incremental**		**ICER**
			Costs	**QALYs**	
Curve fit for OS	Gompertz	Piecewise exponential	-£12,114	1.21	Lenalidomide Dominates
		Piecewise Gompertz	-£12,344	0.96	Lenalidomide Dominates
		Gamma	-£12,677	1.03	Lenalidomide Dominates
		Exponential	-£12,357	1.20	Lenalidomide Dominates
		Weibull	-£13,038	1.10	Lenalidomide Dominates
Curve fit for PFS	Gamma	Lognormal	-£15,076	0.81	Lenalidomide Dominates
		Gompertz	-£16,554	0.83	Lenalidomide Dominates
		Log-logistic	-£12,421	0.82	Lenalidomide Dominates
Curve fit for TTF	Gamma	Lognormal	-£12,421	0.82	Lenalidomide Dominates
		Log-logistic	-£11,627	0.82	Lenalidomide Dominates
		Gompertz	-£7,722	0.83	Lenalidomide Dominates
Method used to derive estimates of efficacy	Mean of covariates method	Corrected group prognosis method (ERG preferred methodology)	-£2,828	0.73	Lenalidomide Dominates

Parameter used to model treatment discontinuation	TTF	PFS	-£1,590	0.87	Lenalidomide Dominates
Bortezomib efficacy source					
Parameter	**Base case assumption**	**Scenario analysis**	**Incremental**		**ICER**
			Costs	**QALYs**	
Source of BOR retreatment evidence	OS: Taverna 2012	OS: Hrusovsky 2010	-£12,364	0.86	Lenalidomide Dominates
		OS: Celgene MTC	-£16,731	0.69	Lenalidomide Dominates
	PFS: Taverna 2012	PFS: Celgene MTC	£7,658	0.86	£8,938
		PFS: Petrucci 2013	-£13,634	0.81	Lenalidomide Dominates
		PFS: Hrusovsky 2010	-£16,516	0.81	Lenalidomide Dominates
		PFS: Sood 2009	-£16,516	0.81	Lenalidomide Dominates
		PFS: Dispenzieri 2010	-£1,568	0.83	Lenalidomide Dominates
	OS & PFS: Taverna 2012	OS & PFS: Celgene MTC	£6,566	0.81	£8,120
		OS & PFS: Hrusovsky 2010	-£15,075	0.86	Lenalidomide Dominates
Cost of bortezomib retreatment					
Parameter	**Base case assumption**	**Scenario analysis**	**Incremental**		**ICER**
			Costs	**QALYs**	
Bortezomib patient access scheme	15% price discount applied for 55% of bortezomib 2nd line patients	Not included	-£19,681	0.81	Lenalidomide Dominates
		15% discount at 2nd line applied for all bortezomib 2nd line patients	-£8,687	0.81	Lenalidomide Dominates
Bortezomib + dex treatment continuation	Until PFS (as implied within efficacy evidence from Taverna 2012)[a]	Maximum of 8 cycles as per SPC	£26,018	0.81	£31,999
		Maximum of 11 cycles - maximum for BOR monotherapy in APEX study	£21,890	0.81	£26,923
		Maximum of 19 cycles – maximum observed in Taverna 2012[a]	£12,528	0.81	£15,409

Time horizon					
Parameter	**Base case assumption**	**Scenario analysis**	**Incremental**		**ICER**
			Costs	**QALYs**	
Time horizon	25 years	5 years	-£17,845	0.43	Lenalidomide Dominates
		10 years	-£15,122	0.77	Lenalidomide Dominates
		15 years	-£13,654	0.81	Lenalidomide Dominates
		20 years	-£13,634	0.81	Lenalidomide Dominates
HRQL					
Parameter	**Base case assumption**	**Scenario analysis**	**Incremental**		**ICER**
			Costs	**QALYs**	
Health state utilities	van Agthoven (2004)	Values from McKenzie & van der Pol	-£13,634	0.81	Lenalidomide Dominates
		Values from Kontodimopoulos	-£13,634	0.83	Lenalidomide Dominates
		Lower utility from fourth line, from Palumbo (2013)	-£13,634	0.76	Lenalidomide Dominates
Note: a Patients in the Taverna *et al* study were still receiving treatment at the time of assessment, therefore the maximum of 19 cycles on treatment is likely to be an underestimate. Applying a maximum number of bortezomib cycles departs from the base case analysis, in which treatment duration is informed by continued response (i.e. TTF).					

Table 29: Clinical validation of efficacy scenarios

Modelling lenalidomide efficacy		Patients alive/ progression free/ on treatment at :			
Parameter	**Scenario analysis**	**1 year**	**5 years**	**10 years**	**20 years**
Curve fit for OS	Base case: Gompertz	89%	42%	6%	0%
	Piecewise exponential	84%	44%	18%	3%
	Piecewise Gompertz	84%	43%	11%	0%
	Gamma	88%	45%	12%	0%
	Exponential	86%	46%	21%	4%
	Weibull	88%	45%	17%	2%
Curve fit for PFS	Base case: Gamma	56%	15%	6%	0%
	Lognormal	58%	14%	5%	0%
	Gompertz	59%	21%	6%	0%
	Log-logistic	59%	14%	6%	0%
Curve fit for TTF	Base case: Gamma	46%	6%	2%	0%
	Lognormal	44%	7%	2%	0%
	Log-logistic	44%	7%	3%	0%
	Gompertz	46%	9%	5%	0%
Method used to derive estimates of efficacy	Base case: mean of covariates	OS: 89%, PFS: 56%, On Treatment: 46%	OS: 42%, PFS: 15%, On Treatment: 6%	OS: 6%, PFS: 6%, On Treatment: 0%	OS: 0%, PFS: 0%, On Treatment: 0%
	Corrected group prognosis method (ERG preferred methodology)	OS: 85%, PFS: 52%, On Treatment: 43%	OS: 37%, PFS: 15%, On Treatment: 7%	OS: 8%, PFS: 7%, On Treatment: 2%	OS: 0%, PFS: 0%, On Treatment: 0%
Parameter used to model treatment discontinuation	Base case: TTF	46%	6%	0%	0%
	PFS	56%	15%	6%	0%
Key: ERG, evidence review group; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure					

Scenario analysis results versus chemotherapy

The following scenario analyses were conducted versus chemotherapy:

- Type of comparison with chemotherapy
- Choice of chemotherapy comparator – cyclophosphamide rather than melphalan (as evidence was also available for this comparator)
- The use of lenalidomide at third line
- Inclusion of subsequent treatment lines in the model
- Different curve fits to model lenalidomide efficacy
- Comparative efficacy assumptions, including use of the ERG's preferred methodology for adjusting for covariates
- Model time horizon
- The source used to model HRQL

Although lenalidomide at second line is above the limits of traditional cost-effectiveness compared to chemotherapy, these results should be assessed in the context of the very small proportion of patients who actually receive them as an anti-myeloma treatment. Market research provided by Celgene with the initial submission show that just 5-10% of patients are likely to be treated with chemotherapy. This is similar to the proportion who receive bendamustine, which the Committee confirmed was not a relevant comparator.

Table 30: Scenario analyses for lenalidomide compared to chemotherapy

Type of comparison and subsequent therapy assumptions					
Parameter	**Base case assumption**	**Scenario analysis**	**Incremental**		**ICER**
			Costs	**QALYs**	
The use of LEN/DEX at third line	As per NICE recommendations (i.e. earlier use of lenalidomide)	As per historical best supportive care (i.e. sub-100% lenalidomide use at third line)	£73,885	1.71	£43,099
		No use of lenalidomide at 3rd line (i.e. a simple Markov model without sequencing)	£88,823	2.29	£38,814
Subsequent therapies	Included	Not included	£88,340	2.29	£38,603
Comparator					
Parameter	**Base case assumption**	**Scenario analysis**	**Incremental**		**ICER**
			Costs	**QALYs**	
Comparator	Defined by user	LD cyclophosphamide + MD-Dex	£56,548	1.00	£56,738
		HD cyclophosphamide + LD-Dex	£58,197	1.00	£58,393
Modelling lenalidomide efficacy					
Parameter	**Base case assumption**	**Scenario analysis**	**Incremental**		**ICER**
			Costs	**QALYs**	
Curve fit for OS	Gompertz	Piecewise exponential	£57,348	1.42	£40,348
		Piecewise Gompertz	£56,081	1.16	£48,322
		Gamma	£56,397	1.24	£45,467
		Exponential	£57,798	1.40	£41,147
		Weibull	£56,712	1.30	£43,773
Curve fit for PFS	Gamma	Lognormal	£54,424	0.99	£55,127
		Gompertz	£54,292	1.04	£52,148
		Log-logistic	£56,335	0.99	£56,908

Curve fit for TTF	Gamma	Lognormal	£56,335	0.99	£56,908
		Log-logistic	£56,633	0.99	£57,159
		Gompertz	£65,558	0.99	£66,414
Method used to derive estimates of efficacy	Mean of covariates method	Corrected group prognosis method (ERG preferred methodology)	£53,611	0.90	£59,728
Parameter used to model treatment discontinuation	TTF	PFS	£95,541	1.01	£94,895
Time horizon					
Parameter	**Base case assumption**	**Scenario analysis**	**Incremental**		**ICER**
			Costs	**QALYs**	
Time horizon	25 years	5 years	£44,458	0.60	£74,206
		10 years	£52,768	0.95	£55,443
		15 years	£54,395	0.99	£54,891
		20 years	£54,414	0.99	£54,898
HRQoL					
Parameter	**Base case assumption**	**Scenario analysis**	**Incremental**		**ICER**
			Costs	**QALYs**	
Health state utilities	van Agthoven (2004)	Values from McKenzie & van der Pol	£54,414	0.77	£70,292
		Values from Kontodimopoulos	£54,414	0.80	£68,433
		Lower utility from fourth line, from Palumbo (2013)	£54,414	0.99	£54,723

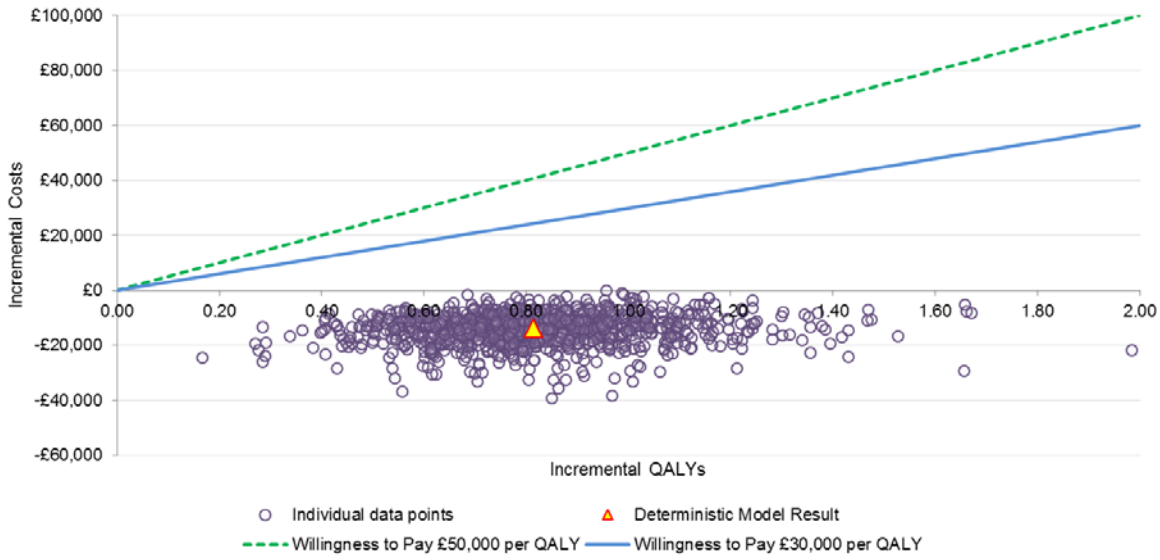
Probabilistic and one-way sensitivity analysis

Base case – Compared to bortezomib retreatment

Probabilistic and one way sensitivity analyses show that lenalidomide is consistently cost-effective (dominant) compared to bortezomib retreatment. The probabilistic incremental results, estimated from 1,000 PSA runs, are a cost saving of £14,067 and a QALY gain of 0.82 per patient, which are consistent with the deterministic results.

One-way sensitivity analysis is presented in terms of the effect on Net Monetary Benefit (NMB, evaluated at a £30,000 threshold value), because lenalidomide is dominant compared to bortezomib retreatment which produces a negative ICER. Negative ICERs cannot be interpreted (as they can result from either a dominant or dominated treatment). The NMB tornado diagram shows the model to be most sensitive to the HR used to inform the comparative efficacy of bortezomib retreatment in terms of PFS; however, when the hazard ratio is varied to both its upper and lower bounds lenalidomide is still cost-effective, shown by a positive NMB.

Figure 8: Cost-effectiveness plane of 1,000 PSA simulations vs bortezomib retreatment



Key: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

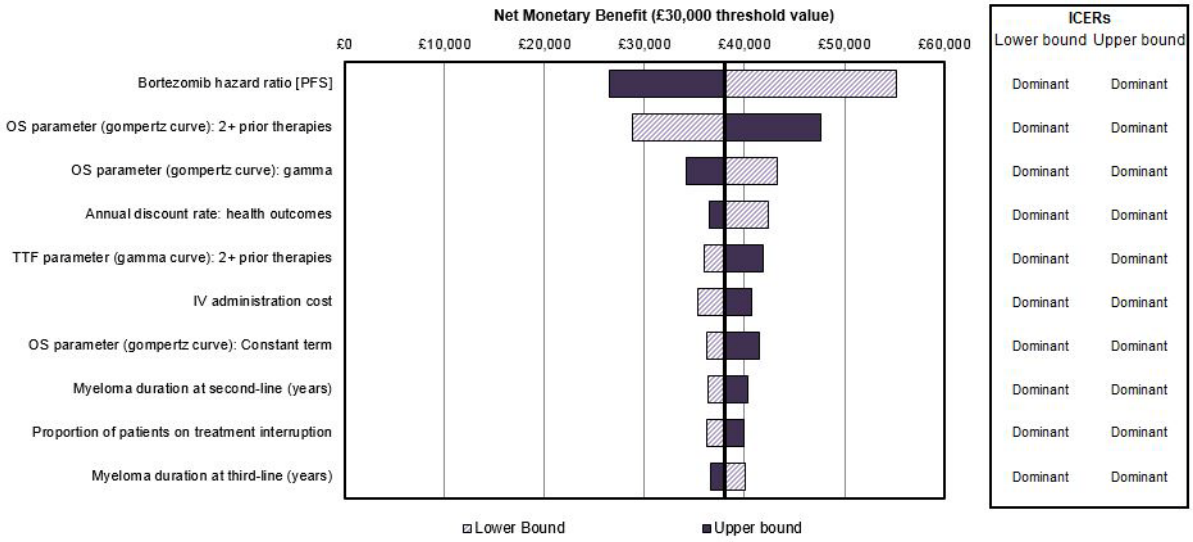
Incremental PSA results

	Mean	SD
Incremental Costs	-£14,067	£5,688
Incremental QALYs	0.82	0.21

PSA ICER	Lenalidomide dominates

Cost-effectiveness threshold	Likelihood of being cost-effective
£20,000/QALY	100%
£30,000/QALY	100%

Figure 9: One-way sensitivity analysis results (NMB evaluated at £30,000 per incremental QALY) vs bortezomib retreatment

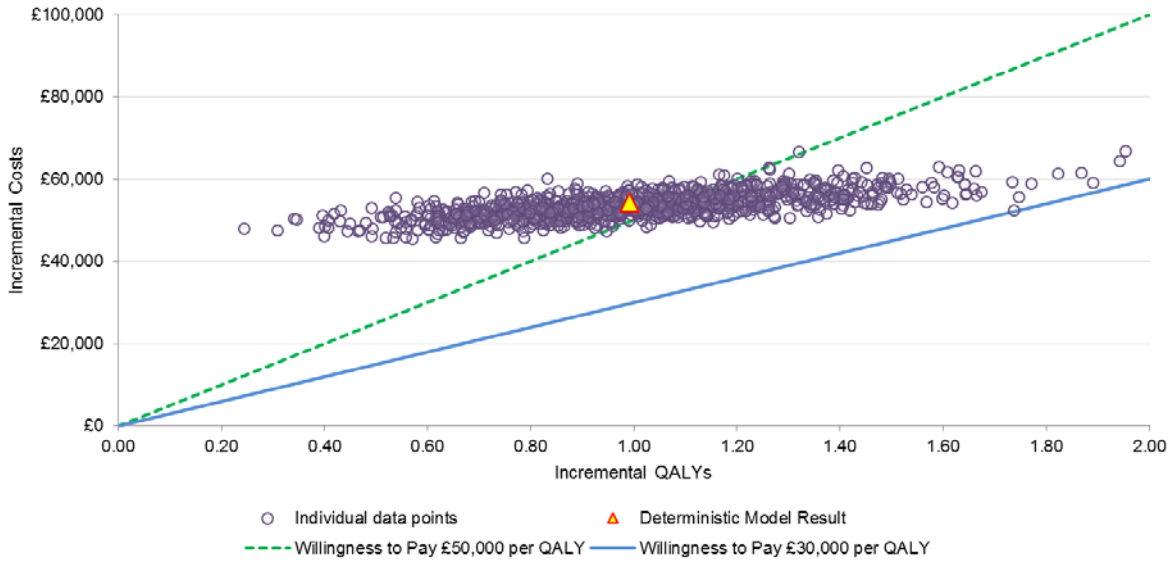


Key: IV, intravenous; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.

Compared to melphalan plus prednisolone

Probabilistic and one-way sensitivity analysis show that the majority of the uncertainty around cost-effectiveness surrounds outcomes rather than costs. In particular, the OS improvement achieved by lenalidomide, and the TTF curve which determines treatment duration, have major impacts on model results.

Figure 10: Cost-effectiveness plane of 1,000 PSA simulations vs MP



Key: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

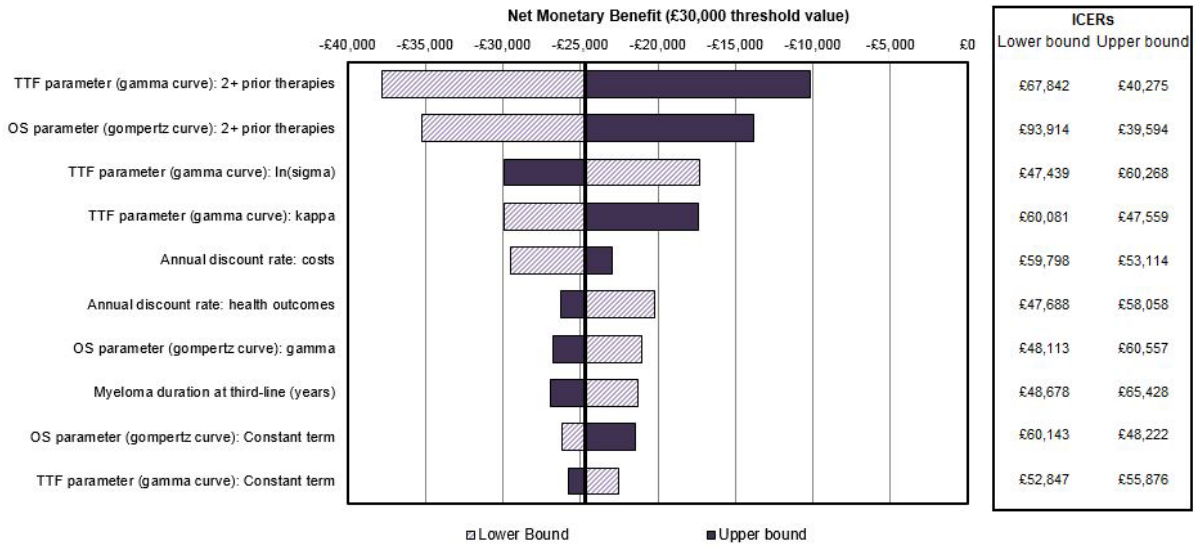
Incremental PSA results

	Mean	SD
Incremental Costs	£53,629	£3,117
Incremental QALYs	1.00	0.27

PSA ICER	£53,686

Cost-effectiveness threshold	Likelihood of being cost-effective
£20,000/QALY	0%
£30,000/QALY	0.1%

Figure 11: One-way sensitivity analysis results (NMB evaluated at £30,000 per incremental QALY) vs MP



Key: OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.

Conclusion

An updated cost-effectiveness analysis has been presented, based upon the ACD. Compared to bortezomib retreatment the base case analysis gives a dominant ICER for lenalidomide plus dexamethasone, generated by a cost saving of £13,634 and a QALY gain of 0.81 per patient.

Compared to melphalan plus prednisolone, a representative chemotherapy agent which is much less widely used than bortezomib, lenalidomide has a deterministic ICER of £54,898 with a cost increase of £54,414 and 0.99 incremental QALYs gained.

Scenario and sensitivity analysis show that lenalidomide remains cost-effective compared with bortezomib retreatment across all assumptions related to the sequencing or lenalidomide and bortezomib, parametric curve fits selected, source of comparator evidence used, uptake of the bortezomib price discount, model time horizon considered and the source of utilities. Lenalidomide has a dominant probabilistic ICER with a 100% chance of cost-effectiveness at a threshold of £20,000/QALY using probabilistic analysis.

The primary scenario found to have a potential effect on the cost-effectiveness of lenalidomide compared to bortezomib retreatment is the number of cycles of bortezomib plus dexamethasone received. If patients are limited to 8 cycles of bortezomib retreatment, without any impact on efficacy, the lenalidomide ICER is £31,999. This is a highly conservative scenario, however; the available evidence, including UK market research conducted by Celgene, indicates outcomes are worse for patients receiving only 8 cycles compared to those who receive more than 8. Receipt of more than 8 cycles appears to be more reflective of current UK practice. Assuming a maximum limit of 19 bortezomib cycles (as per the Taverna *et al* data) lenalidomide remains cost-effective with an ICER of £15,409.

Comparison to initial bortezomib treatment using MTC results – with the MTC informing comparative efficacy, lenalidomide has an ICER of £8,120. This indicates that lenalidomide is cost-effective compared to bortezomib even under the highly extreme assumption of allowing bortezomib retreatment efficacy to equal the efficacy of initial bortezomib.

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Appendices

Appendix A: Visual inspection of parametric curve fits without covariate adjustment

Figure 12: Full OS – unadjusted curves and Kaplan–Meier plot

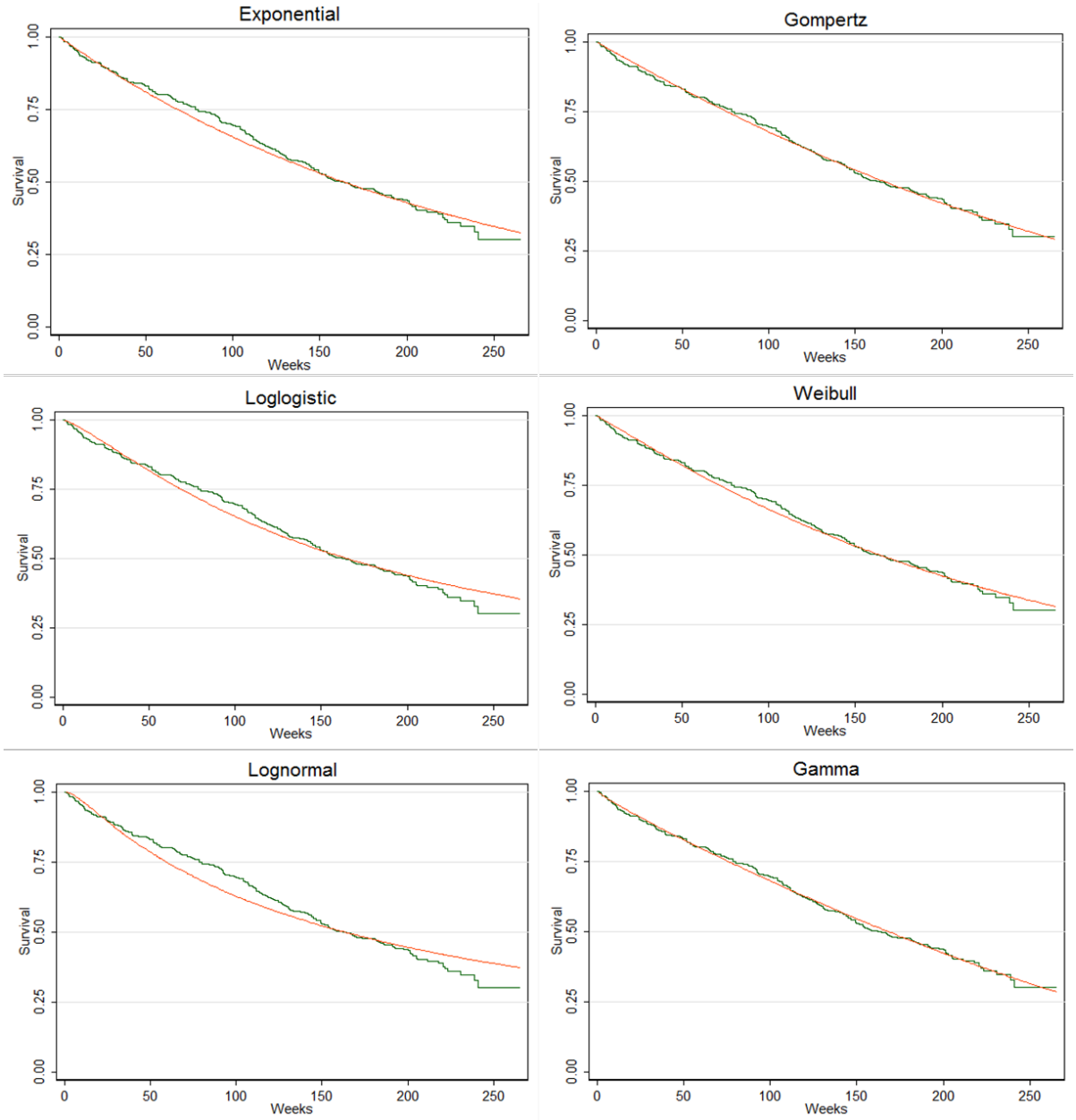


Figure 13: OS beyond 100 weeks – unadjusted curves and Kaplan–Meier plot

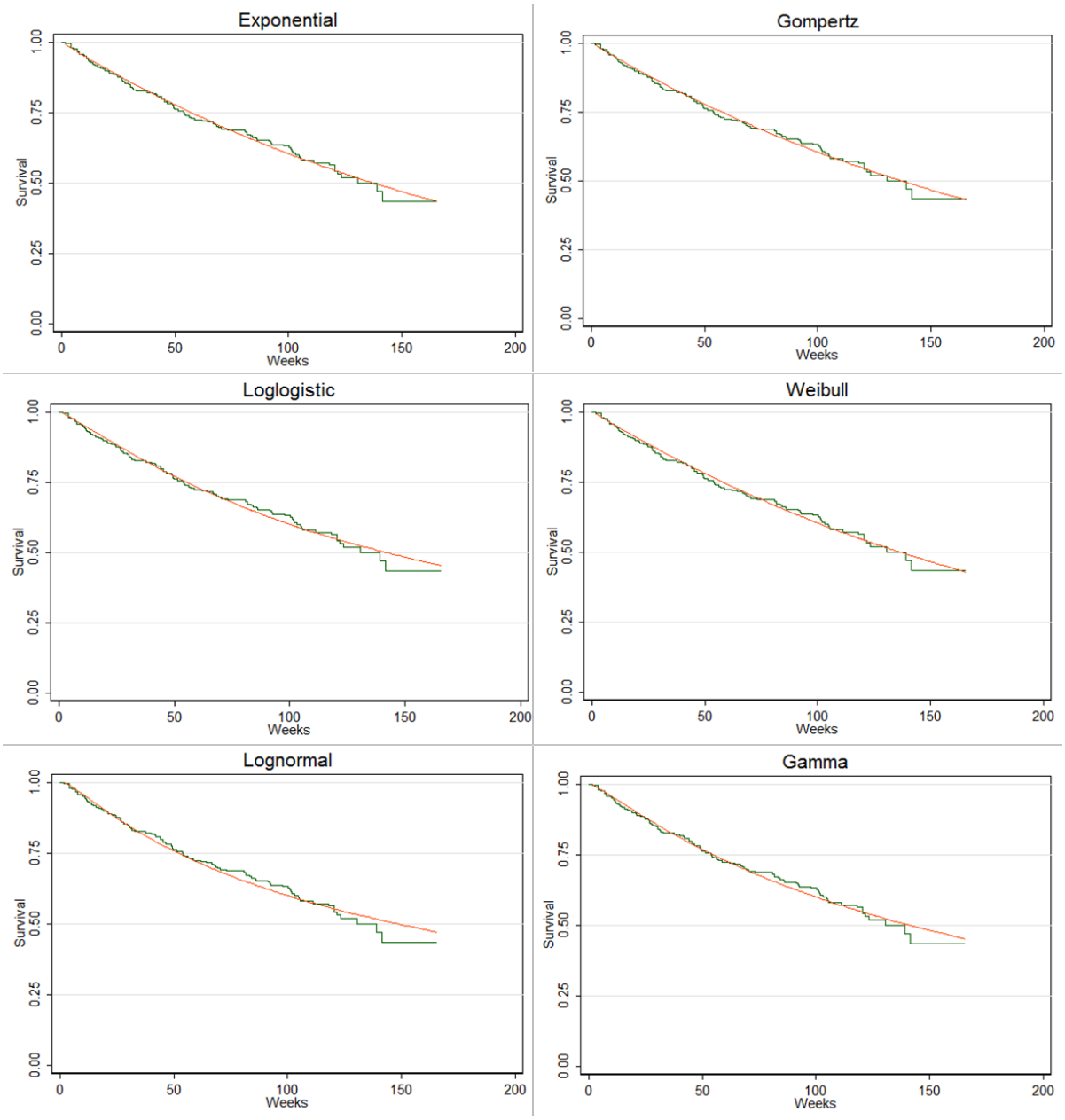


Figure 14: PFS – unadjusted curves and Kaplan–Meier plot

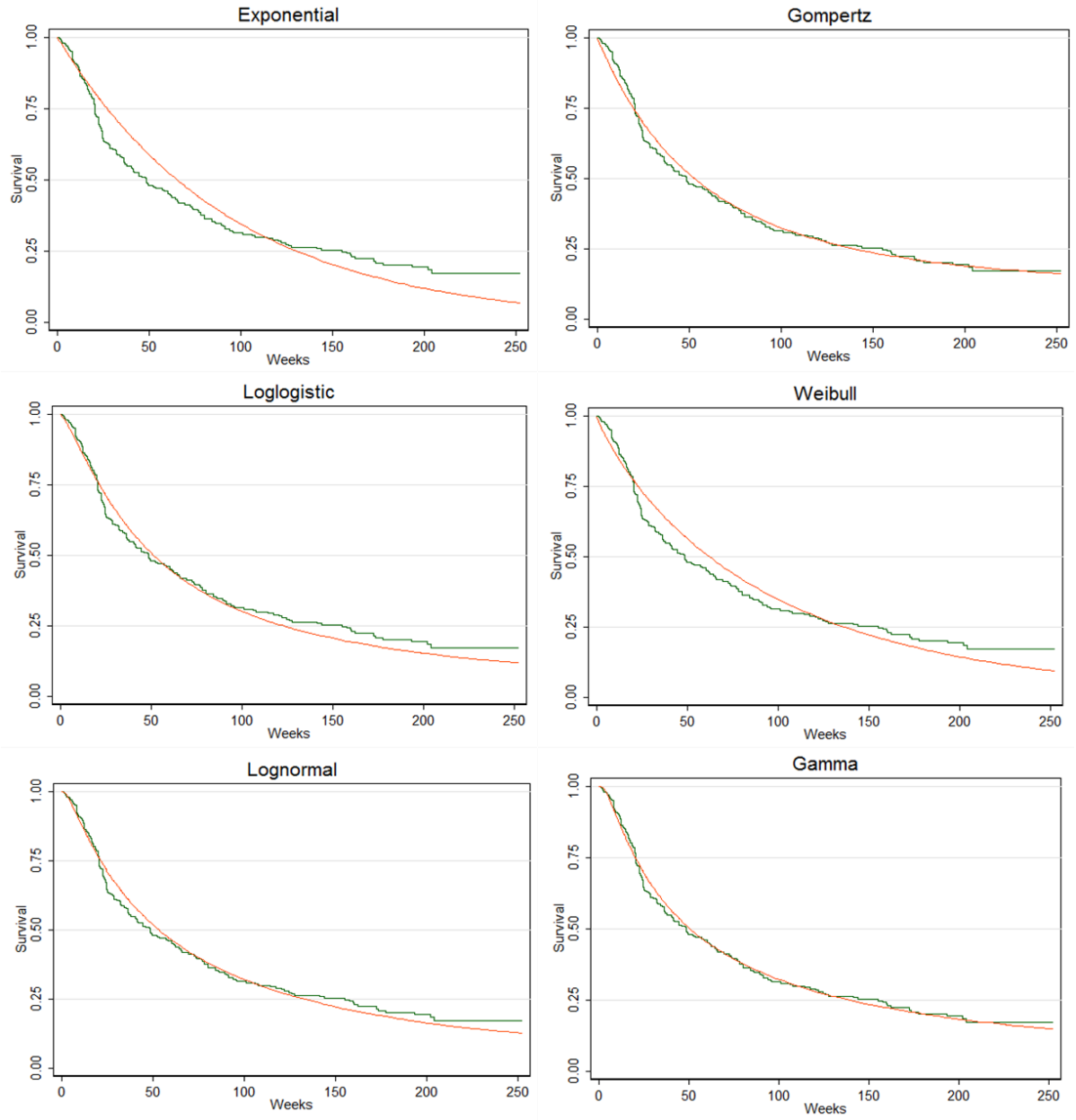
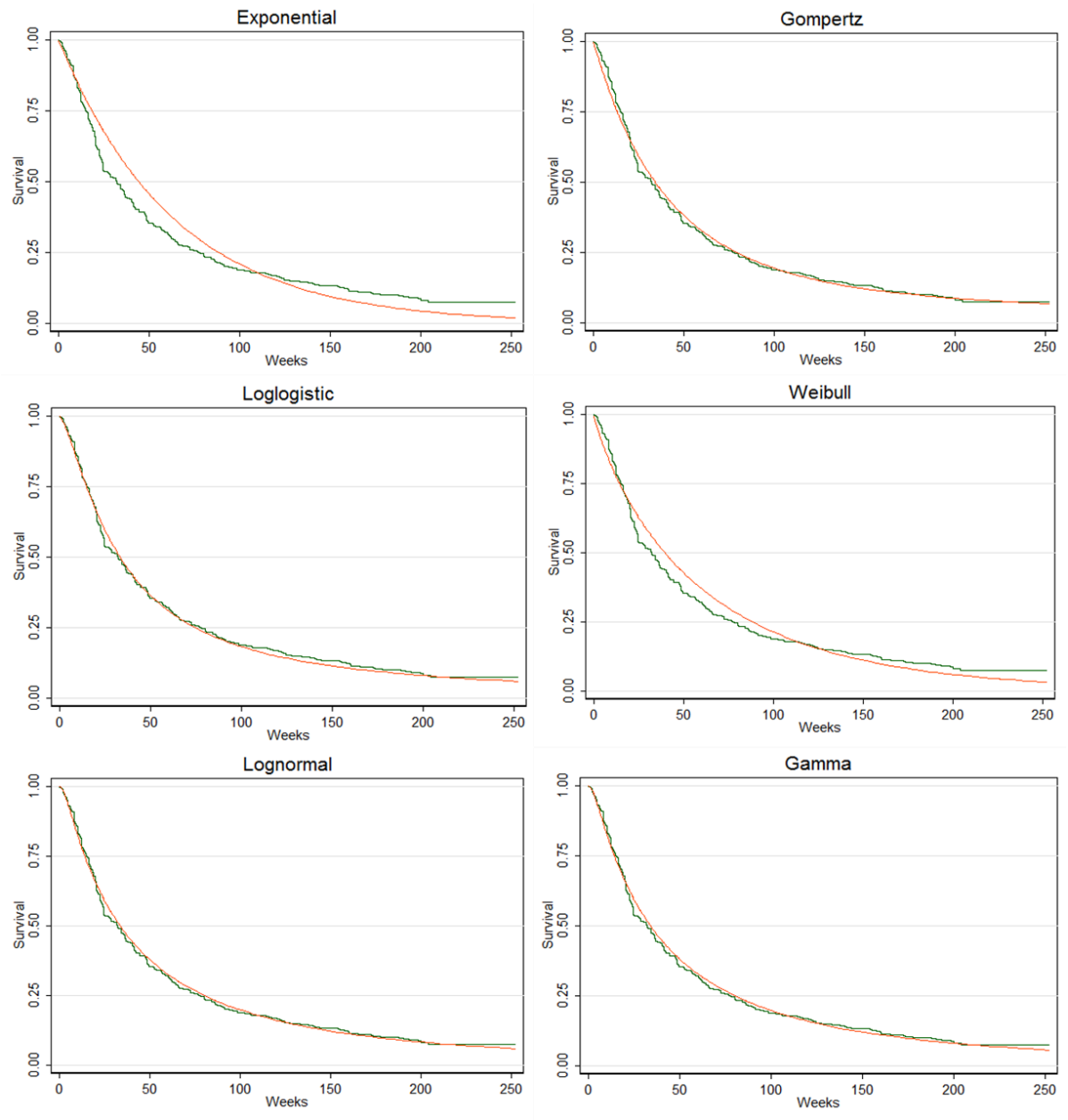


Figure 15: TTF – unadjusted curves and Kaplan–Meier plot



Appendix B: Visual inspection, goodness of fit, stepwise selection of covariates and final models for TTP

Figure 16: TTP – unadjusted curves and Kaplan–Meier plot

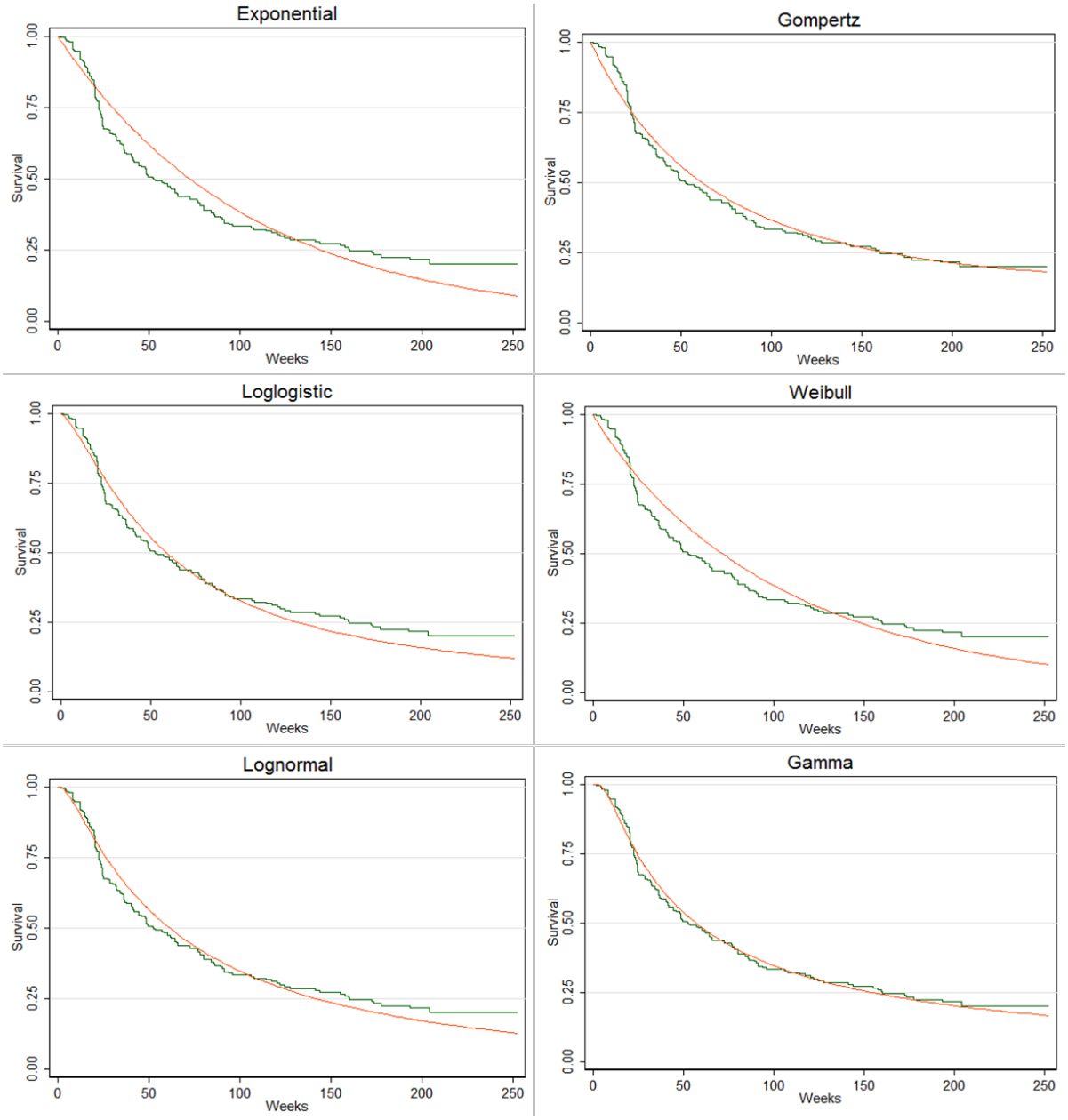


Table 31: Goodness of fit statistics (AIC and BIC) for unadjusted TTP models

Parametric model	AIC	BIC
Gompertz	724.1	731.6
Gamma	694.4 *	705.8 *
Exponential	739.4	743.2
Weibull	740.4	748.0
Log-normal	701.6	709.2
Log-logistic	708.8	716.4

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.
* denotes lowest AIC or BIC statistic

Table 32: Stepwise regression results – TTP

Parameter	P-values					
	Exponential	Gamma	Gompertz	Log-logistic	Log-normal	Weibull
Patient age						
BL ECOG = 0						
BL ECOG = 1						
BL ECOG = 2						
Myeloma duration (yrs)						
Sex = Male						
Beta-2 mic >2.5mg/l	0.005	0.006	0.006	0.004	0.009	0.021
2+ prior therapies	0.019	0.029	0.003	0.015	0.004	0.010
Prior HDT/SCT						
BL plasma = high						
BL plasma = low						
BL bone lesions						
Earlier DEX						
Prior doxorubicin	0.021	0.031		0.018		
Prior melphalan						
Prior thalidomide						
Prior bortezomib	0.008	0.034		0.006		
Worsening Ex PD	0.000	0.000	0.000	0.000	0.000	0.001
Myeloma stage 1						
Myeloma stage 2						
Myeloma stage 3	0.026	0.048		0.024		

BMCA biop, normal						
Hyperplasia	0.049		0.019	0.044	0.043	
Hypoplasia						

Key: ECOG, Eastern Cooperative Oncology Group score; BL, baseline; mic, microglobulin; HDT, high-dose therapy; SCT, stem-cell transplant; DEX, dexamethasone; Ex PD, extramedullary plasmacytoma disease; BMCA biop, bone marrow cellular aspiration/biopsy.

Table 33: Final models – TTP

Parameter	Coefficients			
	Gamma	Gompertz	Log-logistic	Log-normal
Myeloma duration (years)	0.041	-0.049	0.048	0.045
Beta-2 microglobulin >2.5mg/L	-0.365	0.450	-0.524	-0.473
2+ prior therapies	-0.492	0.547	-0.593	-0.547
Worsening Ex PD	-1.069	1.253	-1.078	-1.163
Intercept	4.183	-4.873	4.669	4.646
Gamma			0.684	
Rho				
Sigma	1.186			1.162
Kappa	-0.697			

Key: Ex PD, extramedullary plasmacytoma disease; TTP, time to progression.

Appendix C: Stepwise regression analysis results

Table 34: Stepwise regression results: OS (full)

Parameter	P-values					
	Exponential	Gamma	Gompertz	Log-logistic	Log-normal	Weibull
Patient age						
BL ECOG = 0						
BL ECOG = 1						
BL ECOG = 2						
Myeloma duration (yrs)	0.005	0.003	0.008	0.004	0.006	0.011
Sex = Male						
Beta-2 mic >2.5mg/l	0.000	0.000	0.000	0.000	0.000	0.000
2+ prior therapies	0.001	0.000	0.003	0.000	0.008	0.000
Prior HDT/SCT						
BL plasma = high						
BL plasma = low						
BL bone lesions						
Earlier DEX						
Prior doxorubicin						
Prior melphalan						
Prior thalidomide						
Prior bortezomib						
Worsening Ex PD	0.008	0.005	0.004	0.006	0.005	0.006
Myeloma stage 1						
Myeloma stage 2						
Myeloma stage 3			0.028		0.014	
BMCA biop, normal						
Hyperplasia			0.022		0.011	
Hypoplasia						

Key: ECOG, Eastern Cooperative Oncology Group score; BL, baseline; mic, microglobulin; HDT, high-dose therapy; SCT, stem-cell transplant; DEX, dexamethasone; Ex PD, extramedullary plasmacytoma disease; BMCA biop, bone marrow cellular aspiration/biopsy.

Table 35: Stepwise regression results: OS beyond 100 weeks (scenario analysis)

Parameter	P-values					
	Exponential	Gamma	Gompertz	Log-logistic	Log-normal	Weibull
Patient age						
BL ECOG = 0						
BL ECOG = 1						
BL ECOG = 2						
Myeloma duration (yrs)	0.026	0.025	0.012	0.024	0.019	0.029
Sex = Male						
Beta-2 mic >2.5mg/l	0.002	0.001	0.001	0.001	0.002	0.002
2+ prior therapies	0.006	0.005	0.010	0.005	0.012	0.008
Prior HDT/SCT						
BL plasma = high						
BL plasma = low						
BL bone lesions	0.039	0.037	0.023	0.037	0.024	0.039
Earlier DEX						
Prior doxorubicin						
Prior melphalan						
Prior thalidomide						
Prior bortezomib						
Worsening Ex PD						
Myeloma stage 1						
Myeloma stage 2						
Myeloma stage 3						
BMCA biop, normal						
Hyperplasia						
Hypoplasia						

Key: ECOG, Eastern Cooperative Oncology Group score; BL, baseline; mic, microglobulin; HDT, high-dose therapy; SCT, stem-cell transplant; DEX, dexamethasone; Ex PD, extramedullary plasmacytoma disease; BMCA biop, bone marrow cellular aspiration/biopsy.

Table 36: Stepwise regression results: PFS

Parameter	P-values					
	Exponential	Gamma	Gompertz	Log-logistic	Log-normal	Weibull
Patient age						
BL ECOG = 0						
BL ECOG = 1						
BL ECOG = 2						
Myeloma duration (yrs)					0.049	0.047
Sex = Male						
Beta-2 mic >2.5mg/l	0.000	0.001	0.000	0.000	0.000	0.001
2+ prior therapies	0.001	0.026	0.026	0.002	0.005	0.009
Prior HDT/SCT			0.029		0.019	0.016
BL plasma = high						
BL plasma = low						
BL bone lesions						
Earlier DEX						
Prior doxorubicin	0.001	0.001	0.021	0.001	0.019	0.037
Prior melphalan	0.030			0.032		
Prior thalidomide						
Prior bortezomib						
Worsening Ex PD	0.000	0.001	0.004	0.000	0.003	0.007
Myeloma stage 1						
Myeloma stage 2						
Myeloma stage 3	0.030	0.027	0.013	0.031	0.023	0.031
BMCA biop, normal						
Hyperplasia			0.005		0.010	0.009
Hypoplasia						

Key: ECOG, Eastern Cooperative Oncology Group score; BL, baseline; mic, microglobulin; HDT, high-dose therapy; SCT, stem-cell transplant; DEX, dexamethasone; Ex PD, extramedullary plasmacytoma disease; BMCA biop, bone marrow cellular aspiration/biopsy.

Table 37: Stepwise regression results: TTF

Parameter	P-values					
	Exponential	Gamma	Gompertz	Log-logistic	Log-normal	Weibull
Patient age						
BL ECOG = 0						
BL ECOG = 1						
BL ECOG = 2						
Myeloma duration (yrs)						
Sex = Male						
Beta-2 mic >2.5mg/l	0.000	0.001	0.001	0.000	0.002	0.001
2+ prior therapies	0.000	0.004	0.063	0.001	0.039	0.029
Prior HDT/SCT						
BL plasma = high						
BL plasma = low						
BL bone lesions						
Earlier DEX						
Prior doxorubicin						
Prior melphalan	0.015	0.034		0.021		
Prior thalidomide						
Prior bortezomib						
Worsening Ex PD	0.001	0.007	0.045	0.002	0.033	0.023
Myeloma stage 1						
Myeloma stage 2						
Myeloma stage 3						
BMCA biop, normal						
Hyperplasia	0.007	0.010	0.003	0.009	0.004	0.004
Hypoplasia						

Key: ECOG, Eastern Cooperative Oncology Group score; BL, baseline; mic, microglobulin; HDT, high-dose therapy; SCT, stem-cell transplant; DEX, dexamethasone; Ex PD, extramedullary plasmacytoma disease; BMCA biop, bone marrow cellular aspiration/biopsy.

Appendix D: Final parametric model results

Figure 17: OS – second-line patients

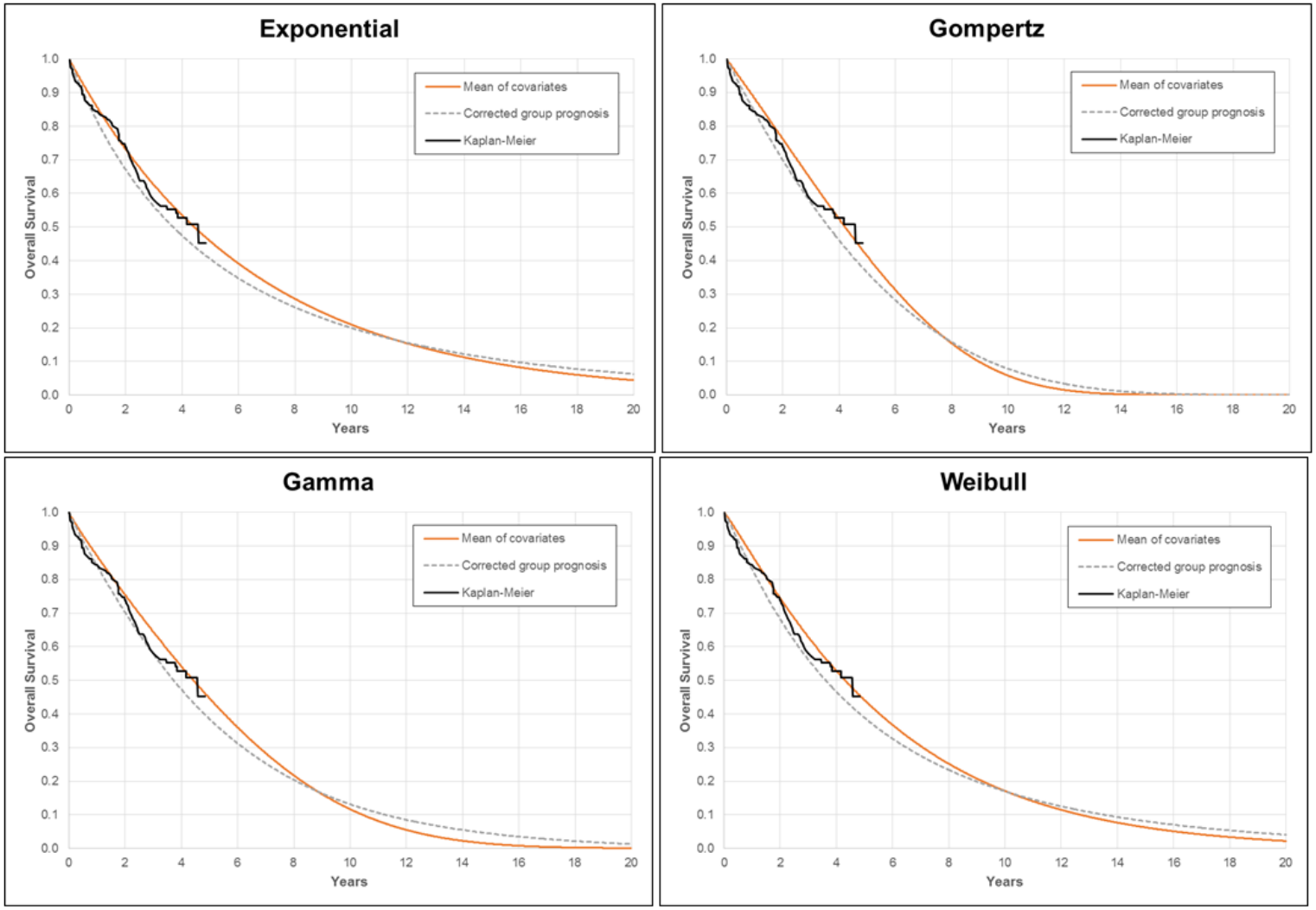


Figure 18: OS – third-line patients

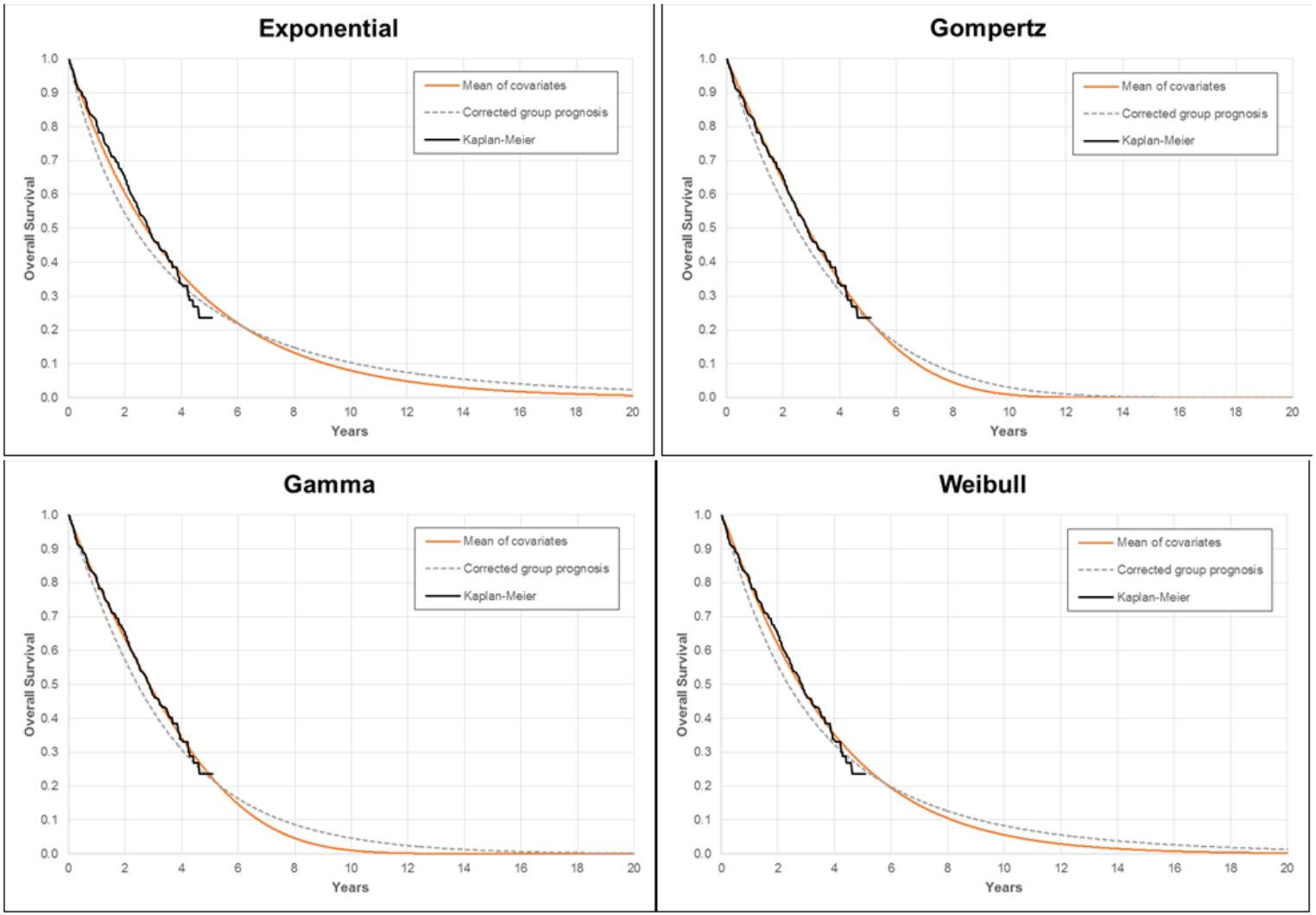


Figure 19: OS – all patients

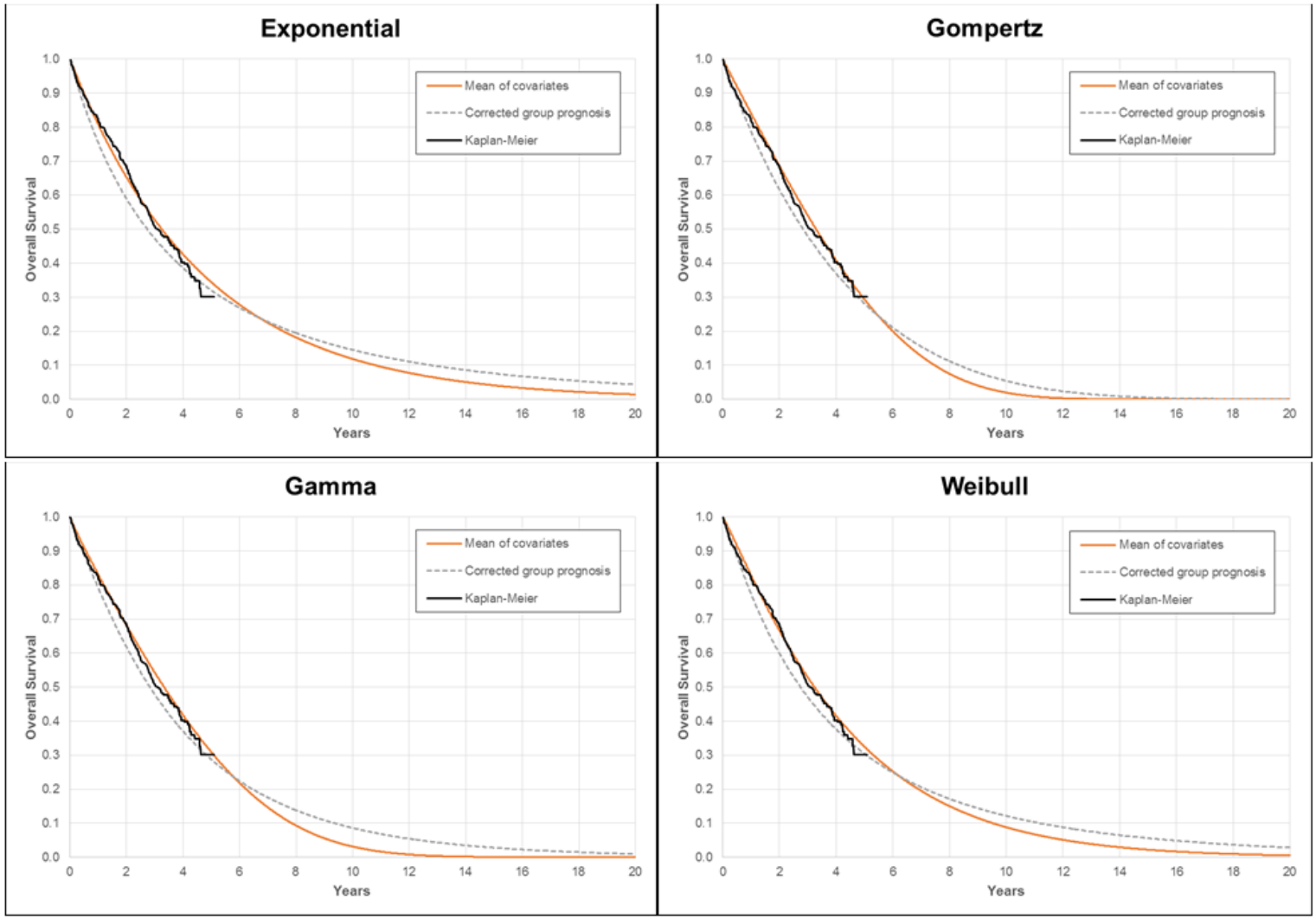


Figure 20: Piecewise OS (Kaplan–Meier to 100 weeks, then curve) – second-line patients

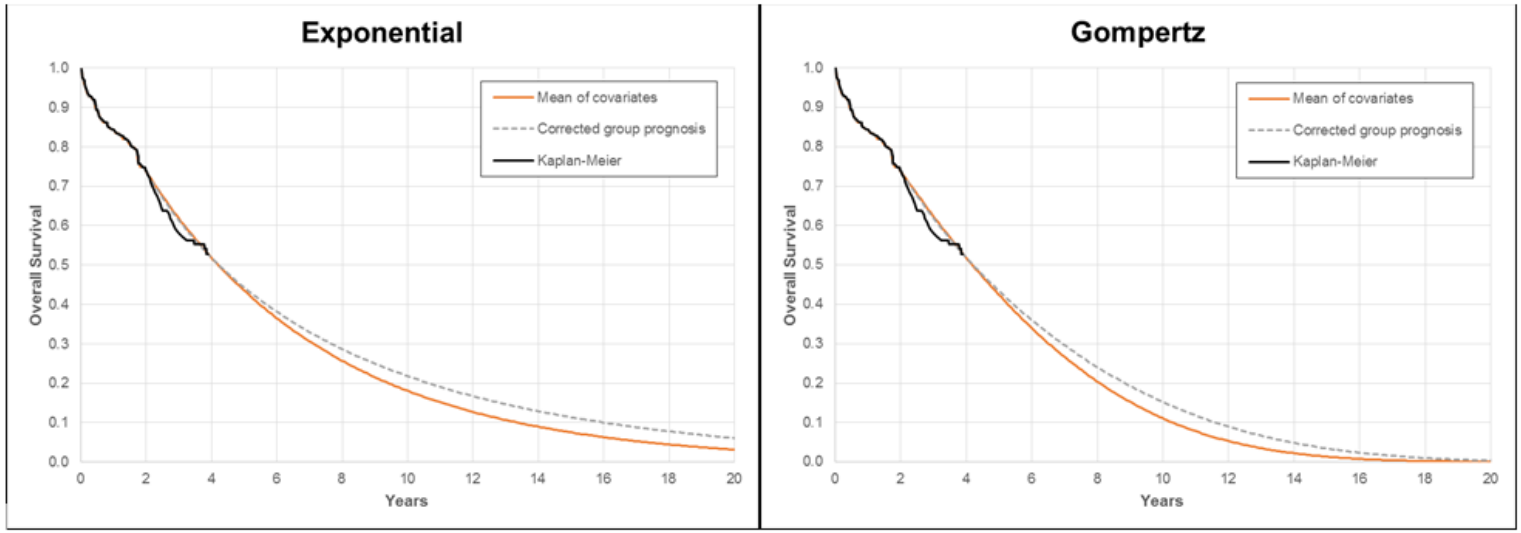


Figure 21: Piecewise OS (Kaplan–Meier to 100 weeks, then curve) – third-line patients

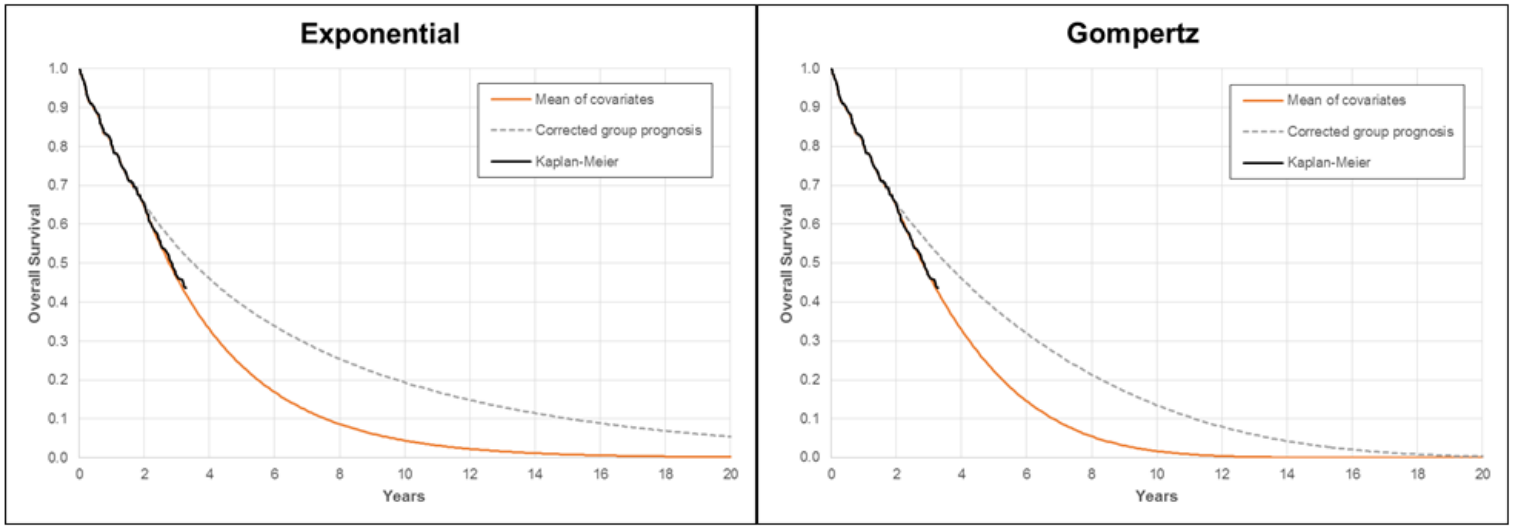


Figure 22: Piecewise OS (Kaplan–Meier to 100 weeks, then curve) – all patients

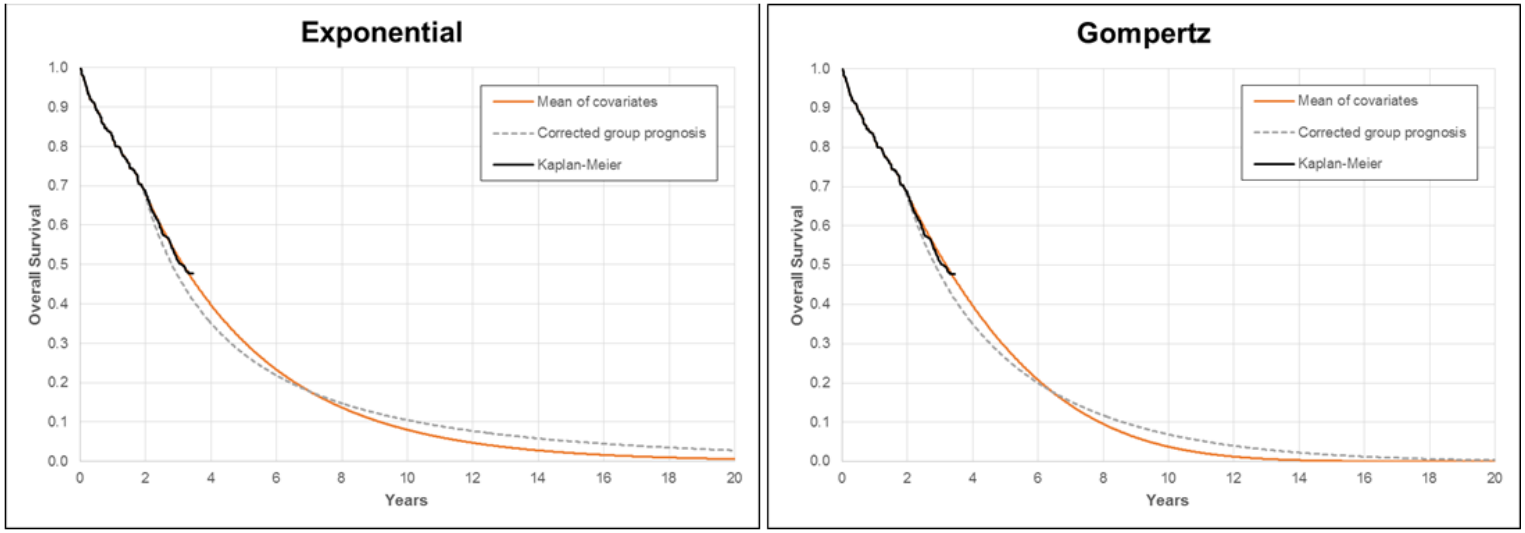


Figure 23: PFS – second-line patients

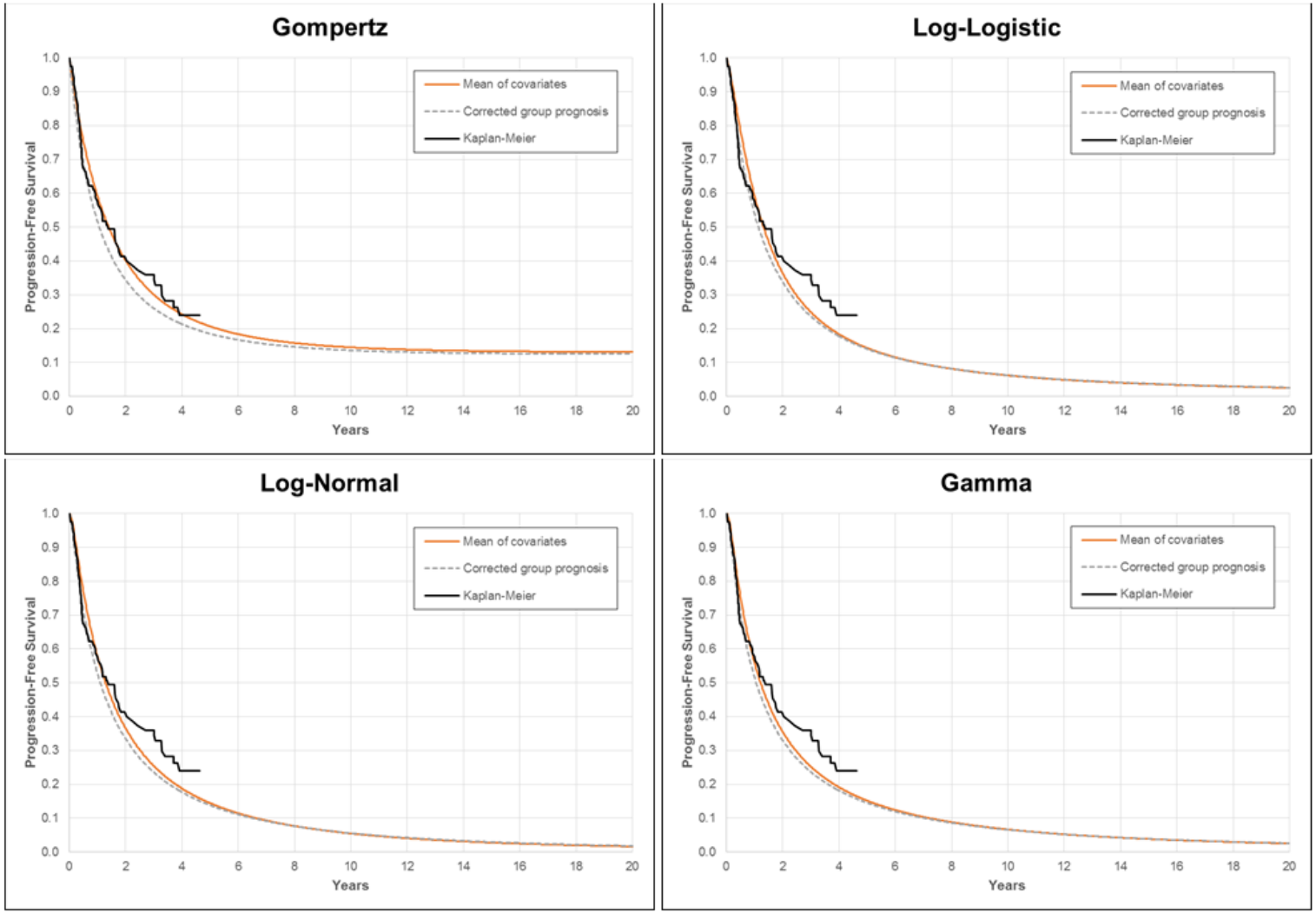


Figure 24: PFS – third-line patients

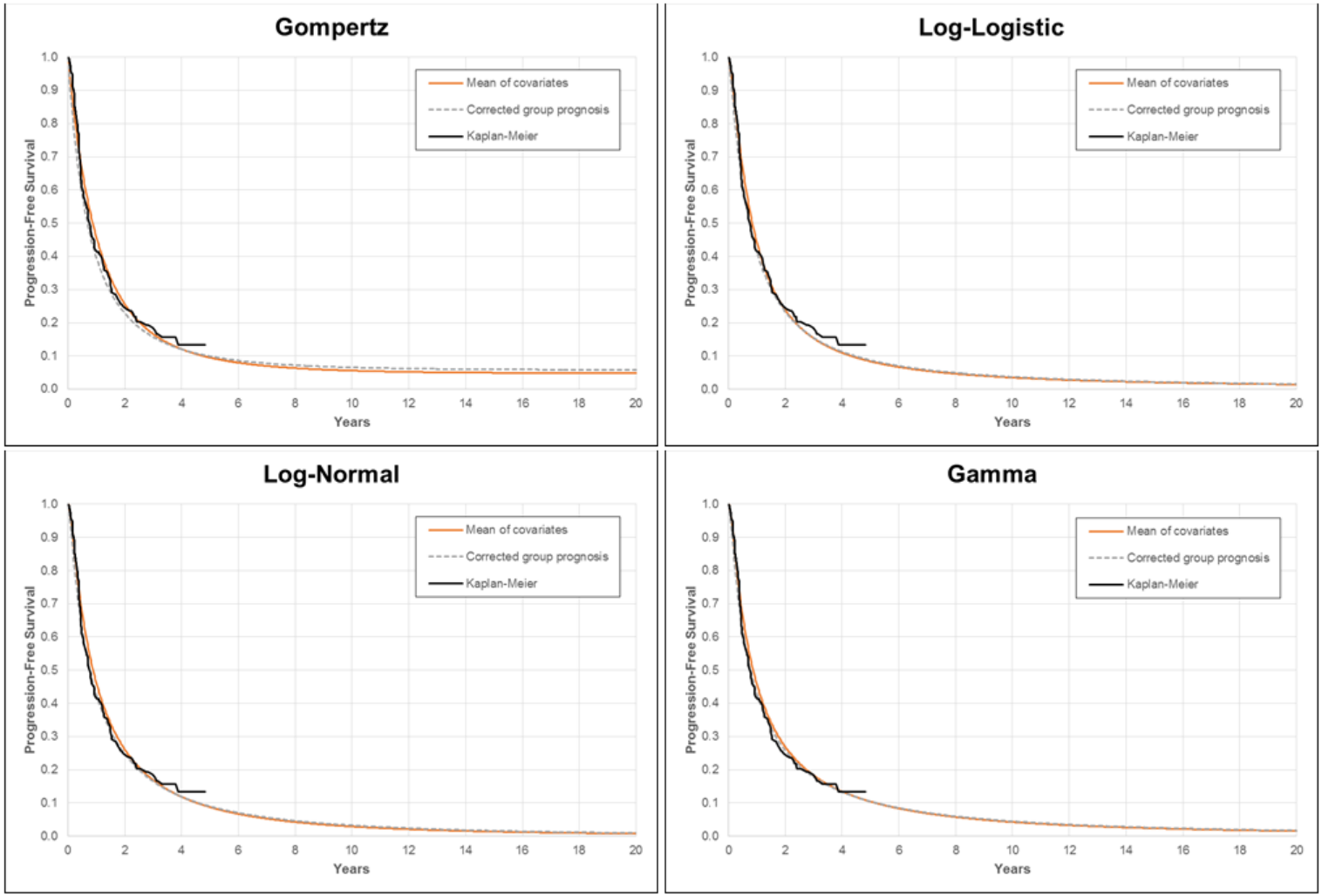


Figure 25: PFS – all patients

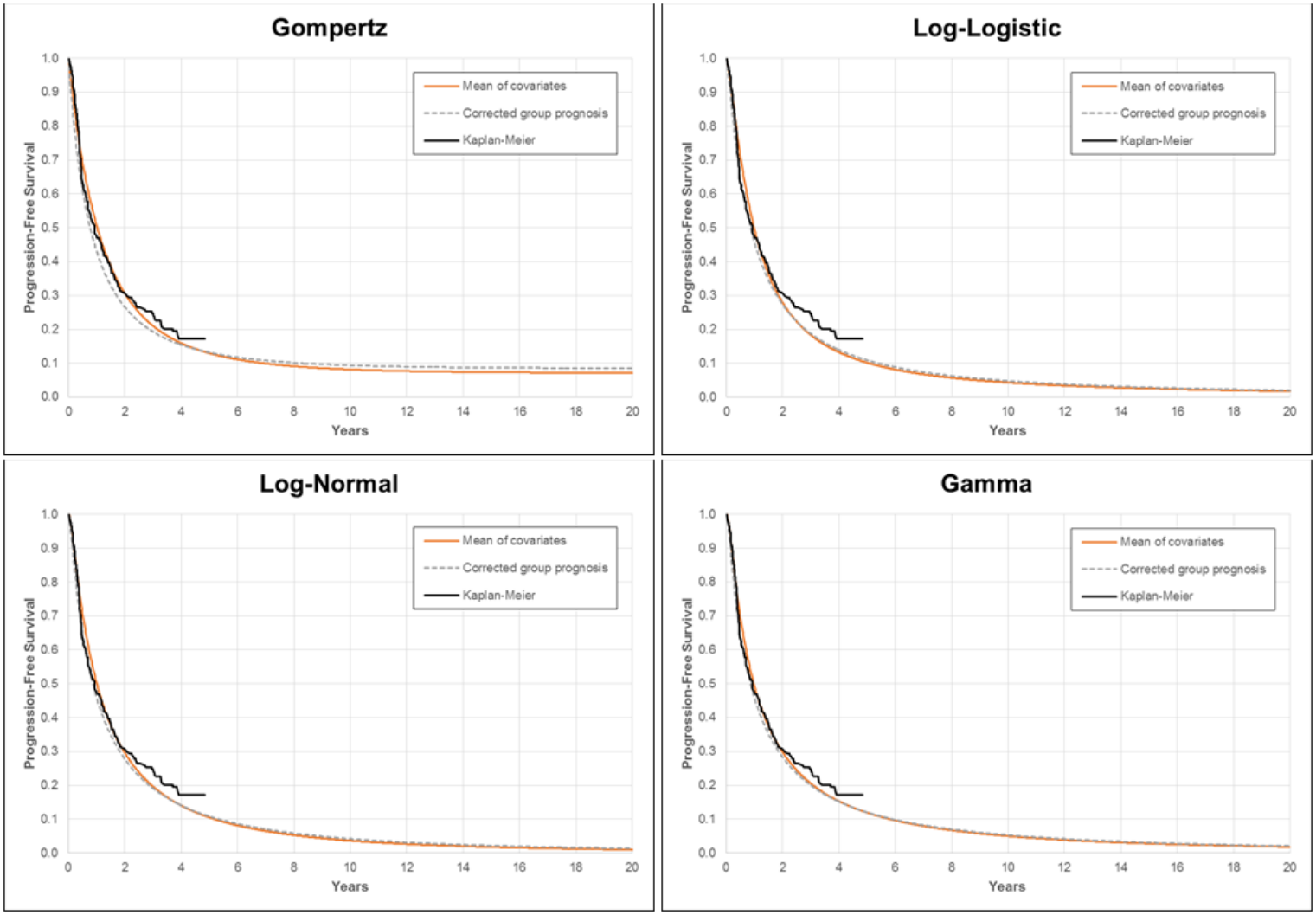


Figure 26: TTF – second-line patients

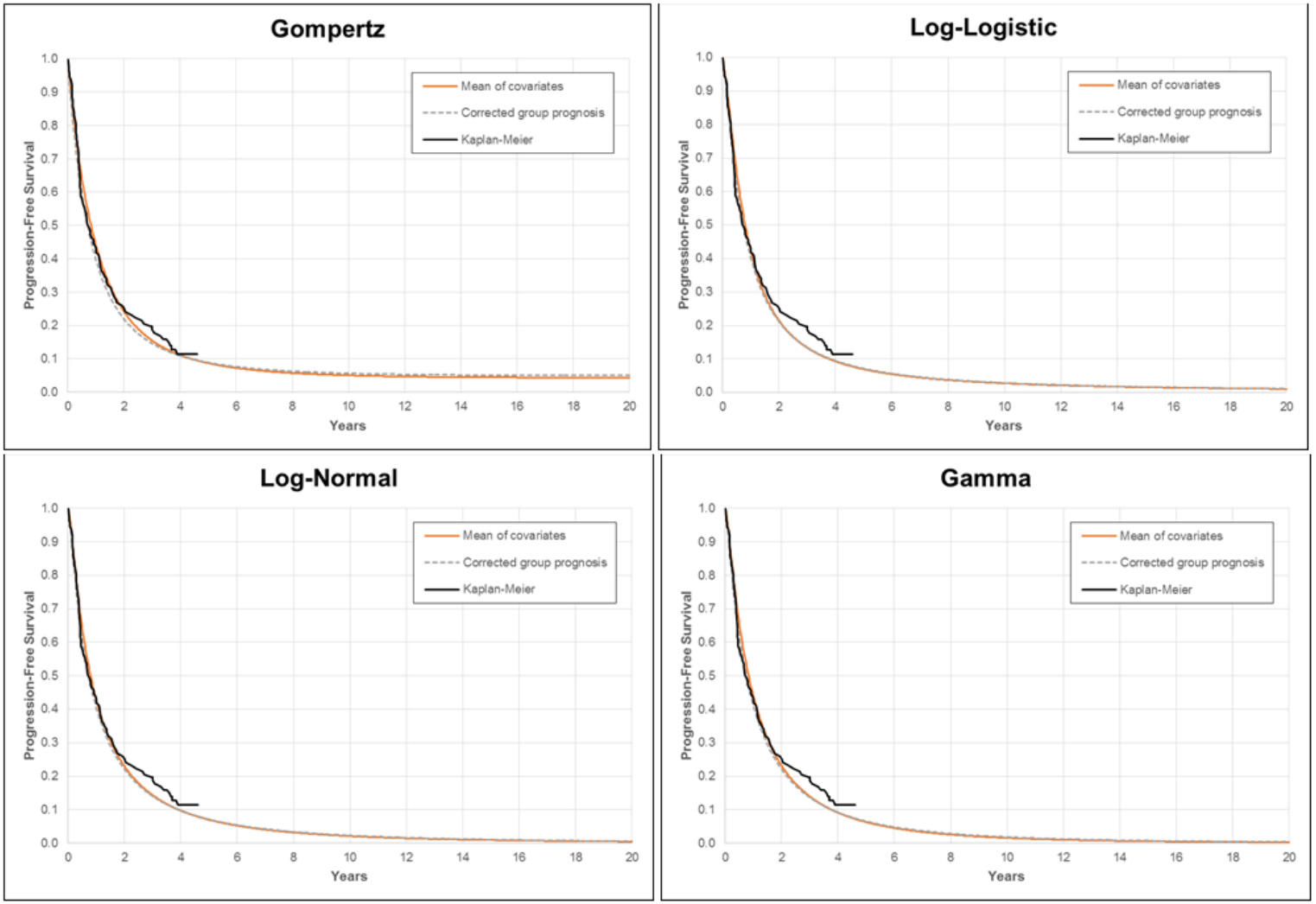


Figure 27: TTF – third-line patients

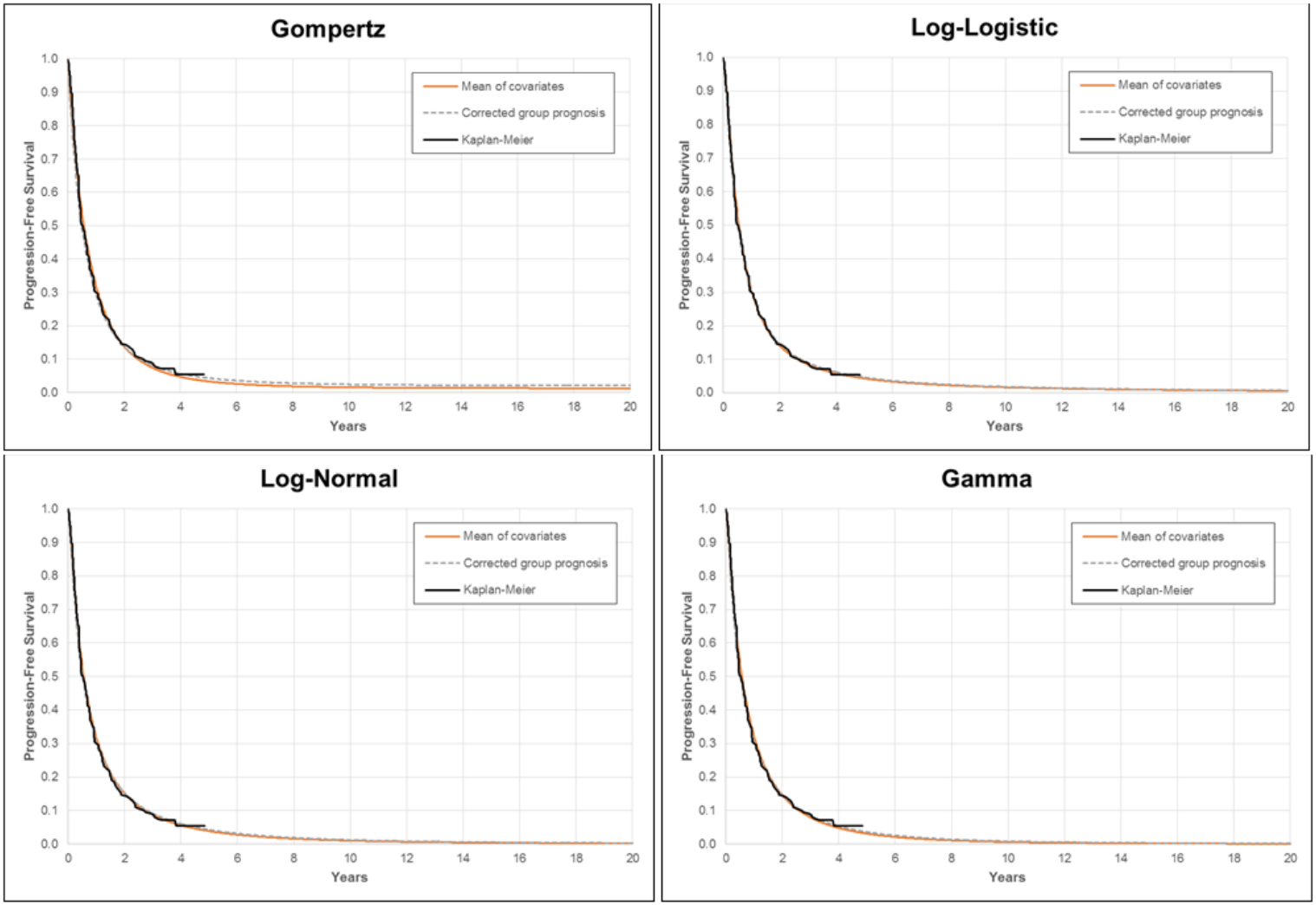
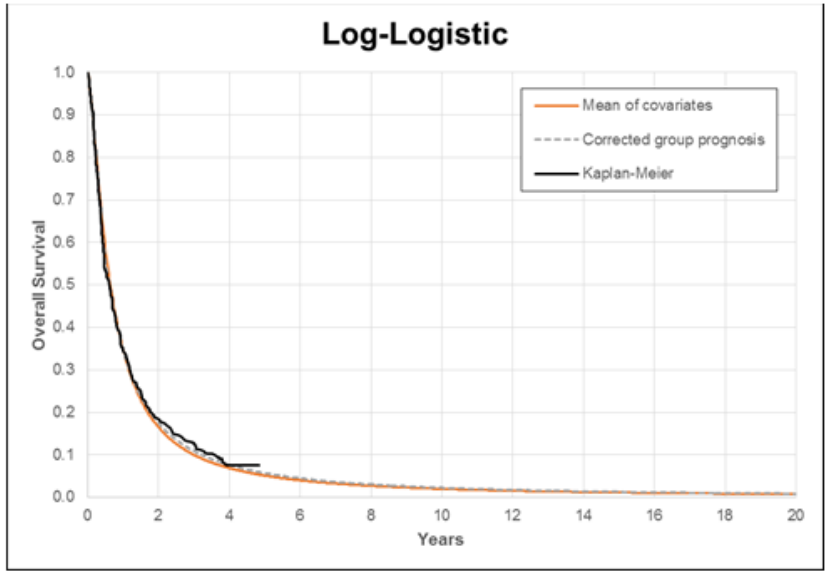
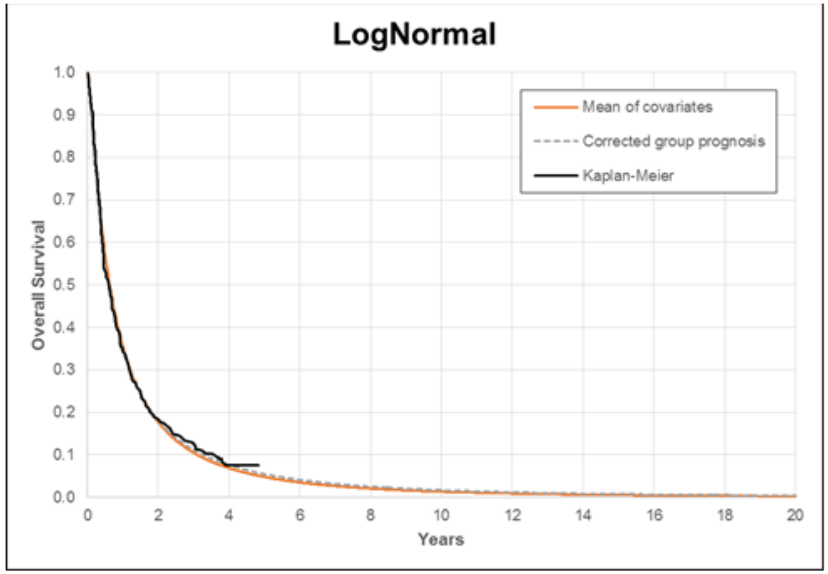
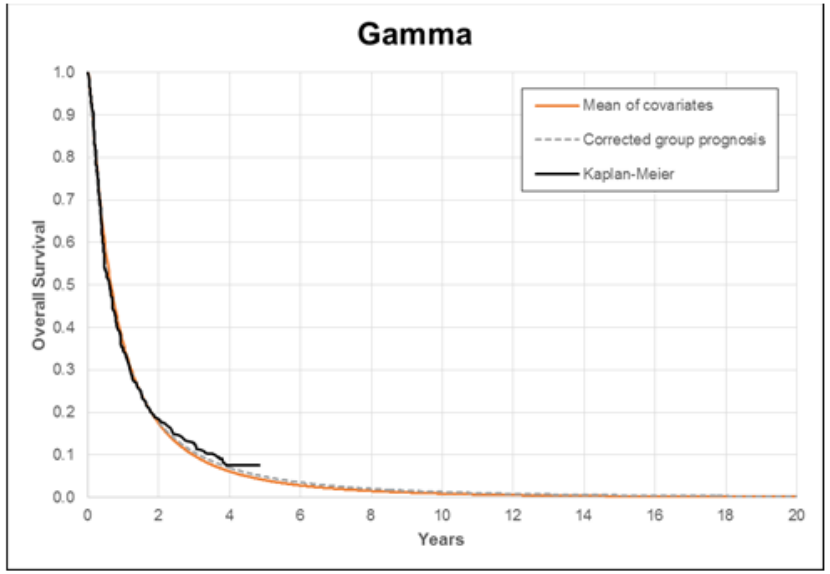


Figure 28: TTF – all patients

Gompertz
Mean of covariates
Corrected group prognosis
Kaplan-Meier
Overall Survival
Years


Log-Logistic
Mean of covariates
Corrected group prognosis
Kaplan-Meier
Overall Survival
Years


LogNormal
Mean of covariates
Corrected group prognosis
Kaplan-Meier
Overall Survival
Years


Gamma
Mean of covariates
Corrected group prognosis
Kaplan-Meier
Overall Survival
Years

Appendix E: Chemotherapy evidence identified

Table 38: Key study & patient characteristics of non-RCTs identified for chemotherapy

Study	Design	Drug & dose	N	Age, median years (range)	Sex, % male	ISS, % per stage	Prior therapies, % per number	Primary outcome(s)	Secondary outcome(s) of interest
Celesti, 1997[20]	Non-randomised study	Cyclophosphamide 1.2 g/m^2 + LD dexamethasone	13	69 (44-74)	54	II = 31; III = 69	1 = 60; 2 = 8; 3 = 24; 4 = 8	ORR	DoR; OS; toxicity
		Cyclophosphamide 0.5 mg/m^2 + MD dexamethasone	15	61 (54-73)	53	I = 7; II = 14; III = 79	1 = 20; 2 = 27; 3 = 33; 4 = 13; 5 = 7		
Petrucci, 1989[21]	Single-arm trial	Melphalan 25 mg/m^2 IV + prednisolone 60 mg/m^2	34	59	59	NR	NR	ORR	DoR; OS; safety

Key: CR, complete response; DoR, duration of response; HD, high dose; HT, haematological toxicity; LD, low dose; MD, medium dose; NR, not reported; ORR, overall response rate; OS, overall survival; WHO, World Health Organisation

Table 39: Key clinical and safety outcomes from non-RCTs identified for chemotherapy

Study	Treatment arm	Survival outcomes, median months	Response outcomes, n (%)	Discontinuations, n (%)	Adverse events, n (%)
Celesti, 1997[20]	HD cyclophosphamide + LD dexamethasone	OS = 9.4	ORR = 5 (38) **Median months** DoR = 7.6	NR	**Toxicity (WHO), %** 0 = 31; 1 = 31; 2 = 31; 3 = 7
	LD cyclophosphamide + MD dexamethasone	OS = 6.3	ORR = 5 (34) **Median months** DoR = 5.2		0 = 53; 1 = 27; 2 = 20
	Overall	OS = 7.8	ORR = 10 (36) **Median months** DoR = 6.3		

Appendix F: Bortezomib retreatment evidence identified

Table 40: Comparative evidence versus bortezomib retreatment

Study	**Taverna et al, 2012[1]**	**Hrusovsky et al, 2010[2]**	**Petrucci 2013 (RETRIEVE)[12]**	**Conner et al, 2008[13]**	**Sood et al, 2009[19]**	**Dispenzieri 2010[14] (ECOG E2A02)**
N	42	60[a]	130	82	32	n=7 retreatment
Patient population	Relapsed MM with ≥1 previous anti-myeloma therapy and response to previous BOR-based therapy	Relapsed MM with ≥1 previous anti-myeloma therapy and response to previous BOR-based therapy	Measurable secretory MM with ≥1 previous anti-myeloma therapy and at least a PR to previous BOR-based therapy	Relapsed MM with 1 prior BOR therapy for ≥ 4 cycles	Relapsed MM with prior BOR therapy and response to previous BOR-based therapy for ≥ 4 months	High risk MM & one prior therapy with bortezomib
Cycles of therapy received	Median: 3 (1–19)	Mean: 4.1 ± 2.5 (1–14)	Median: 7 (1–8)	Median (BOR retreatment): 12 doses i.e. 3 cycles (range 1-76 doses: 1 – 19 cycles)	Median (BOR retreatment): 5 cycles (1-12)	NR for this sub population
Geographical region	Switzerland	Germany and Switzerland	Europe	USA	USA and Canada	USA
Lines of prior therapy (Range)	Median: 2 (1–11)	Mean: 3.7 +/- 2.4 (1–13)	Median: 2 (1–7)	Median: 4	Median: 4 (1-8)	NR
Age, yrs (range)	At start of re-treatment: Median: 63 (40–89)	At start of treatment: Mean: 65.7 ± 10.8 (43–89)	At start of treatment: Median: 67 (38–86)	At start of treatment: Median: 66.5 (43–88)	At start of treatment: Median: 71 (44–83)	For all patients: Median: 63 (41 - 81)

Study	**Taverna et al, 2012[1]**	**Hrusovsky et al, 2010[2]**	**Petrucci 2013 (RETRIEVE)[12]**	**Conner et al, 2008[13]**	**Sood et al, 2009[19]**	**Dispenzieri 2010[14] (ECOG E2A02)**
Time from diagnosis (months)	To initial therapy: Median: 34.1 (2.3–159.2)	To retreatment: Mean: 51.9 ± 39.2 (3.9–176.1)	To retreatment: Median: 54 (9.6–166.8)	To initial BOR treatment: Median 3 years (1-18 years); BOR retreatment, NR	To retreatment: Median: 44 (16-122)	NR
% receiving concomitant DEX/steroid	64.3%	55.0%	72.3%	33% (thalidomide or steroids)	75%	NR
Prior SCT	31.0%	26.7%	30%	NR	13%	NR
Response rate	64.3%	63.3%	40.0%	21%	50%	28.6%
Median OS	20.4 months	20.4 months	NR	NR	NR	NR
Median TTP/PFS	10.5 months	9.3 months	8.4 months for patients who responded to BOR retreatment	NR	6.6 months	7.3 months
Note: a Per-protocol population used for efficacy analysis						