Issue 1 Overall Quality of the ERG Report

Description of problem	General comment on the overall quality and accuracy of the ERG report.
Description of proposed amendment	The ERG report requires significant review and amendment and its overall quality requires improvement. Typographical errors, poorly constructed phrasing and basic factual errors require amendment before this report is presented to the Appraisal Committee as a source of evidence and basis for its deliberations.
Justification for amendment	Celgene is concerned that the version of the ERG report provided for review is potentially unreliable as a source of evidence for the Committee. The ERG is littered with typographical errors, poor and potentially misleading phrasing as well as basic factual inaccuracies.
ERG response	No issue of factual accuracy identified.

Issue 2 General Tone and Language Used by the ERG

Description of problem	Celgene has significant concerns with regard to the style and tone of language adopted in the ERG report.
Description of proposed amendment	Celgene believes that the ERG report should be thoroughly reviewed and subjected to considerable editing to ensure that the report presents a balanced and sensible account of the Celgene submission with both strengths and weaknesses explored in an appropriate manner.
Justification for amendment	Throughout the document, points are fraught with opinion within summary sections where they should be descriptive and objective, before presenting a critical review. Some examples are: • Page 55, in reference to statistical methods employed by Celgene: "*It is claimed that* Beta-2 microglobulin count … were all found to be significant predictors of PFS, TTF and OS in MM-010." • Page 15, in reference to not assessing time to next treatment: "This *departs from* the outcome measures considered in the scope." • Page 91, in reference to incorrectly citing Celgene's response to ERG clarifications: "This is a *very surprising argument* given that in their initial request for clarification, the ERG asked Celgene. … [This approach] *would only make sense if* the

	first approach had been taken." The ERG should be scientific and descriptive in critiquing any submission. The use of subjective and inflammatory language throughout the ERG report sets an unprofessional negative tone, which may influence the Committee's ability to assess the decision problem objectively.
ERG response	The ERG agree with the issue regarding page 91 of the report. Unfortunately we have overlooked the fact that where it is mentioned *"Celgene clarified that the **second** approach had been taken. However, Celgene's explanation for excluding the number of prior therapies as a covariate would only make sense if the **first** approach had been taken."* this should in fact read *"Celgene clarified that the **first** approach had been taken. However, Celgene's explanation for excluding the number of prior therapies as a covariate would only make sense if the **second** approach had been taken."* However, once the amendment is in place, the ERG are confident in the appropriateness of their comment.

Issue 3 Difference in the ICER Compared to TA171

Description of problem	On page 10 the statement is made: • "Celgene's revised economic model reports base case dominant ICERs, which significantly depart from the ICERs presented in TA171." This is reiterated on page 125.
Description of proposed amendment	This statement is irrelevant to the decision problem and should be removed.

Justification for amendment	The ERG's statement is irrelevant and misleading. The original TA171 was based upon all patients treated after 1 prior therapy. This departs from the present decision problem, which is concerned with patients treated in the second-line setting *following prior bortezomib.* This is a different patient population. Furthermore, the data source used in TA171 is not the same and had included the APEX study with patients receiving bortezomib for the first time i.e. not retreatment). As such, ICERs presented in TA171 are not relevant to the decision problem and should not be compared with ICERs in the present submission.
ERG response	No issue of factual accuracy identified.

Issue 4 Data Extrapolation Process

Description of problem	On page 91 the statement is made: "Furthermore, Celgene decided to exclude the number of prior therapies as a potential outcome predictor from all models. The reason used to substantiate this decision was that "*the population of interest is treated in the second-line setting*". This is a very surprising argument given that in their initial request for clarification, the ERG asked Celgene to clarify if for the original economic analysis: 1. The full MM-0010 dataset had been used, with resulting outcomes being adjusted with covariate estimates for the second-line setting, 2. or if the dataset used in the analysis had been stratified and so only the second-line treatment population was included in the economic analysis. Celgene clarified that the second approach had been taken. However, Celgene's explanation for excluding the number of prior therapies as a covariate would only make sense if the first approach had been taken."

Description of proposed amendment	Celgene have previously confirmed to the ERG that the full MM-010 dataset with a covariate to adjust for the second-line setting was the approach taken. This should be fully reflected in the ERG report. Given this, the use of strong critical language such as “this is a very surprising argument” and “would only make sense if the first approach had been taken” should be removed. Additionally as explained to the ERG the impact of treatment in the second-line setting is taken into account within the approach and therefore the statement that this was not accounted for is incorrect.
Justification for amendment	The ERG’s statement is factually incorrect. In response to the ERG request for clarifications (question B8), Celgene confirmed that the full MM-010 dataset was used with a covariate to adjust for the second-line setting. In the ERG questions, the two methods were listed in the opposite order to that shown in the ERG report. In response to the ERG questions, Celgene confirmed that the second approach had been used – which was the full dataset in response to the question posed. The ERG report does make a correct reference to Celgene’s response on page 32, and is therefore inconsistent with itself. Second-line treatment is included in the model as a binary variable (which is set to 0 when second-line treatment is to be considered and 1 when third or later lines of treatment are to be considered). Second-line treatment is therefore not excluded in the model in fact setting this variable to 0 includes only the predicted impact of second-line treatment (i.e. not later lines of therapy). It is disappointing that the ERG have failed to consider Celgene’s response to their clarification request with due diligence. This wrongly implies that Celgene have been inconsistent in their extrapolation methods. This could unfairly influence Committee decision.
ERG response	The ERG agree with Celgene. Unfortunately we have overlooked the fact that where it is mentioned *“Celgene clarified that the **second** approach had been taken. However, Celgene’s explanation for excluding the number of prior therapies as a covariate would only make sense if the **first** approach had been taken.”* **this should in fact read** *“Celgene clarified that the **first** approach had been taken. However, Celgene’s explanation for excluding the number of prior therapies as a covariate would only make sense if the **second** approach had been taken.”* However, once the amendment is in place, the ERG are confident in the appropriateness of their comment.

Issue 5 Poor Fit of Parametric Models to Overall Survival Data

Description of problem	The ERG report suggests that the parametric models used to characterise clinical outcomes provide poor fits to the MM-010 study data, and potentially overestimate OS (pages 104-6). In their summary of the issue, the ERG state that they present Figures 15 from the original submission. The ERG present figures showing ill-fitting parametric models alongside Kaplan-Meier plots for OS.
Description of proposed amendment	Firstly, the ERG actually presents Figure 28 from the original submission, rather than Figure 15 as stated. This should be corrected. Figure 15 within the original submission shows OS of the pooled MM-009 and MM-010 studies, stratified by number of prior therapies. Figure 28 in the original submission shows the K-M plot and parametric curve fit for the full ITT population. More importantly, the ERG's critique is based upon an invalid comparison of K-M plots and parametric curves. The K-M curve produced by the ERG is that of the entire ITT population within MM-010, whereas the parametric models are based on ITT survival *adjusted using a second-line treatment covariate*. The ERG based their critique upon comparing these items, which fundamentally show different outcomes.
Justification for amendment	The ERG have performed an invalid comparison, and therefore any assertion regarding how well the parametric models fit the data based upon this is fundamentally incorrect. Figure 28 in the original submission, described as Figure 15 in the ERG report, shows the K-M plot and fitted piecewise exponential model for the entire ITT population; these can be compared like-for-like and the curve visually provides a strong fit to the data. This was made clear in Celgene's response to clarifications requested by the ERG (response to question B8, sent on 12 December 2013). In response to the previous ERG requests, Celgene provided figures showing the K-M for second-line patients alongside the fitted exponential model, based upon the ITT population *adjusted using the second-line covariate*. This is in line with the methodology employed by Celgene, which was incorrectly described by the ERG (see Issue 3). MM-010 patients treated in the second-line setting provide a small sample size, contributing to a less 'smooth' K-M plot and slightly weaker visual fit to the data compared to the K-M plot and curve for the larger ITT population. The ERG's apparent failure to consider Celgene's response to their original request for clarifications on this matter is disappointing. Suggestions of incorrectly estimated survival should not have been made based upon an invalid comparison of the full ITT population with modelled survival which includes a second-line covariate. Any conclusions derived from this misunderstanding are

	therefore factually incorrect and flawed.
ERG response	The ERG make mention to Figure 15 in the ERG report and not in the manufacturer submission. In the ERG submission, Figure 15 presents Figure 28 in Celgene's submission and is sourced as such. We agree with Celgene that it is more appropriate to compare the extrapolated curves against the KM curves for second-line patients.

Issue 6 Poor Fit of Parametric Models to PFS and TTF Data

Description of problem	The ERG report suggests that the parametric models used to characterise clinical outcomes provide poor fits to the MM-010 study data, and potentially overestimate PFS and TTF (pages 92-5). In their summary of the issue, the ERG state that they present Figures 13 and 14 from the original submission. The ERG produces figures showing ill-fitting parametric models alongside Kaplan-Meier plots for PFS and TTF.
Description of proposed amendment	The ERG actually presents Figures 24 and 26 from the original submission, rather than Figures 13 and 14 as stated. This should be corrected. Figures 13 and 14 within the original submission show time to progression and PFS of the pooled MM-009 and MM-010 studies, stratified by number of prior therapies. Figures 24 and 26 in the original submission show K-M plots and parametric curves fit for the full ITT population. The problem that occurred with the ERG's critique of fitting parametric OS models is also apparent for PFS and TTF. The ERG's critique is again based upon an invalid comparison of K-M plots and parametric curves. The K-M curves produced by the ERG represent the entire ITT population within MM-010, whereas the parametric models are based on the ITT population *adjusted using a second-line treatment covariate*. The ERG based their critique upon comparing these items, which fundamentally show different outcomes.
Justification for amendment	The ERG have performed an invalid comparison, and therefore any assertion regarding how well the parametric models fit the data based upon this is fundamentally incorrect. Figures 24 and 26 in the original submission, described as Figures 13 and 14 in the ERG report, show the K-M plot and fitted log-logistic models for the entire ITT population; these can be compared like-for-like, and the curves visually provides a good fit to the data. Celgene's use of parametric models based upon the ITT population *adjusted using the second-line covariate* is in line with the

	methodology employed, which was incorrectly described by the ERG (see Issue 3) of the present response. Suggestions of incorrectly estimated PFS and TTF should not have been made based upon invalid comparisons of the full ITT population and modelled estimates which include a second-line covariate. This inaccuracy appears to stem from Issue 3, whereby the ERG failed to note that Celgene used the full MM-010 dataset with a second-line covariate, as clarified at the ERG's request. Any conclusions derived from this misunderstanding are therefore factually incorrect and flawed.
ERG response	The ERG make mention to Figure 13 and Figure 14 in the ERG report and not in the manufacturer submission. In the ERG submission, Figure 13 and Figure 14 present Figure 25 and Figure 26 in Celgene's submission, respectively, and are sourced as such. We agree with Celgene that it is more appropriate to compare the extrapolated curves against the KM curves for second-line patients.

Issue 7 Inconsistency in Recommendations Regarding Model Structure

Description of problem	On pages 82 and 83 of their report, the ERG provide an alternative model structure which they argue would have been more accurate than the model developed by Celgene, by incorporating progression at third-line. On page 88 of their report, the ERG question the value of including treatment lines beyond second-line therapy in the cost-effectiveness analysis. These issues are raised again on page 124 of the ERG report, where it is first argued that a "post-relapsed" PFS state should have been incorporated, and then questions the value of modelling the costs of third and fourth-line therapies.
Description of proposed amendment	The ERG report should be more consistent. Currently these two arguments are in opposition; it is unclear whether modelling subsequent therapies in increased detail or not at all would have been preferable.
Justification for amendment	The ERG report is inconsistent in terms of what model structure it suggests Celgene should have adopted. On page 83 of their report, the ERG provide a potential model structure including a "post-relapsed" PFS state, which would require the incorporation of PFS on third-line therapy. On page 82 the ERG state that this alternative structure "to be more accurate" and that it "could be adopted in both arms of the economic model". • In their MTA in 2010, undertaken as part of TA228, the Southampton Health Technology Assessments Centre (SHTAC) developed a model which did not incorporate PFS "post-relapse", but did include the cost of subsequent therapies. However, on page 88 of their report, the ERG questions the value of including treatment lines beyond second-line, since "only cost

	data is available" and "the basket of drugs considered might not accurately reflect current clinical practice." • Modelling the cost of subsequent therapy lines is not a novel modelling approach. It was undertaken by SHTAC in their MTA as part of TA228. It takes into account costs which may be directly influenced by an intervention and are therefore relevant to the decision problem. • The ERG's assertion that the basket of drugs might not accurately reflect current practice is correct in so far as *any* basket of drugs at *any* line of treatment might not be a perfectly accurate reflection of clinical practice. However Celgene consulted a UK real-world data source to inform this, to ensure the treatment basket modelled is founded by evidence and likely to be valid. • The ERG have failed to take account of the fact that the historical treatments forming BSC third-line (when lenalidomide is not used) were allowed within the MM-010 trial and their effect is therefore already included in the OS curves presented. • Additionally, the ERG concede that their alternative model structure would require additional effectiveness data to understand how PFS and TTF occur for patients on "real-world" treatment baskets. • Finally scenario analysis is provided around the proportion of patients receiving the cost and effect of third-line lenalidomide (which includes adjustment for the additional efficacy of lenalidomide at third-line) on page 191, the ERG fail to acknowledge this additional analysis and also fail to acknowledge the fact that the costs and efficacy of treatments other than lenalidomide at third-line are highly unlikely to impact the ICER. The cost of other therapies as presented on page 81 is only £204 on the lenalidomide arm and as the efficacy of these other therapies is already included in the survival curves from MM010 as patients were allowed to receive best supportive care after lenalidomide in MM010, the same applies to the Taverna study for bortezomib retreatment. It is unclear whether the ERG would have been more favourable towards a model with subsequent therapy lines included or excluded.
ERG response	No issue of factual accuracy identified. The ERG suggest an alternative model structure for the model presented by Celgene (i.e. for the model including third and fourth-line treatment options). The ERG also acknowledges that this alternative structure would require additional data to be inputted into the model. Separately, the ERG question (and therefore suggest that the Committee consider) the value of including third and fourth-line treatment options given data used in the model.

Issue 8 Parametric Curves Crossing Over

Description of problem	The ERG criticise the fact that the parametric PFS and TTF curves cross with the OS curve in the cost-effectiveness analysis.
Description of proposed amendment	The removal of the following phrase from “and a not acceptable one” from the following statement page 107 of the ERG report: • “However this is still an implausible scenario **and a not acceptable one**, for the reasons explained before.”

Justification for amendment	To state that this is not acceptable is very strong negative language, serving to invalidate the cost-effectiveness model. This is exaggerating the impact of curves crossing for the following reasons:
	• Crossover occurs very late in the model, as noted in the ERG report, where the curve is purely based upon extrapolation given there are no follow-up data at this stage.
	• At the point of crossover the curves are very similar.
	• Given the similarity of the curves, the pragmatic and logical amendment of using the OS curve is not fundamentally detrimental to model outcomes.
	  o Setting the time horizon to 924 weeks (17.7 years), just prior to any form of crossover, produces a dominant ICER with the log-logistic curve used to characterise OS.
	  o Similarly, setting the time horizon to 404 weeks (7.7 years) with piecewise exponential OS still produces a dominant ICER.

ERG response	We agree with Celgene that this might be seen as negative language. We will remove “ and a not acceptable one” from the sentence aforementioned.

Issue 9 Inconsistency in Excel Model Patient Flow Sheets

Description of problem	On page 81 the following statement is made: • “Celgene claim to have made the excel flow sheets consistent across intervention and comparator arms of the model. However, to the best of the ERG knowledge, no changes in the model structure were taken.”
Description of proposed amendment	The points about the Excel flow sheets being made consistent, and there being no changes to the model structure, should be fully separated.

Justification for amendment	Celgene did make amendments to the patient flow sheets of the Excel model, as noted in response the ERG's request for clarifications (page 5 of Celgene's response to the final ERG clarification request). The intervention flow sheet layout was made consistent with the comparator sheet, which requires an additional level of complexity since patients are able to receive lenalidomide as a third-line therapy. Since patients on the intervention arm do not receive lenalidomide as a third-line treatment, some of the columns in its structure became redundant and were been left blank for the intervention arm. The statement in the ERG report could be misconstrued, in that the model structure and consistency in the model worksheets may be viewed as the same issue. These were two different issues raised by the ERG; consistency in patient flow sheets is a technical one, while critique of the model structure is a conceptual discussion. Additionally, related to inconsistencies in the patient flow sheets, it would have been helpful for details of corrections the ERG claim to have made to the model in their report. These were not provide and Celgene were therefore unable to assess the validity of such amendments.
ERG response	Agreed. It can be made clearer that the consistency in the excel flow sheets and the model structure are two different issues.

Issue 10 Treatment Pathway Diagram

Description of problem	The ERG present a flow diagram showing the current care pathway on page 52 of their report (Figure 11). Table 33 and Table 39 present third-line treatment 'baskets' as applied in the cost-effectiveness analysis. The ERG note that these tables do not match Figure 11.
Description of proposed amendment	• Etoposide use at third-line following Len/Dex should be 31%. • "Cisp/Dox/Etop" use at third-line following bortezomib should be 31%.
Justification for amendment	Celgene would like to take this opportunity to address these inaccuracies. • Etoposide use at third-line following Len/Dex should be 31%, which is consistent with Tables 33 and 39. • "Cisp/Dox/Etop" use at third-line following bortezomib should be 31%, which is the sum of cisplatin, doxorubicin and etoposide use and is consistent with Tables 33 and 39.

Issue 11 Questioning the Selection of Relevant Comparators

Description of problem	On page 12 the following statement is made: • "Though Celgene justify their selection of comparator treatments it is unclear if this reflects clinical practice, particularly given its rapidly evolving nature in relation to new combination regimens." On page 15 the following statement is made: • "Thalidomide could potentially be a relevant comparator for second or third-line treatment options."
Description of proposed amendment	These statement should be removed from the ERG report.
Justification for amendment	Comparator treatments were established in the final scope, which was the result of extensive consultation with various sources including myeloma experts and patients. It is outside the remit of the ERG to call into question the final scope. Further, it is not relevant to decision problem for the ERG to comment on "new combination therapies", which is ambiguous and may refer to treatments which do not currently form any part of clinical practice. The ERG go on to specify the exclusion of thalidomide as a comparator. Thalidomide was not included in the final scope and as such the ERG's statement is irrelevant to this submission.
ERG response	No issue of factual accuracy identified.

Issue 12 Clinical Effectiveness Searches

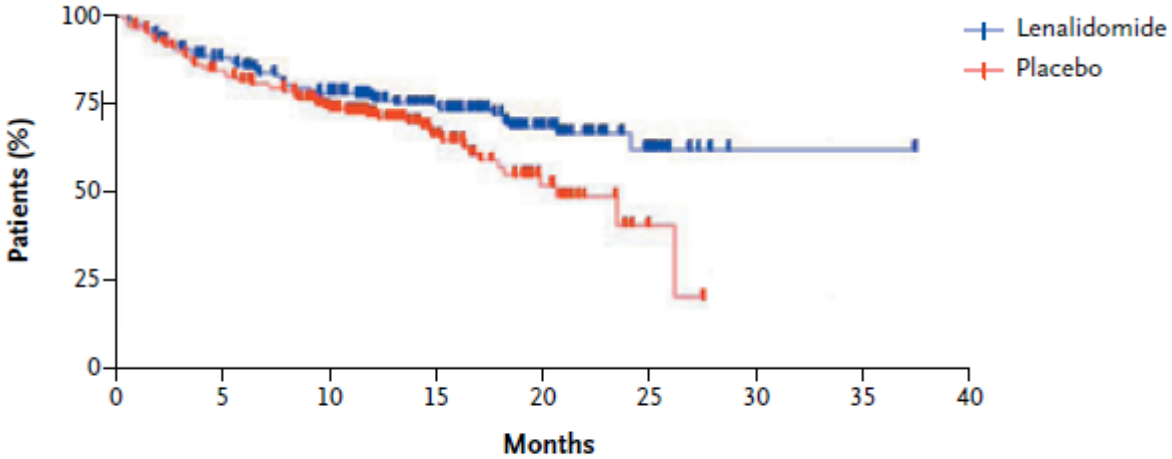
Description of problem	The ERG state that important information regarding the second clinical effectiveness search was not provided, which was performed having removed restrictive terms (relapse/recurrence) from the initial search. The following statements is made on page 16 of the ERG report that: • "Celgene have not indicated if their second searches located any additional studies for consideration which the ERG consider to be crucial information."
Description of proposed amendment	This statement should be removed from the ERG report.

Justification for amendment	Celgene performed a second search in response to the ERG's request for clarifications. Clarification B1 requested the following: B1. **Priority question**: The search strategy limits searches by themes such as 'relapse' and 'recurrence' (page 216, lines 6-12 of the MEDLINE strategy), which could affect the retrieval of potentially relevant studies (e.g. Bendamustine studies). Therefore: • Please provide the rationale for this decision. • Please re-run the effectiveness searches removing this cluster and list any additional studies not previously identified. In response to this request dated 12 December 2013, Celgene provided a spreadsheet containing second search results (with the relapse/recurrence term removed). This was also provided within the original submission for the first search. While it is correct that Celgene did not explicitly list any additional studies not previously identified, to state that this information was not provided is factually incorrect. Provision of the results spreadsheet for the second search would have allowed the ERG to compare the original and second set of search results.
ERG response	No issue of factual accuracy identified. Celgene have not explicitly indicated if their second searches located any additional studies for consideration.

Issue 13 Submission Failing to Present Time to Treatment Failure

Description of problem	On page 47 on their report, the ERG are critical of TTF not being presented in the clinical effectiveness summary of the submission. The following statement is made; • "TTF was reported in both CSRs for the ITT population up to study unblinding and given its relevance to the economic analysis, should have been included in the clinical evidence synthesis reported by Celgene."
Description of proposed amendment	This statement should be removed from the ERG report.
Justification for amendment	Time to treatment failure was not requested in the final scope. This is presented in the economic section of the submission, where the outcome is used to inform the cost-effectiveness analysis.
ERG response	No issue of factual accuracy identified. Even though TTF was not requested in the scope it is a key input of the economic model.

Issue 14 Failing to Present Numbers at Risk for Overall Survival

Description of problem	On page 39 on their report, the ERG state; • "It can be noted that **Error! Reference source not found.** does not provide the number of patients at risk throughout time. We requested clarification from the manufacturer regarding the number of patients at risks in MM-010, however the manufacturer failed to provide these data."
Description of proposed amendment	No amendment required, however, information provided for future clarity.
Justification for amendment	It is acknowledged that the wrong figure was sent in response to the initial ERG questions. Please find the correct figure below which is taken from Dimopolous 2007:  **No. at Risk** Lenalidomide 176 142 116 82 44 14 2 2 Placebo 175 140 104 50 20 3 1 1