NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy with bortezomib (partial review of TA171)

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

The following documents were considered by the Committee at a meeting on 23 March 2017:

2. **Consultee and commentator comments on the November 2016 Appraisal Consultation Document** from:
   - Celgene
   - Myeloma UK
   - UK Myeloma Forum

     The Royal College of Physicians endorses the UKMF comments. The Department of Health indicated that they had no comments

The following documents were considered by the Committee at a meeting on 1 February 2018:

3. **Multiple myeloma - lenalidomide (post bortezomib) (part review TA171) [ID667]: Updated ICER calculations (November 2017)** from Celgene

4. **Evidence Review Group critique of November 2017 document** – prepared by the Peninsular Technology Assessment Group
   - Critique /addendum (22 Jan 2018)
   - Additional addendum (26 Jan 2018

After the February 2018 meeting the company replaced their complex Patient Access Scheme with a simple discount. The following documents were considered by the Committee:

5. **The steps to replace the lenalidomide complex patient access scheme (PAS) with a simple discount – March 2019** from Celgene

6. **Evidence Review Group critique of March 2019 document** – prepared by the Peninsular Technology Assessment Group

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Lenalidomide plus dexamethasone for multiple myeloma after 1 treatment with bortezomib

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Celgene	Celgene would like to thank the committee and the ERG for their perseverance during this long and complex appraisal. We acknowledge that the model is large and complex and recognise that we have not been able to identify any further useable sources for MP data despite a full systematic literature review and contacting a number of registries. We would also like to highlight the unmet need for lenalidomide in this small sub-group of patients who have received bortezomib at first line and are ineligible for both transplant and thalidomide containing regimens. As bortezomib re-treatment is no longer funded via the Cancer Drugs Fund (CDF) the only remaining option is cytotoxic chemotherapy (such as MP) for which evidence of effectiveness is extremely limited in a second-line setting.	Comments noted. The committee's considerations about unmet clinical need for this population has been described in section 3.3 of the final appraisal document.
Celgene	The benefits of lenalidomide Lenalidomide has been shown in MM-009[i]/ MM-010[ii] to be an effective treatment option when compared to dexamethasone with a median progression free survival (PFS) benefit of 6.5 months and a median overall survival (OS) benefit of 6.4 months even when 48% of patients in the dexamethasone arm received subsequent lenalidomide. We appreciate that on page 5 of the ACD the committee recognised that patients value oral treatments such as lenalidomide and would further highlight that (as stated on page 6 of the ACD) in the opinion of clinical and patient experts the preferred option for many patients who cannot receive thalidomide is lenalidomide.	Comments noted. The committee's considerations about the benefits of lenalidomide have been described in the final appraisal document in sections 3.4 to 3.6.

Consultee	Comment [sic]	Response
Celgene	1. <u>The paucity of the comparator evidence base available</u> Celgene acknowledge the limitations of the data underpinning the analyses vs. MP (see section 3 below) but would like to reiterate that we have done the best we could with the data available in the public domain. We have not been able to identify any further useable sources for MP data despite a full systematic literature review and contacting a number of registries. Celgene were able to access some data from the HMRN registry in northern England, however the patients in this dataset are considerably older that those in the trials and there is a lack of information recorded on most other important patient characteristics which would make adjusting for covariates impossible. As such, our belief remains that the only useable data on the actual effectiveness of MP comes from the Petrucci 1989[iii] study which when analysed produces ICERs which are approvable.	Comments noted. The committee's considerations about Petrucci 1989 are outlined in sections 3.9 to 3.12 of the final appraisal document.

Consultee	Comment [sic]	Response
Celgene	<u>The possible scenarios for decision making</u> As highlighted by the committee in the ACD, there are 2 main sources which can be considered for decision making when comparing to MP: the use of the dexamethasone arm of MM-009[1]/MM-010[2] as a proxy for MP, and the Petrucci 1989[3] dataset. Both options have benefits and weakness and we appreciate that neither is free from uncertainty.	Comments noted. The sample size and power of Facon et al to detect a difference between dexamethasone and melphalan is discussed in section 3.15 of the final appraisal document.
	The committee mention the reasons why they prefer the analyses using the dexamethasone arm as a proxy on page 13 of the ACD and we agree that there are definite benefits to this approach (as highlighted in our response the request for additional analysis). However, as the committee highlight on page 14 of the ACD, the Facon 2006[4] paper which Celgene used to provide evidence of equivalence was underpowered and we cannot be certain that MP and dexamethasone would have equal outcomes.	Comments noted.
	We also cannot be sure that the 48% of patients who receive subsequent lenalidomide are reflective of clinical practise in the UK as clinical experts have told Celgene that their belief is that all eligible patients would receive lenalidomide at 3rd line if they not had it in an earlier line as lenalidomide is standard of care at 3rd line.	
	Celgene agree that the Petrucci 1989[3] data is uncertain due to the issues highlighted by the committee and ERG in the ACD. One of the concerns of the committee and the ERG was the use of medians to produce a 'crude HR' as technically these should only be applied when using an exponential distribution for the extrapolation of curves. Celgene would like to highlight that we have provided an analysis based on the Petrucci 1989[3] dataset which uses digitised KM curves and the Guyot 2012[4] algorithm to generate simulated individual patient level data to which survival curves could be fitted (provided in Celgene PAS template, February 2016). This analysis produced a very similar ICER to that from using the crude HR from medians of £23,618 which would be within the approvable range.	Comments noted. This information (about Petrucci et al, and Guyot et al) was presented to the committee and had been considered in previous meetings. Section 3.9 of the final appraisal document lists concerns with the evidence from Petrucci et al, and the crude indirect comparison which led to the committee conclusion that the crude indirect comparison was not suitable for decision making.
	All of the ICERs generated from analyses utilising this actual MP data have fallen within generally acceptable ranges.	
	A further concern of the ERG was that the adjustments for subsequent lenalidomide in the MP arm of the model lack face validity. However, when looking at the comparison to MP, the results are intuitive when examining the addition of subsequent lenalidomide. The addition of lenalidomide as a subsequent therapy adds [redacted] life years (LYs) to the MP arm of the model (post-progression LYs without subsequent lenalidomide = [redacted] and post-progression LYs with subsequent lenalidomide = [redacted]).	Comment noted. Section 3.11 states "the company agreed that the model produced illogical results, but only when using bortezomib as a comparator and said that this was not the case for the comparison with melphalan".

Consultee	Comment [sic]	Response
Celgene	Summary and conclusions Celgene would like to thank the committee and the ERG for their perseverance during this long and complex appraisal. We acknowledge that the model is large and complex and has gone through many iterations with some errors being identified as a result of work by both company and ERG (in part caused by complexity of the model or as a knock-on from Celgene errors). The ICER range is between [redacted] and [redacted] and is dependent on the evidence base used for decision making. We believe that the Petrucci 1989[3] data whilst subject to limitations should not be discounted fully as it is the only actual source of MP data available. Celgene would re-iterate that the use of the Guyot algorithm[5] which overcomes the limitations of the 'crude HR' calculated from medians also produced an approvable ICER of [redacted]. Finally we would like to highlight the unmet need at this crucial stage of treatment where this sub-group of patients will have no option but cytotoxic chemotherapy (such as MP) which will not be suitable for all. References 1)Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. The New England Journal of Medicine. 2007; 357(21):2133-42. 2) Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. The New England Journal of Medicine. 2007; 357(21):2123-32. 3)Petrucci T, Avvisati G, Tribalto M, et al. Intermediate-dose (25 mg/m2) intravenous melphalan for patients with multiple myeloma in relapse or refractory to standard treatment. Eur J Haematol 1989;42:233-237 4)Facon T, Mary J-Y, Pegourie B, et al. Dexamethasone-based regimens versus melphalan-prednisone for elderly multiple myeloma patients ineligible for high-dose therapy. BLOOD, 2006; 107(4): 1292-1298 5)Guyot P, Ades AE, Ouwens JNM, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Medical Research Methodology 2012, 12:9	Thank you for your comment. Since these comments were received the company provided a revised patient access scheme for lenalidomide. It is now recommended for multiple myeloma after 1 treatment with bortezomib. References noted

Consultee	Comment [sic]	Response
UK Myeloma Forum	On behalf of the UK Myeloma Forum we urge the appraisal committee to reconsider the ACD decision. This decision is flawed as a result of inappropriate comparators and will have a direct detrimental effect on myeloma patients for whom 2nd line bortezomib is unsuitable in terms of both morbidity and mortality risk.	Thank you for your comments. Please see responses to each point below. (Please note: since these comments were received the company provided a revised patient access scheme for lenalidomide. It is now recommended for multiple myeloma after 1 treatment with bortezomib.)

Myeloma Forum UK	1. Has all the relevant evidence been taken into account? a. Whilst within the context of the perverse choice of comparators for the appraisal the "evidence" has been taken into account this in no way represents what any myeloma clinician would consider an appropriate choice of 2nd line therapy. Furthermore there is absolutely no evidence in the modern era to suggest that conventional chemotherapy is a suitable 2nd line treatment. The decision to use only cytotoxic chemotherapy as a comparator for 2nd line therapy is entirely unrealistic in the context of modern myeloma therapy. b. A significant proportion of patients will receive 1st line bortezomib based therapy either via TA311 if transplant eligible at the time of 1st line therapy, or via TA228 if transplant ineligible and thalidomide contraindicated. c. At the time of 2nd line therapy a large proportion of those who had TA311 + transplant would no longer be considered eligible to have a 2nd transplant due to either co-morbidities or suboptimal duration of response following first transplant (a 2nd autograft at relapse is only commissioned if there has been at least an 18 month response duration following 1st transplant). There has been a chaotically applied communication approach from NHSE which has resulted in some centres not treating 2nd line patients with bortezomib as per TA129. The alluded to change in commissioning for bortezomib retreatment communicated from NHSE appears a direct contradiction of NICE TA129. d. Bortezomib retreatment is only suitable for patients who had at least a Partial Response (>50% paraprotein reduction), response duration of at least 6 months and did not suffer excess toxicity (in particular peripheral neuropathy)with first bortezomib treatment. The evidence to support bortezomib retreatment is limited (Petrucci et al. Brit J Haem 2013) and at best suggests approximately 40 - 50% of patients will have at least the partial response with Duration of response of 6.5 months (in responders) required. e. Regardless of access to bortezomib a large number of patients would not be suitable to receive 2nd line bortezomib due to poor depth or duration of response to 1st line bortezomib or because of prior bortezomib associated toxicity. This patient group currently have no suitable 2nd line therapy that has any evidence base to support it as a direct result of the inflexible approach taken by NICE	Comment noted. The lack of evidence for cytotoxic chemotherapy being an effective treatment is described in section 3.4 of the final appraisal document. However, committee heard from clinical experts at the meeting in the absence of lenalidomide cytotoxic chemotherapy was used in clinical practice. It therefore met the criteria to be considered a comparator for the purpose of this technology appraisal. Comment noted. The population in the scope for this technology appraisal are people for whom transplant is not suitable and who have had one prior treatment with bortezomib. Comment noted. People who are eligible for transplant and who have had bortezomib are outside the population considered in this appraisal. TA129 (recommendations for bortezomib taken second line) was published before the technology appraisals recommending bortezomib first line (TA228 + TA311) and bortezomib retreatment after relapse on first line bortezomib was not specifically considered in TA129. Comment noted. Bortezomib retreatment was not considered a comparator because it is not commissioned by NHS England or on the Cancer Drugs Fund and as such is not available in the NHS for this indication (section 3.2 of the final appraisal document). Comment noted. The unmet clinical need for this population is discussed in section 3.3 of the final appraisal document. This appraisal has been conducted within the remit and appraisal objective set out in the final NICE scope. It has also followed

Consultee	Comment [sic]	Response
	during the appraisal process and the lack of leadership and consistency taken by NHSE (e.g. Geographically close London hospitals currently having different access to bortezomib). f. The enforced use of conventional chemotherapy as comparator for 2nd line is a result of no other options because of the conditions imposed on the appraisal process and in no way reflect either clinical practice in the UK or certainly outside of the UK. Therefore the question proposed in the appraisal process to the Pharma company is neitherclinically appropriate or. The evidence is quite clear that Len Dex when used as a 2nd line therapy is superior to when it is used as a 3rd line therapy (Stadtmauer et al. Eur J Haem 2009). There are no suggestions of cross resistance with bortezomib, hence to criticise the study for having few prior bortezomib treated patients is not relevant to the efficacy of lenalidomide. The only suitable comparator would be bortezomib retreatment but should have taken into account prior bortezomib toxicity as a contraindication for further bortezomib. g. It is clear from recently published Phase 3 trial data that have used lenalidomide / dexamethasone as the gold standard control arm for treating patients with 1-3 prior lines of treatment that, with careful management and dose modification, response rates and response durations are significantly better than those in the original MM009/MM010 clinical trials (ASPIRE trial Stewart et al. NEJM 2015; ELOQUENT-2 trial Lonial et al. NEJM 2015; TOURMALINE MM-1 trial Moreau et al. NEJM 2016; POLLUX trial Dimopoulos et al. NEJM 2016).	the process and methods as outlined in the process and methods guide for technology appraisals Comments noted. The unmet clinical need is considered in section 3.3 of the final appraisal document and patient and clinician preference for lenalidomide earlier in the treatment pathway is discussed in section 3.3. Comments noted. The clinical effectiveness evidence presented by the company for lenalidomide is discussed in section 3.4-3.6 of the final appraisal document.

Consultee	Comment [sic]	Response
UK Myeloma Forum	Myeloma therapy has evolved over the last 7 years since lenalidomide was initially approved as a 3rd line therapy. The UK treatment pathway has changed with many more patients receiving bortezomib 1st line and the rigid NICE treatment pathway should reflect these changes. Patient care and outcomes will suffer as a direct result of this negative ACD limiting the access to an active and well tolerated therapy and will retard the significant progress that has been made on overall survival with this disease in the UK in the last 10 years. The recommendations are not a sound basis to make the guidance and should be reconsidered. Lenalidomide should be available for 2nd line patients who have previously been treated with bortezomib and for whom further bortezomib is not suitable and we urge the committee to reconsider this very poor decision which is likely to have an adverse impact on patient outcomes.	Thank you for your comment. The committee considered the comments received in response to the appraisal consultation document and the company submitted a revised patient access scheme for lenalidomide (provided by the company after these comments were presented to committee). Therefore lenalidomide plus dexamethasone is now recommended for multiple myeloma after 1 treatment with bortezomib.
National Cancer Research Institute; Association Cancer Physicians; Royal College Physicians; Royal College Radiologists	We would like to endorse the response submitted by UK Myeloma Forum.	Comment noted.

Consultee	Comment [sic]	Response
Myeloma UK	Myeloma UK response to the NICE appraisal consultation document on Revlimid® (lenalidomide) for the treatment of myeloma in people who have received at least one prior therapy with Velcade® bortezomib (partial review of TA171) We welcome the opportunity to comment on the NICE appraisal consultation document (ACD) relating to Revlimid in combination with dexamethasone at first relapse. Whilst we understand the difficult role that NICE has in assessing new medicines, we are extremely disappointed that this ongoing and lengthy appraisal continues to result in a negative outcome and that this subgroup of patients are still unable to access Revlimid at first relapse on the NHS. In our earlier responses to the appraisal and to the past two ACDs, we have repeatedly outlined the clinical and patient case for access to Revlimid in this setting. Revlimid is a safe and effective treatment at all stages of myeloma and NICE has clearly accepted the patient benefit of accessing aneffective oral treatment. The ACD also acknowledges that there is a strong consensus amongst clinicians, patients and carers that this should be made available at first relapse. We are strong supporters of NICE and understand that NICE cannot approve drugs where the health economic case is uncertain. However, we are concerned that in this case health economic debate is getting in the way of the appropriate treatment and care of myeloma patients living in England and Wales. Our main concern is that there continues to be an unnecessary and illogical gap in the myeloma treatment pathway. For myeloma patients at first relapse, who cannot have thalidomide or Velcade, there is no available novel agent combination for them to receive. Clinicians are having to deal with this situation through prescribing treatment combinations which have limited effect on their myeloma. As a consequence, if we do not get a positive outcome in this appraisal, patients in this setting are likely to continue receiving a sub-optimal treatment combination at an extremely critical time in their disease pathway. This may advantage the evolution of the myeloma clone to the extent that they may not fully benefit from approved NICE guidance further down the treatment pathway. We therefore strongly advocate for an urgent and positive resolution to this appraisal.	Comments noted. Since these comments were received the company provided a revised patient access scheme for lenalidomide. Lenalidomide plus dexamethasone is now recommended for multiple myeloma after 1 treatment with bortezomib. Comments noted. These benefits have been described in section 3.3 of the final appraisal document. Comments noted. The unmet clinical need for patients in the absence of lenalidomide is described in section 3.3 of the final appraisal document. Comments noted. The unmet clinical need was considered by the committee in section 3.3 of the final appraisal document.

Comments received from clinical experts and patient experts

None

Comments received from commentators

None

Comments received from members of the public

None

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10 CELGENE EUROPE

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Dear Dr Goodall,

RE: **Multiple myeloma - lenalidomide (post bortezomib) (part review TA171) [ID667] Appraisal Consultation Document (ACD)**

Please see below Celgene's response to the ACD.

Celgene would like to thank the committee and the ERG for their perseverance during this long and complex appraisal. We acknowledge that the model is large and complex and recognise that we have not been able to identify any further useable sources for MP data despite a full systematic literature review and contacting a number of registries.

We would also like to highlight the unmet need for lenalidomide in this small sub-group of patients who have received bortezomib at first line and are ineligible for both transplant and thalidomide containing regimens. As bortezomib re-treatment is no longer funded via the Cancer Drugs Fund (CDF) the only remaining option is cytotoxic chemotherapy (such as MP) for which evidence of effectiveness is extremely limited in a second-line setting.

Yours Sincerely,

[redacted]

The benefits of lenalidomide

Lenalidomide has been shown in MM-009[1]/ MM-010[2] to be an effective treatment option when compared to dexamethasone with a median progression free survival (PFS) benefit of 6.5 months and a median overall survival (OS) benefit of 6.4 months even when 48% of patients in the dexamethasone arm received subsequent lenalidomide.

We appreciate that on page 5 of the ACD the committee recognised that patients value oral treatments such as lenalidomide and would further highlight that (as stated on page 6 of the ACD) in the opinion of clinical and patient experts the preferred option for many patients who cannot receive thalidomide is lenalidomide.

1. The paucity of the comparator evidence base available

Celgene acknowledge the limitations of the data underpinning the analyses vs. MP (see section 3 below) but would like to reiterate that we have done the best we could with the data available in the public domain. We have not been able to identify any further useable sources for MP data despite a full systematic literature review and contacting a number of registries.

Celgene were able to access some data from the HMRN registry in northern England, however the patients in this dataset are considerably older that those in the trials and there is a lack of information recorded on most other important patient characteristics which would make adjusting for covariates impossible. As such, our belief remains that the only useable data on the actual effectiveness of MP comes from the Petrucci 1989[3] study which when analysed produces ICERs which are approvable.

2. The possible scenarios for decision making

As highlighted by the committee in the ACD, there are 2 main sources which can be considered for decision making when comparing to MP: the use of the dexamethasone arm of MM-009[1]/MM-010[2] as a proxy for MP, and the Petrucci 1989[3] dataset. Both options have benefits and weakness and we appreciate that neither is free from uncertainty.

The committee mention the reasons why they prefer the analyses using the dexamethasone arm as a proxy on page 13 of the ACD and we agree that there are definite benefits to this approach (as highlighted in our response the request for additional analysis). However, as the committee highlight on page 14 of the ACD, the Facon 2006[4] paper which Celgene used to provide evidence of equivalence was underpowered and we cannot be certain that MP and dexamethasone would have equal outcomes.

We also cannot be sure that the 48% of patients who receive subsequent lenalidomide are reflective of clinical practise in the UK as clinical experts have told Celgene that their belief is that all eligible patients would receive lenalidomide at 3rd line if they not had it in an earlier line as lenalidomide is standard of care at 3rd line.

Celgene agree that the Petrucci 1989[3] data is uncertain due to the issues highlighted by the committee and ERG in the ACD. One of the concerns of the committee and the ERG was the use of medians to produce a 'crude HR' as technically these should only be applied when using an exponential distribution for the extrapolation of curves. Celgene would like to highlight that we have provided an analysis based on the Petrucci 1989[3] dataset which uses digitised KM curves and the Guyot 2012[5] algorithm to generate simulated individual patient level data to which survival curves could be fitted (provided in Celgene PAS template, February 2016). This analysis produced a very similar ICER to that from using the crude HR from medians of [redacted] which would be within the approvable range.

All of the ICERs generated from analyses utilising this actual MP data have fallen within generally acceptable ranges.

A further concern of the ERG was that the adjustments for subsequent lenalidomide in the MP arm of the model lack face validity. However, when looking at the comparison to MP, the results are intuitive when examining the addition of subsequent lenalidomide. The addition of lenalidomide as a subsequent therapy adds [redacted] life years (LYs) to the MP arm of the model (post-progression LYs without subsequent lenalidomide = [redacted] and post-progression LYs with subsequent lenalidomide = [redacted]).

Summary and conclusions

Celgene would like to thank the committee and the ERG for their perseverance during this long and complex appraisal. We acknowledge that the model is large and complex and has gone through many iterations with some errors being identified as a result of work by both company and ERG (in part caused by complexity of the model or as a knock-on from Celgene errors).

The ICER range is between [redacted] and [redacted] and is dependent on the evidence base used for decision making. We believe that the Petrucci 1989[3] data whilst subject to limitations should not be discounted fully as it is the only actual source of MP data available. Celgene would re-iterate that the use of the Guyot algorithm[4] which overcomes the limitations of the 'crude HR' calculated from medians also produced an approvable ICER of [redacted].

Finally we would like to highlight the unmet need at this crucial stage of treatment where this sub-group of patients will have no option but cytotoxic chemotherapy (such as MP) which will not be suitable for all.

References

[1] Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. The New England Journal of Medicine. 2007; 357(21):2133-42.

[2] Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. The New England Journal of Medicine. 2007; 357(21):2123-32.

[3] Petrucci T, Avvisati G, Tribalto M, et al. Intermediate-dose (25 mg/m2) intravenous melphalan for patients with multiple myeloma in relapse or refractory to standard treatment. Eur J Haematol 1989;42:233-237

[4] Facon T, Mary J-Y, Pegourie B, et al. Dexamethasone-based regimens versus melphalan-prednisone for elderly multiple myeloma patients ineligible for high-dose therapy. BLOOD, 2006; 107(4): 1292-1298

[5] Guyot P, Ades AE, Ouwens JNM, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Medical Research Methodology 2012, 12:9

Dr Melinda Goodall,
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National Institute for Health and Care Excellence
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Friday 2 December 2016

Dear Dr Goodall

Myeloma UK response to the NICE appraisal consultation document on Revlimid® (lenalidomide) for the treatment of myeloma in people who have received at least one prior therapy with Velcade® bortezomib (partial review of TA171)

We welcome the opportunity to comment on the NICE appraisal consultation document (ACD) relating to Revlimid in combination with dexamethasone at first relapse.

Whilst we understand the difficult role that NICE has in assessing new medicines, we are extremely disappointed that this ongoing and lengthy appraisal continues to result in a negative outcome and that this subgroup of patients are still unable to access Revlimid at first relapse on the NHS.

In our earlier responses to the appraisal and to the past two ACDs, we have repeatedly outlined the clinical and patient case for access to Revlimid in this setting. Revlimid is a safe and effective treatment at all stages of myeloma and NICE has clearly accepted the patient benefit of accessing an effective oral treatment. The ACD also acknowledges that there is a strong consensus amongst clinicians, patients and carers that this should be made available at first relapse.

We are strong supporters of NICE and understand that NICE cannot approve drugs where the health economic case is uncertain. However, we are concerned that in this case health economic debate is getting in the way of the appropriate treatment and care of myeloma patients living in England and Wales. Our main concern is that there continues to be an unnecessary and illogical gap in the myeloma treatment pathway. For myeloma patients at first relapse, who cannot have thalidomide or Velcade, there is no available novel agent combination for them to receive. Clinicians are having to deal with this situation through prescribing treatment combinations which have limited effect on their myeloma.

As a consequence, if we do not get a positive outcome in this appraisal, patients in this setting are likely to continue receiving a sub-optimal treatment combination at an extremely critical time in their disease pathway. This may advantage the evolution of the myeloma clone to the extent that they may not fully benefit from approved NICE guidance further down the treatment pathway. We therefore strongly advocate for an urgent and positive resolution to this appraisal.

If we can provide any further information or assistance in this case, please do not hesitate to contact us.

Yours sincerely

Eric Low
Chief Executive

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2nd December 2016

To the chair
Regarding NICE Part review TA171

On behalf of the UK Myeloma Forum we urge the appraisal committee to reconsider the ACD decision. This decision is flawed as a result of inappropriate comparators and will have a direct detrimental effect on myeloma patients for whom 2nd line bortezomib is unsuitable in terms of both morbidity and mortality risk.

1. Has all the relevant evidence been taken into account?
    a. Whilst within the context of the perverse choice of comparators for the appraisal the "evidence" has been taken into account this in no way represents what any myeloma clinician would consider an appropriate choice of 2nd line therapy. Furthermore there is absolutely no evidence in the modern era to suggest that conventional chemotherapy is a suitable 2nd line treatment. The decision to use only cytotoxic chemotherapy as a comparator for 2nd line therapy is entirely unrealistic in the context of modern myeloma therapy.
    b. A significant proportion of patients will receive 1st line bortezomib based therapy either via TA311 if transplant eligible at the time of 1st line therapy, or via TA228 if transplant ineligible and thalidomide contraindicated.
    c. At the time of 2nd line therapy a large proportion of those who had TA311 + transplant would no longer be considered eligible to have a 2nd transplant due to either co-morbidities or suboptimal duration of response following first transplant (a 2nd autograft at relapse is only commissioned if there has been at least an 18 month response duration following 1st transplant). There has been a chaotically applied communication approach from NHSE which has resulted in some centres not treating 2nd line patients with bortezomib as per TA129. The alluded to change in commissioning for bortezomib retreatment communicated from NHSE appears a direct contradiction of NICE TA129.
    d. Bortezomib retreatment is only suitable for patients who had at least a Partial Response (>50% paraprotein reduction), response duration of at

least 6 months and did not suffer excess toxicity (in particular peripheral neuropathy)with first bortezomib treatment. The evidence to support bortezomib retreatment is limited (Petrucci et al. Brit J Haem 2013) and at best suggests approximately 40 - 50% of patients will have at least the partial response with Duration of response of 6.5 months (in responders) required.

e. Regardless of access to bortezomib a large number of patients would not be suitable to receive 2nd line bortezomib due to poor depth or duration of response to 1st line bortezomib or because of prior bortezomib associated toxicity. This patient group currently have no suitable 2nd line therapy that has any evidence base to support it as a direct result of the inflexible approach taken by NICE during the appraisal process and the lack of leadership and consistency taken by NHSE (e.g. Geographically close London hospitals currently having different access to bortezomib).
f. The enforced use of conventional chemotherapy as comparator for 2nd line is a result of no other options because of the conditions imposed on the appraisal process and in no way reflect either clinical practice in the UK or certainly outside of the UK. Therefore the question proposed in the appraisal process to the Pharma company is neitherclinically appropriate or. The evidence is quite clear that Len Dex when used as a 2nd line therapy is superior to when it is used as a 3rd line therapy (Stadtmauer et al. Eur J Haem 2009). There are no suggestions of cross resistance with bortezomib, hence to criticise the study for having few prior bortezomib treated patients is not relevant to the efficacy of lenalidomide. The only suitable comparator would be bortezomib retreatment but should have taken into account prior bortezomib toxicity as a contraindication for further bortezomib.
g. It is clear from recently published Phase 3 trial data that have used lenalidomide / dexamethasone as the gold standard control arm for treating patients with 1-3 prior lines of treatment that, with careful management and dose modification, response rates and response durations are significantly better than those in the original MM009/MM010 clinical trials (ASPIRE trial Stewart et al. NEJM 2015; ELOQUENT-2 trial Lonial et al. NEJM 2015; TOURMALINE MM-1 trial Moreau et al. NEJM 2016; POLLUX trial Dimopoulos et al. NEJM 2016).

Myeloma therapy has evolved over the last 7 years since lenalidomide was initially approved as a 3rd line therapy. The UK treatment pathway has changed with many more patients receiving bortezomib 1st line and the rigid NICE treatment pathway should reflect these changes. Patient care and outcomes will suffer as a direct result of this negative ACD limiting the access to an active and well tolerated therapy and will retard the significant progress that has been made on overall survival with this disease in the UK in the last 10 years.

2. The recommendations are not a sound basis to make the guidance and should be reconsidered. Lenalidomide should be available for 2nd line patients who have previously been treated with bortezomib and for whom further bortezomib is not suitable and we urge the committee to reconsider this very poor decision which is likely to have an adverse impact on patient outcomes.

Thank you for the opportunity to respond to the ACD we hope that our comments are taken into consideration

Your sincerely

[redacted]

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RE. Multiple myeloma - lenalidomide (post bortezomib) (part review TA171) [ID667]: Updated ICER calculations

Dear Dr George,

Celgene would like to thank NICE for the opportunity to work together to try to make it possible for patients to receive lenalidomide at this point in the multiple myeloma pathway (2nd line patients who are ineligible for transplant, unsuitable for thalidomide and have received bortezomib at 1st line), where the unmet need for an effective treatment is high and the only currently available option is cytotoxic chemotherapy (such as MP) for which evidence of effectiveness is extremely limited in a second-line setting.

Celgene understand the committee's reticence to make decisions based upon the only available data for MP (Petrucci 1989) and their preference to use the dexamethasone arm of MM-009/010 as a proxy for the effectiveness of MP. As such, we have worked to reduce the cap level of our existing 26 cycle cap based upon the ICERs produced against the dexamethasone arm of MM-009/010. We have explored the impact of the additional savings that the NHS will benefit from outside of the scope of this appraisal from the change in PAS applying to all current NICE approved indications (this revised PAS is also being offered in the ongoing appraisal in newly diagnosed multiple myeloma (ID474)).

At a reduced PAS of a [redacted], the ICER when the savings the NHS would realise at 3rd line are included is [redacted]. This analysis shows that 2nd line lenalidomide for multiple myeloma patients ineligible for transplant, unsuitable for thalidomide and who have had bortezomib at first line can be considered a cost-effective treatment at the usual willingness to pay threshold (£20,000 – 30,000 per QALY).

Yours sincerely,

[redacted]

1. The unmet need at this point in the patient pathway

There is a clear unmet need for an effective and tolerable treatment option at this point in the treatment pathway. This unmet is described eloquently by the patient group Myeloma UK and the clinician group UK Myeloma Forum in their responses to the ACD.

Myeloma UK states that:

"*Our main concern is that there continues to be an unnecessary and illogical gap in the myeloma treatment pathway… if we do not get a positive outcome in this appraisal, patients in this setting are likely to continue receiving a sub-optimal treatment combination at an extremely critical time in their disease pathway. This may advantage the evolution of the myeloma clone to the extent that they may not fully benefit from approved NICE guidance further down the treatment pathway".*[1]

The recent NICE recommendation of carfilzomib plus dexamethasone (Cd) does not meet this unmet need as TA457 specifies that patients must be bortezomib naïve to receive Cd.

If bortezomib re-treatment became available again, this also would not solve the unmet need, as explained by UK Myeloma Forum:

"Regardless of access to bortezomib a large number of patients would not be suitable to receive 2nd line bortezomib due to poor depth or duration of response to 1st line bortezomib or because of prior bortezomib associated toxicity. This patient group currently have no suitable 2nd line therapy that has any evidence base to support it…".[1]

Additional evidence included in this submission

The 2nd line (patients who are ineligible for transplant, unsuitable for thalidomide and who have had bortezomib at first line) cost effectiveness and budget impact model was updated to estimate the effect of a proposed change in the patient access scheme (PAS) for lenalidomide.

Currently lenalidomide is given free of charge after 26 cycles for the 3rd line multiple myeloma (TA171) and MDS del(5q) (TA322) indications. Celgene propose to revise the PAS so that lenalidomide is given free of charge after [redacted] for these indications if the 2nd line multiple myeloma patient subgroup is recommended.

The assumptions around the patient population for budget impact analysis have also been updated as the treatment of multiple myeloma has evolved in the UK since the start of this appraisal in 2013.

2. Updated budget impact calculation (results presented in separate document)

An updated budget impact for the 2nd line treatment of multiple myeloma for patients ineligible for transplant, unsuitable for thalidomide and who have had bortezomib at first line has been calculated to both provide more up to date estimates of patient numbers likely to be eligible at 2nd line [redacted] account for the savings generated by this revised PAS.

An updated ICER was also calculated for the 2nd line treatment of multiple myeloma for patients ineligible for transplant, unsuitable for thalidomide and who have had bortezomib at first line, to account for the benefits at 3rd line generated from the revised PAS, for which the patient number calculations play a role (explained in detail below).

All changes made to the economic model are highlighted in green within the model to aid review. No other changes were made to the model or its formatting, calculations and code.

Budget Impact Calculation

Objective

An updated Budget Impact was calculated to estimate the savings generated by the proposed revised PAS and estimate the full budget impact of a decision to reimburse lenalidomide for the 2nd line treatment of multiple myeloma for patients ineligible for transplant, unsuitable for thalidomide and who have had bortezomib at first line. The budget impact includes, savings generated due to the revised PAS being applied to existing NICE guidance for 3rd line lenalidomide treatment (TA171) and use of lenalidomide in MDS del 5q (TA322) and the impact of lenalidomide being made available as a 2nd line myeloma treatment for patients ineligible for transplant, unsuitable for thalidomide and who have had bortezomib at first line.

Methods

The budget impact calculation on the 'BI' sheet of the model was updated with a new base case column F, this is shown beside the original model data in column G.

The following changes have been made:

The latest multiple myeloma incidence data used (4,399) is based on Cancer Incidence in England 2015.[2] This was updated as this data source is more accurate.

Annual growth in incidence is assumed to be zero, based on UK ONS data[2] which demonstrates that over the last 5 years there has been no trend in the observed incidence either upwards or downwards

The incident population of 2nd line multiple myeloma patients ineligible for transplant, unsuitable for thalidomide and who have had bortezomib at first line (683) eligible for lenalidomide is calculated using the data shown below in Table 1. This data has been updated using market research data and the latest data from the literature and is shown alongside the original values used in TA171.[3]

Table 1: 2nd Line Multiple Myeloma Incidence Calculation

	Base Case[4-6]	Original Values[3, 7]	Reason for change
Proportion of patients unsuitable for SCT	66.97%	86.4%	Latest data from BSBMT used. Treatment has evolved since 2013 with more patients receiving transplants
Proportion of patients unable to tolerate thalidomide (Thal)	38.0%	15.0%	Bortezomib market share from Q2 2017 used as a proxy for thalidomide intolerance (due to recommendation in TA228)
Proportion of patient reaching 2nd line treatment	61.0%	86.5%	A large real-world study including 753 UK patients was published in 2016. This provides more accurate data than the previous estimate

SCT; Stem Cell Transplant, BSBMT; The British Society of Blood and Marrow Transplantation

The total number of patients treated with lenalidomide at 3rd line (3,409) is calculated from actual full year sales data from 2016 combined with unique electronic prescription authorisation form (ePAF) IDs (excluding Scotland, Jersey and private sales).[8] These patient numbers are then used to estimate savings created by the reduced PAS in the 3rd line indication and a reduction in patient numbers treated with lenalidomide in this line if lenalidomide was recommended for 2nd line multiple myeloma patients ineligible for transplant, unsuitable for thalidomide and who have had bortezomib at first line.

The proportion of patients (78.4%) requiring 3rd line therapy having started at 2nd line is derived from existing calculations within the comparator patient flow sheet. This is used to estimate from actual patient numbers the number of patients (2,873) who would now be eligible for lenalidomide at 3rd line. This assumes that death happens equally across all health states post completion of 2nd line therapy.

[redacted]

Based upon these calculations the number of patients treated per indication can be found in Table 2. It also shows the distribution of patients in 2nd line and who are ineligible for transplant, unsuitable for thalidomide and who have had bortezomib at first line who are treated with lenalidomide + dexamethasone or melphalan + prednisone (MP) over 5 years and how this changes in line with the market share assumptions. The number of 3rd line patients treated with lenalidomide is assumed to decrease with time proportional to the number of lenalidomide patients treated at 2nd line (ineligible for transplant, unsuitable for thalidomide and who have had bortezomib at first line).

Table 2: Total number of patients treated per year and line of treatment

Year	2nd Line SCT & Thal Ineligible Incident Patients	2nd Line Patients treated with lenalidomide + dexamethasone	2nd Line Patients treated with MP	3rd Line lenalidomide (Less 2nd SCT & Thal Ineligible Patients modelled)	3rd Line Patients treated with lenalidomide
1	683	[redacted]	[redacted]	2,873	[redacted]
2	683	[redacted]	[redacted]	2,873	[redacted]
3	683	[redacted]	[redacted]	2,873	[redacted]
4	683	[redacted]	[redacted]	2,873	[redacted]
5	683	[redacted]	[redacted]	2,873	[redacted]

SCT; Stem Cell Transplant, MP; melphalan + prednisone

The patient numbers estimated to be treated with lenalidomide at 2nd line (ineligible for transplant, unsuitable for thalidomide and who have had bortezomib at first line) are higher than estimated previously as treatment has evolved since the appraisal began. As can be seen from Table 1, more new patients are receiving bortezomib for newly diagnosed multiple myeloma than were expected to be thalidomide contraindicated/intolerant in TA228 and treatment has shifted to more patients being transplanted.[7] The number of patients expected to receive 2nd line therapy has been slightly reduced based upon a real-world study rather than an extrapolation of trial data in TA228.

Celgene have also cross-referenced the expected lenalidomide treated patient numbers with the numbers of patients actually treated in this indication when lenalidomide was funded via the Cancer Drugs Fund (April 2014- March 2015).[9] During the time on CDF, 244 patients were treated with lenalidomide.

It can be seen from Table 2, that we have estimated [redacted] treated patients, increasing to [redacted] over 5 years. Thus, we believe these estimates are robust and could even be an over-estimate of uptake, as during CDF funding, the highest month for treatment gave 28 treated patients which extrapolated for 12 months would give an upper bound of 336 lenalidomide treated patients.

3. Updated cost-effectiveness calculation – Including revised PAS

Objective

The cost effectiveness calculation for 2nd line lenalidomide in multiple myeloma patients (ineligible for transplant, unsuitable for thalidomide and who have had bortezomib at first line) was also updated to reflect the proposed change in the PAS. The base case model was updated based upon committee's preferred analysis which assumes that MP has the same clinical effectiveness as dexamethasone (ACD November 2016).[10] Whilst there are some limitations to the base case model, the uncertainty lies in both directions as acknowledged in

the ACD (lack of inclusion or benefit from lenalidomide being an oral therapy vs lack of certainty around the comparative effectiveness of MP vs dexamethasone).

The ICER shown in Table 3 includes the savings generated in second line and the benefits of the PAS change to 3rd line lenalidomide treatment. NICE methods guide section 5.12.7 allows for inclusion of costs outside of indication

"If implementation of the technology could have substantial resource implications for other services, the effects on the submitted cost-effectiveness evidence for the technology should be explored".[11]

In TA428 the first instance of inclusion of benefits from change in the PAS for other indications within decision making was observed. The technology appraisal guidance (TAG) states:

"It [the committee] was also aware that there would be a wider benefit to the NHS because the simple discount agreed in the patient access scheme would apply across all indications".[12]

The methods used in TA428 are not clear from the information available, therefore, given that the majority of cost savings are expected to come from the 3rd line multiple myeloma indication the cost savings from the change to the PAS are included based upon existing calculations within the cost-effectiveness model and benefits from savings within the MDS del(5q) indication have not been included. The majority of the 3rd line population which results in these savings is not included in the original modelled population for the part review of TA171 (as this is limited to patients ineligible for transplant, unsuitable for thalidomide and who have had bortezomib at first line).

The economic model was updated to allow for the cost-effectiveness analysis to show an ICER inclusive of the savings generated to the wider NHS of the proposed PAS changes (Table 3).

Methods

The economic model was updated to explore the effects of a change in the PAS on the cost effectiveness of lenalidomide treatment in 2nd line multiple myeloma patients ineligible for transplant, unsuitable for thalidomide and who have had bortezomib at 1st line. The functionality already programmed into the model's patient flow sheets to calculate the current PAS at 3rd line was used, with functionality added to allow for the calculation of different, 3rd line lenalidomide treatment costs generated by two patient access schemes (in this instance the current scheme where lenalidomide is given free of charge after 26 cycles and the proposed scheme where lenalidomide is given free of charge after [redacted]).

The difference between the revised PAS and current PAS is then calculated. The savings associated with the change are added to the intervention arm in the model. The cost saving per patient within the model is calculated by subtracting the saving for those 3rd line lenalidomide patients captured in the MP arm (thalidomide intolerant, post-bortezomib) treated under the revised PAS from those 3rd line lenalidomide patients captured in the MP arm (thalidomide intolerant, post-bortezomib) treated under the current PAS.

[redacted]

The MP arm is not affected as we're comparing to current care today and the change in the PAS would not come into effect unless lenalidomide receives a positive recommendation in this appraisal.

No other changes were made to the model or its formatting, calculations and code.

Results

Table 3: Updated ICER to show proposed [redacted] PAS change

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
MP	[redacted]	[redacted]	[redacted]	-	-	-	-
lenalidomide + dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The resulting ICER (presented in Table 3 above) is [redacted] per QALY.

4. Conclusions

There is a clear unmet need for an effective and tolerable treatment option at this point in the treatment pathway. This unmet is described eloquently by the patient group: Myeloma UK and the clinician group: UK Myeloma Forum, in their responses to the ACD.[1]

Once the impact of the change in PAS on the wider NHS is included, this analysis shows that 2nd line lenalidomide for multiple myeloma patients ineligible for transplant, unsuitable for thalidomide and who have had bortezomib at first line can be considered a cost-effective treatment at the usual willingness to pay threshold (£20,000 – 30,000 per QALY).

5. Visual representation of the UK pathway and the expected change if lenalidomide is recommended at 2nd line.

Figure 1: Current treatment pathway

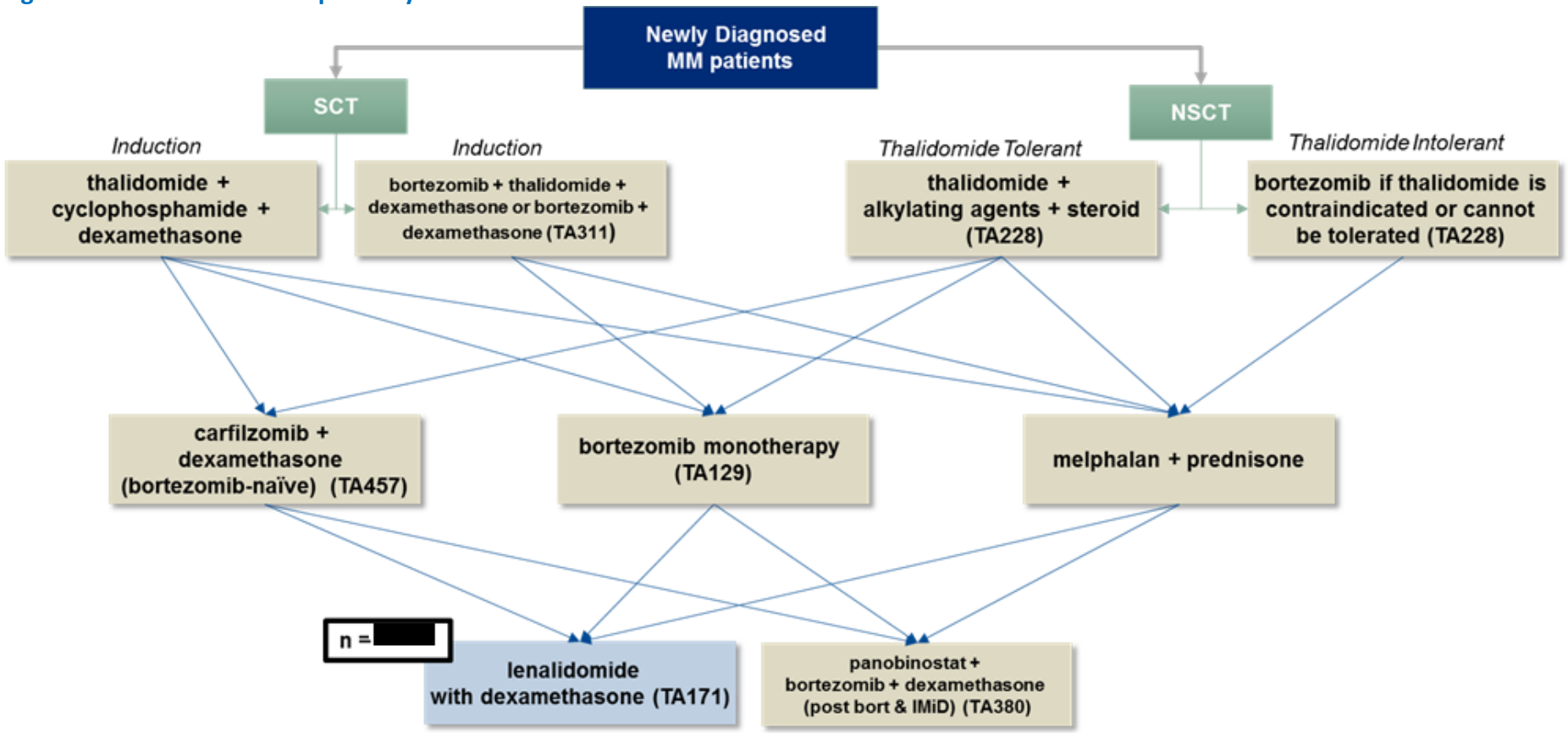
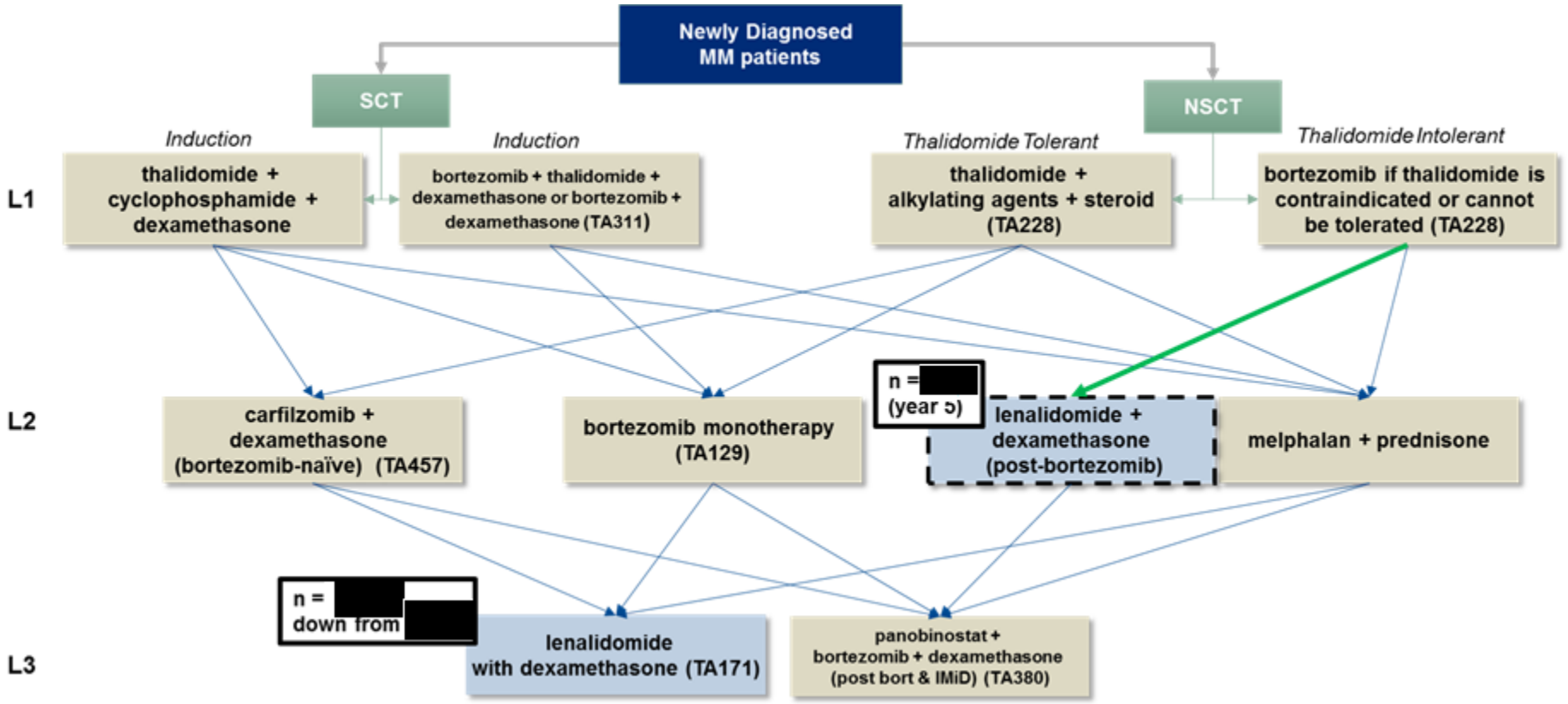


Figure 2: Proposed treatment pathway if lenalidomide is recommended at 2nd line



The green arrow shows where the patients who could receive lenalidomide at 2nd line would be coming from (SCT ineligible, thalidomide ineligible, treated with bortezomib).

The number of patients treated with lenalidomide at 3rd line will drop if lenalidomide is recommended at 2nd line.

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The clinical and cost-effectiveness of lenalidomide for people who have received at least one prior therapy with bortezomib (partial review of TA171)

A critique of the submission from Celgene

22nd January 2018 Addendum

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Date completed

22nd January 2018

Any 'commercial in confidence' data provided by companies, and specified as such, is [redacted].

1 Background

This addendum presents a response to comments that we, the ERG, received from Celgene in January 2018, as part of the NICE STA ID667 "Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy with bortezomib (partial review of TA171)".

In our latest Addendum, 4th October 2016, we presented our base case ICERs for:

- lenalidomide + dexamethasone (LEN+DEX) vs. melphalan (MP).
- lenalidomide + dexamethasone (LEN+DEX) vs. bortezomib retreatment.

Our base cases for LEN+DEX vs. MP allowed for:

- correcting for Celgene's error in modelling the acquisition cost of MP, and
- a shorter tail for the PFS curve for DEX.

Our base cases for LEN+DEX vs. bortezomib allowed for:

- reduction in the mean duration of bortezomib from 6.6 to 3.8 treatment cycles, and
- a shorter tail for the PFS curve for DEX.

For both comparisons, we also presented scenarios analyses in which we:

- adjusted OS for DEX for line of treatment.
- assumed equal mortality between treatment arms after progression.

1.1 PFS curve for DEX

In our October 2016 Addendum, we explained that by comparing our PFS fit and Celgene's to the 2008 data cut (Figure 1 and Figure 2), we considered our curve fit (Figure 2) to be more appropriate than that of Celgene (Figure 1). However, we also noted that the ICERs for LEN+DEX vs. MP and LEN+DEX vs. bortezomib, in the scenario assuming PFS and OS for MP and BOR equal to DEX, are rather insensitive to the choice of fit.

Figure 1. PFS DEX Celgene curve fit

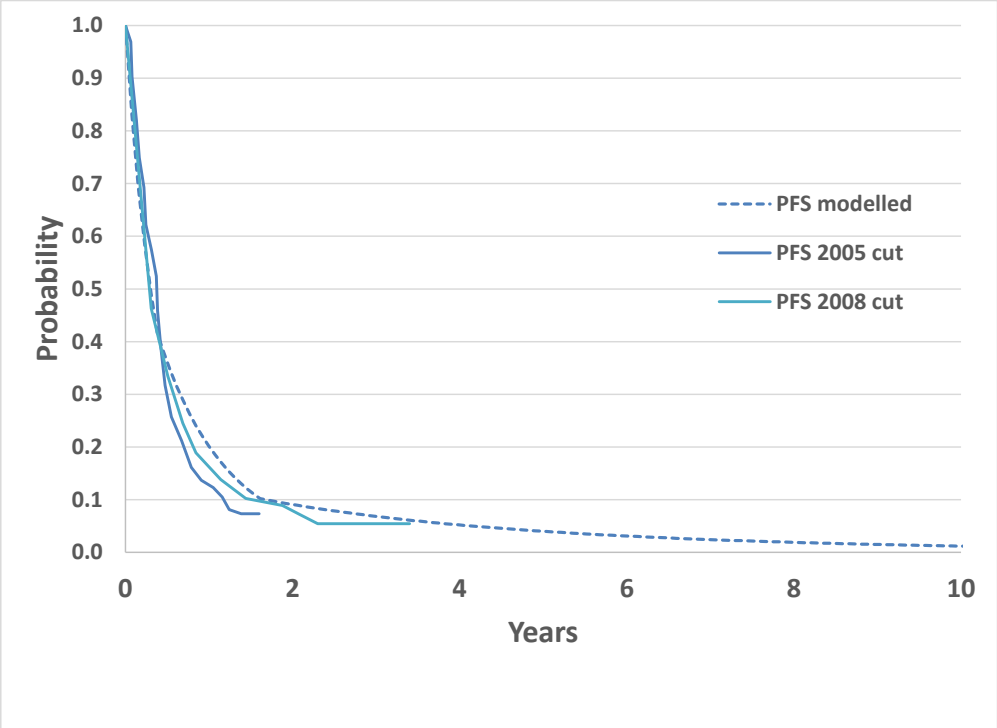
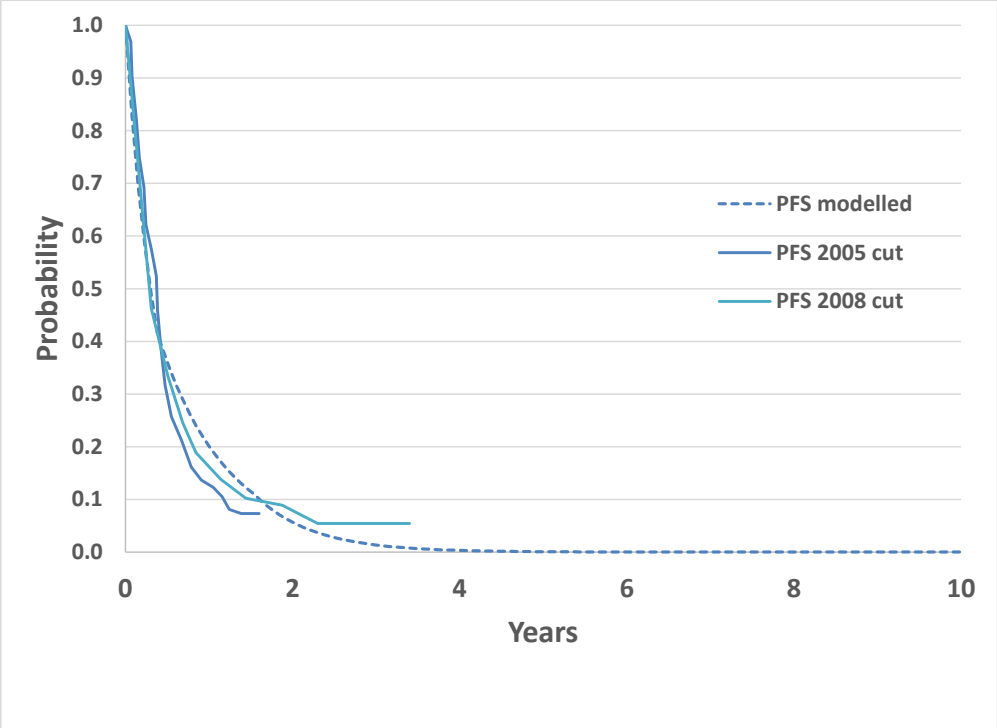


Figure 2. PFS DEX PenTAG curve fit



1.2 OS curve for DEX

In our October 2016 Addendum, we wrote the text in italics below.

This remains our opinion.

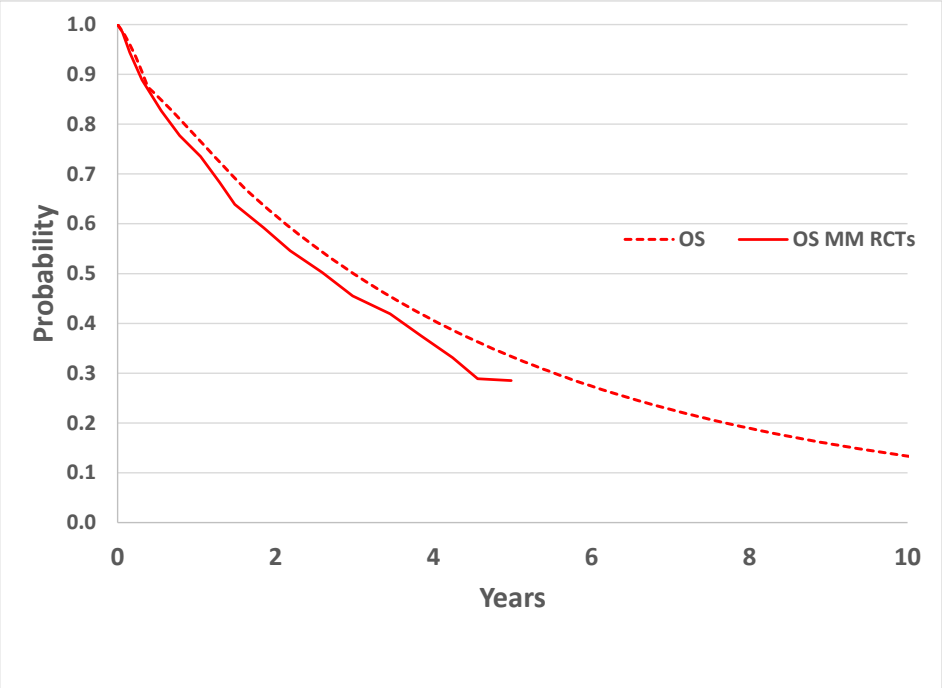
In our Addendum of 14th September 2016, we claimed that OS for DEX had not been implemented correctly in Celgene's model for the scenario in which OS for MP is set equal to that for DEX from the MM RCTs.

We also claimed that Celgene had used OS for DEX for 2nd and 3rd-lines combined from the MM RCTs, whereas we need to consider 2nd line data only. We therefore presented a scenario analysis in which we attempted to correct for this.

In response, Celgene now concede that when DEX is used as a comparator, they model OS for DEX incorrectly. However, they claim that in the scenario analysis in which OS for MP is set equal to that for DEX, there is no error, i.e. OS for MP is then correctly set equal to that for DEX. They also disagree with our assertion that they fit OS for DEX to 2nd- and 3rd-line data combined from the MM RCTs, claiming that they fit to 2nd-line data.

We are now prepared to accept all of Celgene's responses above, subject to the important caveat that we have no way to validate their modelled OS for 2nd-line DEX. We find that their modelled OS for 2nd-line DEX is slightly longer tailed than the Kaplan-Meier for 2nd and 3rd-line combined from the MM RCTs (Figure 3). However, we can only check their modelled OS for DEX if we have access to the Kaplan-Meier data for 2nd-line use from the MM RCTs (as we do for the LEN+DEX arm, see Fig. 4 our Addendum of 14th Sept 2016). Given this uncertainty, we retain our scenario analysis of estimating 2nd-line OS for DEX in Section 4.2.

Figure 3. OS DEX: Celgene fit for 2nd-line vs. MM RCT Kaplan-Meier data for 2nd and 3rd-lines combined



1.3 PenTAG base case 2016

In 2016, our results for LEN+DEX vs. MP, assuming PFS and OS for MP equal to DEX were as follows. This shows that our base case ICER for LEN+DEX vs. MP was >£[redacted] per QALY, where the ">" captures the fact that we expected MP to be at least as effective as DEX.

Table 1. PenTAG 2016 analysis: Impact on the ICER for LEN+DEX vs. MP of additional analyses undertaken by PenTAG assuming PFS and OS for MP equal to DEX

Scenario	ICER (£/QALY) LEN+DEX vs. MP
Celgene current analysis	[redacted]
1: Error MP acquisition cost	[redacted]
2: DEX PFS tail shortened	[redacted]
1 & 2	[redacted]
3: DEX OS longer tailed PenTAG adjustment for line of treatment	[redacted]
1 & 2 & 3	[redacted]
4: Equal mortality between treatment arms after progression	[redacted]
1 & 4	[redacted]
1 & 2 & 4	[redacted]

Key: DEX, dexamethasone; LEN, lenalidomide; MP, melphalan plus prednisolone.

1.4 ACD after fourth NICE committee meeting on 5th October 2016

We, the ERG, attended the fourth NICE committee meeting on 5th October 2016. NICE released an ACD, dated November 2016, after this meeting. Importantly, the ACD reports that the committee:

- no longer considered bortezomib re-treatment a comparator, so that melphalan is the only comparator (Section 4.3).
- assumed that the clinical effectiveness of melphalan is at least as great as for dexamethasone (Section 4.14 & 4.15).
- found it difficult to identify a preferred extrapolation curve for PFS for DEX because it did not have access to the Kaplan–Meier curves from the trial that showed the number of patients at risk. Without this information, its best estimate was that the true curve was likely to be somewhere between the company's and ERG's approaches (Section 4.17).
- concluded that lenalidomide did not meet the criteria to be considered for use within the Cancer Drugs Fund (Section 4.23).
- The End of Life criterion for life expectancy for MP was not met, and so LEN+DEX did not meet the End of Life criteria (Section 4.25).

Under these assumptions, the committee concluded that the most plausible ICER lay above either £[redacted] or £[redacted] per QALY gained because melphalan was likely to be more effective than dexamethasone (FAD Section 4.20). The £[redacted] per QALY corresponded to our correction in the cost of MP acquisition only, and the £[redacted] per QALY corresponded to this correction and use of the shorter tail for PFS for DEX.

The ACD makes no mention of our scenario analysis in which we adjusted OS for DEX for line of treatment. Therefore, henceforth, we consider this no further.

1.5 Fifth NICE committee meeting, March 2017

We did not attend the fifth NICE committee meeting in March 2017. But we understand the committee had no substantive changes of opinion compared to the fourth meeting.

2 Celgene recent changes to economic model

Since the fifth appraisal committee meeting in March 2017, Celgene have made two changes to their economic model, both of which act to reduce the ICER of LEN+DEX vs. MP substantially.

First, they have changed the PAS for LEN.

Second, in their calculation of the ICER for LEN+DEX vs. MP, they have included a very unusual methodology, in which they take credit for cost savings for patients taking ***3rd-line*** LEN given that the revised PAS will also affect the cost of treatment for these patients. The methodology is highly unusual in that Celgene are claiming cost savings for treatment of a group of patients (3rd-line) that are different to those that are the subject of the current HTA (2nd-line).

2.1 Changes to Lenalidomide PAS

Celgene have changed the PAS cap from 26 to [redacted] cycles of lenalidomide, so that now lenalidomide is given free of charge after [redacted] cycles. Previously, it was given free after 26 cycles.

2.2 Offsetting costs for 3rd line patients

Celgene claim that their novel methodology is allowable, citing the 2013 NICE Methods guide section 5.12.7:

"*If implementation of the technology could have substantial resource implications for other services, the effects on the submitted cost-effectiveness evidence for the technology should be explored*".

Celgene say that lenalidomide is also used to treat patients with MDS del(5q). However, they have not considered cost savings from the revised PAS for such patients.

The estimate of the cost offset is made with a series of detailed calculations, as follows.

Celgene are now effectively making the following comparison. First consider if LEN is not recommended in the current appraisal:

- **Patients in current appraisal**, adults with multiple myeloma for whom thalidomide is contraindicated and whose disease has progressed after ≥1 prior treatment with bortezomib:
    - 2nd-line MP, 3rd-line LEN+DEX with existing 26-cycle cap, and
- **Patient from TA171 >=3rd-line treatment of multiple myeloma minus patients in current appraisal**:
    - 3rd-line LEN with existing 26-cycle cap.

Versus suppose LEN is recommended in the current appraisal:

- **Patients in current appraisal**:
    - 2nd-line LEN with new 20-cycle cap,
- **Patient from TA171 >=3rd-line treatment of multiple myeloma minus patients in current appraisal**:
    - 3rd-line LEN with new 20-cycle cap.

Define:

N_2: Number of patients in the 2nd-line TA171 population.

N_3: Number of patients in the 3rd-line TA171 population.

n_2: Number of patients in the 2nd-line population for the current HTA

n_3: Number of patients in the 3rd-line population for the current HTA

c_3(old PAS): Per patient cost of a course of LEN treatment when taken 3rd-line, assuming the old PAS for LEN (26 cycles).

c_3(new PAS): Ditto for the new PAS for LEN ([redacted] cycles).

Note that the lower case "n" is used because this refers to the smaller, more restricted, patient group in this HTA, and upper case "N" is used as this refers to the large patient group in TA171. The patient population in the current HTA is smaller because it refers to just those patients for whom thalidomide is contraindicated and whose disease has progressed after ≥1 prior treatment with bortezomib, whereas in TA171, thalidomide was not contraindicated and patients had not necessarily previously taken bortezomib.

Now again consider the two scenarios above.

First suppose LEN is not recommended in the current appraisal. Then the total acquisition cost of LEN, when used for both 2nd- and 3rd-line patients, is:

n_2c_3(old PAS) +

$(N_3 – n_2)c_3$(old PAS)

Where the first term above represents the total cost of LEN treatment for all patients in the current HTA who take MP 2nd-line, followed by LEN 3rd-line (with the old PAS).

The second term above represents the total cost of LEN treatment for all patients in TA171 minus those in the current HTA (as they are included in the first term) who take LEN third line (at the old PAS).

Alternatively, suppose LEN is recommended in the current appraisal. Then the total cost of LEN acquisition, when used for both 2nd- or 3rd-line patients, is:

n_2c_2(new PAS) +

$(N_3 – n_2)c_3$(new PAS)

Where the first term above represents patients in the current HTA who take LEN 2nd-line (at new PAS).

The second term above represents patients in TA171 minus those in the current HTA (as they are included in the first term) who take LEN third line (at the new PAS).

The difference in the costs above, **per patient in the current HTA, n_2**, is then given as:

$(1/ n_2)[n_2c_2$(new PAS) + $(N_3 – n_2)c_3$(new PAS) - n_2c_3(old PAS) - $(N_3 – n_2)c_3$(old PAS)]

= c_2(new PAS) - c_3(old PAS)

+ $(n_2-N_3)/n_2$. (c_3(old PAS) - c_3(new PAS))

The first line above is simply the difference in total costs of LEN 2nd-line with the new PAS minus total costs of LEN 3rd-line with the old PAS. This is as traditionally calculated in HTA models.

The second line represents the novel methodology of taking credit for costs saving in the use of LEN 3rd-line for patients not subject to the current HTA. Celgene estimate this cost saving as [redacted] (per 2nd-line patient).

2.2.1 Relative sizes of patient populations in current HTA vs. TA171 (3rd-line)

Celgene estimate:

$N_3 - n_2$ = 3,023

n_2 = [redacted]

and hence the absolute value of the factor $(n_2-N_3)/n_2$ as [redacted], i.e. the patient population in TA171 (at 3rd line), minus the patient population in the current HTA is [redacted] times larger than the patient population in the current HTA.

More precisely, they estimate the denominator, n_2, [redacted], as:

Number of eligible 2nd-line patients in the current HTA (683)

Multiplied by proportion of such patients treated with LEN 5 years after introduction of the NICE recommendation in this appraisal ([redacted]%).

Celgene in turn estimate the 683 as equal to the product of the following quantities, with sources given in italics:

Annual multiple myeloma incidence 4,399

"Cancer Incidence in England 2015"

X Proportion unsuitable for SCT 67%

" Latest data from BSBMT, bsbmt.org/2016-activity/"

X Proportion unable to tolerate thalidomide 38%

"*Bortezomib market share from Q2 2017 used as a proxy for thalidomide intolerance (due to recommendation in TA228 Market research data based on 115 UK clinicians 2015*."

X Proportion reaching 2nd line therapy 61%

"*A large real-world study including 753 UK patients was published in 2016. This provides more accurate data than the previous estimate" Yong K, Delforge M, Driessen C, et al. Multiple myeloma: patient outcomes in real-world practice. Br J Haematol. 2016; 175(2):252-64."*

We agree that Celgene have correctly extracted the estimate of the annual multiple myeloma incidence, 4,399 patients, from the ONS data (specifically for disease code C900).

Concerning the proportion of patients unsuited to SCT, the web link provided does not exist. Instead, we assume Celgene used the following link, which does exist: http://bsbmt.org/activity/2016/. However, it is not clear to us how Celgene have estimated the value of 67% from the data on this web page.

We are unable to check the value of 38% for the proportion of patients unable to tolerate thalidomide, as the reference data is not in the public domain.

Inspection of the Yong et al. (2016) reference confirms that this publication cites an estimate of 61% for the proportion of multiple myeloma patients reaching 2nd-line treatment. These patients were from several European countries. Also, the patients were not those the subject to this HTA, namely they were not restricted to those ineligible for thalidomide, having received 1st-line bortezomib. Therefore, we consider the figure of 61% to be uncertain for our purposes.

Next, they estimate the numerator, $N_3 - n_2$, of the relative sizes of populations as:

Number of 3rd-line patients at year 5 – number of 2nd-line patients in current HTA at year 5

+

2nd-line patients in current HTA treated with MP at year 5

x Proportion of patients reaching 3rd line from 2nd-line treatment.

= 2,873 + [redacted] x 78% (Equation 1)

First, Celgene estimate the number of 2nd-line patients in the current HTA treated with MP at year 5 as [redacted], equal to the total number of 2nd-line patients in this HTA, 683, minus the number of patients 2nd-line subject to the current appraisal treated with LEN, [redacted]. Both these figures have been discussed above.

Celgene estimate the first quantity of Equation 1, the number of 3rd-line patients at year 5 – number of 2nd-line in the current HTA at year 5 as:

Number of patients currently treated with LEN at 3rd-line

- Number of 2nd-line patients in current HTA

X Proportion of patients reaching 3rd line therapy from 2nd-line

= 3,409 – 683 X 78%.

We have already discussed the derivation of the number of 2nd-line patients in current HTA, 683.

Celgene estimate the 78% for the number of patients reaching 3rd line therapy from 2nd-line from their model. We agree with Celgene's use of their model for this purpose. As an aside, we also note that the source Celgene previous used, Yong et al (2016) suggests this figure should be 38%/61% = 62%, slightly lower than Celgene's estimate of 78%. Nonetheless, we find that the ICERs are rather insensitive to this parameter, so we pursue this matter no further.

Celgene calculate the number of patients currently treated with LEN at 3rd-line, [redacted], from "*actual full year sales data from 2016 combined with unique electronic prescription authorisation form (ePAF) IDs (excluding Scotland, Jersey and private sales)*." The source of this data is given as "*Data on file. Average annual sales 2016 (unique patient numbers). 2016*." Clearly we have no way of checking the source of this data.

However, we believe there is an alternate method of estimating the number of patients currently treated with LEN at 3rd-line, which is consistent with Celgene's other calculations:

Multiple myeloma incidence p.a.

X Proportion patients reaching 2nd line therapy

X Proportion reaching 3rd line from 2nd-line.

= 4,399 x 61% * 78%

= 2,105.

Where all components of this product have been discussed before.

This figure then gives an estimate of the relative populations sizes at 3rd-line compared to 2nd-line of 3.5, and an ICER for LEN+DEX vs. MP of £[redacted] per QALY (Table 2, p15).

2.2.2 Cost savings of new PAS for 3rd-line patients

Celgene use their model to estimate the cost saving for third line patients from the change in the LEN PAS,

c_3(old PAS) - c_3(new PAS), as:

[redacted] = £9,047 - [redacted]

We agree with this calculation.

2.3 Celgene cost-effectiveness results

Celgene say that with the changes explained above, the ICER for LEN vs MP reduces to £[redacted] per QALY. We agree that this is the output from their model with their preferred assumptions.

3 Critique of Celgene new base case

3.1 Changes to Lenalidomide PAS

Celgene have correctly implemented the new PAS for LEN in their model.

3.2 Offsetting costs for 3rd line patients

In our opinion, the quote above from the NICE Methods guide section, does suggest that it is reasonable to consider the cost savings of the new PAS on 3rd-line treatment with lenalidomide. However, the Guide does not explicitly recommend that such a cost saving should be incorporated in ICER calculations.

We imagine that such cost offsetting could have been applied in many previous NICE HTAs, where drugs are used in different therapeutic lines for the same condition. But we are not aware that this has been considered in any previous NICE HTAs. This does not, of course, necessarily mean that the methodology is flawed.

We leave the NICE committee to decide whether it is appropriate to include the cost savings in the ICER calculation.

Next, Celgene's calculations are based on the current use of lenalidomide for multiple myeloma.

However, lenalidomide might soon be recommended for **1st-line** use for multiple myeloma. We understand the NICE committee will also be discussing the use of lenalidomide 1st line in a separate discussion (ID474) for the first time on 1st February, on the same day, and just after the committee meeting for the current HTA for 2nd-line use. The patient group is for adults with previously untreated multiple myeloma for whom stem-cell transplantation is considered inappropriate.

If the NICE committee recommend lenalidomide for 1st-line use, it is likely that use of lenalidomide at 3rd-line would reduce substantially. Indeed, this has been confirmed by our clinical expert, Claudius Rudin, who suggests that, for example, pomalidomide, rather than lenalidomide, might be used 3rd-line in such a scenario. It is also possible that use of lenalidomide at 2nd-line, specifically for patients in the current appraisal (post bortezomib), would also reduce substantially.

The net result of this is that the introduction of lenalidomide for 1st-line use is likely to affect the factor of [redacted] greatly. But it is difficult to say how the factor would change. To investigate this, we consider the impact in the possible reduction in use of lenalidomide 3rd-line. Assuming a 50% reduction in the factor from [redacted] to [redacted], Celgene's ICER for LEN+DEX vs MP increases from £[redacted] to £[redacted] per QALY, and from £[redacted] to £[redacted] per QALY, assuming our PFS DEX curve (Table 2, p15).

3.2.1 Relative sizes of patient populations in current HTA vs. TA171 (3rd-line)

In Section 2.2.1, we stated that we were unable to check some of the components of Celgene's calculation for the relative sizes of the patient populations in the current HTA vs. TA171 (3rd-line).

Nonetheless, our clinical advisor, haematologist Dr Claudius Rudin, considers Celgene's ratio of population size of [redacted] to be reasonable. We consider this as an important face validity check. Note that Dr Rudin's estimate was more in line with Celgene's ratio of [redacted] than our estimate of [redacted] from Section 2.2.1, p9.

3.2.2 Cost savings of new PAS for 3rd-line patients

We agree with Celgene's model calculation of the cost saving from the reduction in the cost of PAS for third line patients of [redacted].

3.3 PFS DEX tail

In their recent addendum, Celgene have ignored our critique of their choice of curve fit to the PFS for DEX, and the Committee's reference to this. In particular, they have not adjusted the curve for PFS DEX as we suggested.

However, in their model, they have correctly incorporated the functionality to give the option of assuming our choice of PFS for DEX.

We demonstrate the impact of this amendment on the ICER in Table 2, p15.

3.4 MP acquisition costs

Celgene have indeed corrected the error in the MP acquisition costs.

We stated in our Addendum of 4th Oct 2016 that we considered their correction appropriate.

4 PenTAG revised estimates of cost-effectiveness

In all our analyses in Table 2 below, the ">" sign indicates that we, and the NICE committee, assume PFS and OS for MP is at least as good as for DEX.

Table 2. Impact on the ICER for LEN+DEX vs. MP of additional analyses undertaken by PenTAG

Scenario	ICER (£/QALY) LEN+DEX vs. MP
Celgene current analysis	[redacted]
1: DEX PFS tail shortened (Section 3.3, p14)	[redacted]
2: No cost saving from 3rd-line LEN	[redacted]
3: Halve number of 3rd-line LEN patients	[redacted]
4: Number of 3rd-line LEN patients reduced from 3,409 to 2,105 (Section 2.2.1, p9)	[redacted]
1 & 2	[redacted]
1 & 3	[redacted]
1 & 4	[redacted]

Key: DEX, dexamethasone; LEN, lenalidomide; MP, melphalan plus prednisolone.

4.1 End of Life Criteria

The estimated life expectancy under the comparator, MP, is unchanged and so LEN+DEX still does not meet the End of Life criteria.

The clinical and cost-effectiveness of lenalidomide for people who have received at least one prior therapy with bortezomib (partial review of TA171)

A critique of the submission from Celgene

30th January 2018 Addendum

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Any 'commercial in confidence' data provided by companies, and specified as such, is [redacted].

Market share of LEN 2nd-line

On the request of NICE, the following additional analyses on the estimated market share of LEN 2nd-line were carried out.

Celgene assume [redacted] patients would take LEN 2nd-line if recommended by the committee. As explained in our first Addendum of January 2018, this is calculated as:

Number of eligible 2nd-line patients in the current HTA (683)
X by % of such patients treated with LEN 5 years after introduction of the NICE recommendation in this appraisal ([redacted]%).

In our previous addendum, we critiqued Celgene's figure 683, but did not critique the [redacted]%.

Celgene estimate the [redacted]% market share 5 years from the time of recommendation of LEN 2nd-line. They justify the [redacted]% as the "*market share based on the peak market share at 3rd line*" (their Addendum). They claim "*we believe these estimates are robust and could even be an over-estimate of uptake*".

In response, this all seems plausible. But we have no way to check that the peak market share at 3rd-line was indeed [redacted]%.

Assuming market share of LEN 2nd-line = 100%

In our first January 2018 Addendum, we gave the following table:

Table 1. Impact on the ICER for LEN+DEX vs. MP of additional analyses undertaken by PenTAG

Scenario	ICER (£/QALY) LEN+DEX vs. MP
Celgene current analysis	[redacted]
1: DEX PFS tail shortened	[redacted]
2: No cost saving from 3rd-line LEN	[redacted]
3: Halve number of 3rd-line LEN patients	[redacted]
4: Number of 3rd-line LEN patients reduced from 3,409 to 2,105	[redacted]
1 & 2	[redacted]
1 & 3	[redacted]
1 & 4	[redacted]

Key: *DEX, dexamethasone; LEN, lenalidomide; MP, melphalan plus prednisolone.*

If instead we assume a market share for LEN 2nd-line of 100%, then:

Table. As above, but market share for LEN 2nd-line increased from [redacted]% to 100%

Scenario	ICER (£/QALY) LEN+DEX vs. MP

Celgene current analysis (+ adjust market share)	[redacted]
1: DEX PFS tail shortened	[redacted]
2: No cost saving from 3rd-line LEN	[redacted]
3: Halve number of 3rd-line LEN patients	[redacted]
4: Number of 3rd-line LEN patients reduced from 3,409 to 2,105	[redacted]
1 & 2	[redacted]
1 & 3	[redacted]
1 & 4	[redacted]

Key: *DEX, dexamethasone; LEN, lenalidomide; MP, melphalan plus prednisolone.*

Correction for error in estimated saving per 3rd-line patient

Further to our critique of the company's submission with the new PAS, outlined in our first Addendum of January 2018, we have identified what we consider as an important error in how the company have calculated the wider savings.

Celgene use their model to estimate the cost saving from the change in the LEN PAS per 3rd-line patient as [redacted] (PenTAG recent Addendum).

We have recently noticed that Celgene have overlooked the fact that they assume, quite correctly, that, of the patients on 2nd-line MP in their model, only 48% proceed to subsequent LEN 3rd-line. This is correct, as it is consistent with the clinical data. Also, Celgene have ignored that only 78.44% of patients in the MP arm subsequently receive 3rd-line treatment.
In order just to estimate the cost saving from the change in the LEN PAS per 3rd-line patient using Celgene's model, it is necessary to model all patients in the MP subsequently being treated with 3rd-line LEN. This is because we are concerned with the cost saving for all 3rd-line patients under the existing NICE recommendation, not just related to patients in the current appraisal. The model can be corrected simply by dividing cell D51 in the "Results" worksheet by 37.3% = 48% x 78.44%. This then gives an estimated saving from the change in the LEN PAS per 3rd-line patient as [redacted] / (48% x 78.44%) = [redacted].

With this correction the ICERs are as follows. Please note that we have changed analysis 3, as this now seems most relevant:

Table. Correction for error in estimated cost saving per 3rd-line patient

Scenario	ICER (£/QALY) LEN+DEX vs. MP

Celgene current analysis (corrected for error in estimated cost saving per 3rd-line patient)	[redacted]
1: DEX PFS tail shortened	[redacted]
2: No cost saving from 3rd-line LEN	[redacted]
3: Market share 2nd-line LEN increased from 72% to 100%	[redacted]
4: Number of 3rd-line LEN patients reduced from 3,409 to 2,105	[redacted]
1 & 2	[redacted]
1 & 3	[redacted]
1 & 4	[redacted]

Key: *DEX, dexamethasone; LEN, lenalidomide; MP, melphalan plus prednisolone.*

The steps to replace the lenalidomide complex patient access scheme (PAS) with a simple discount

Introduction

Celgene are replacing the existing complex PAS for lenalidomide (cycle cap scheme under which the drug cost for people who remain on treatment for more than 26 cycles is met by the company) with a confidential simple discount. Because a simple discount applies to all current and future indications, the discount level must ensure lenalidomide is cost-effective in the least cost-effective indication among those with positive National Institute for Health and Care Excellence (NICE) Guidance and those currently undergoing appraisals.

There are currently two suspended Final Appraisal Determinations (FADs) for ongoing appraisals of lenalidomide which were reviewed with the inclusion of the complex PAS with the cycle cap reduced to [redacted] cycles;

- ID667: Lenalidomide for treating multiple myeloma after 1 prior treatment with bortezomib (part rev TA171)[1]
- ID474: Lenalidomide in combination with dexamethasone for previously untreated multiple myeloma[2]

To ensure that lenalidomide remains cost-effective in these appraisals based on the simple discount, [redacted]. This was possible for ID474, but not for ID667 as it is not clear what the committee's decision making ICER or incremental NMB was (see Appendix 1, section 2.1 below). Therefore, the level of discount in ID667 was calculated [redacted].

The discount levels for these indications have been calculated using the models submitted in the respective NICE appraisals. The only changes made to the models (except for correcting a minor costing error identified in the model for ID474 where the administration cost of the cycle cap was applied irrespective of the number of patients on treatment) have been to remove the cycle cap and apply the simple discount to the list price of lenalidomide in its place. The updated models have been provided and the steps for removing the cycle cap and applying the simple discount for lenalidomide are presented in Appendix 1.

NICE has published positive guidance for lenalidomide in the following indications based on the currently operational 26 cycle cap:

- Multiple myeloma in people who have received two or more prior therapies (TA171)[3]
- Myelodysplastic syndromes (MDS) associated with an isolated deletion 5q cytogenetic abnormality (TA322)[4]

The discount required for lenalidomide to be cost-effective in these indications was calculated as the equivalent discount provided by the 26 cycle cap, based on the associated guidance and supporting documentation published on the NICE website.

Calculation of discount level for 'Multiple myeloma (newly diagnosed) – lenalidomide [ID474]'

In contrast to the Celgene base case, the Evidence Review Group (ERG) preferred[5, 6]:

- to assume time on treatment for bortezomib (VMP) is equal to thalidomide (MPT) and assume the same parametric distribution for MPT/VMP as the intervention (Weibull);
- lower administration costs for the comparator; and
- minor changes to the comparator utility

The level of discount required [redacted] is not affected by these changes, as they do not affect lenalidomide acquisition costs (Table 1). The discount level ([redacted]) is therefore reflective of the discount that was provided by the proposed [redacted] cycle cap.

Table 1: Newly diagnosed multiple myeloma (ID474) discount levels

Scenario	Incremental NMB (Rd vs. VMP) ([redacted], £)	ICER (Rd vs. VMP) (£ per QALY)	Discount required [redacted]
Celgene base case	[redacted]	[redacted]	[redacted]
Celgene base case [with correction]*	[redacted]	[redacted]	[redacted]
ERG base case (scenario 1, 3 & 5)	[redacted]	[redacted]	[redacted]
ERG base case (scenario 1, 3 & 5) [with correction]*	[redacted]	[redacted]	[redacted]

Key: ERG, evidence review group; NMB, net monetary benefit; Rd, lenalidomide plus dexamethasone; VMP, bortezomib plus melphalan plus prednisolone; [redacted]

Notes: *See Appendix 1, section 1.1 for further detail on the correction made

Calculation of discount level for 'Multiple myeloma – lenalidomide (post-bortezomib) (part review TA171) [ID667]'

As described in Appendix 1, section 2.1, an approach was taken in this appraisal which incorporated savings for patients in third line multiple myeloma (TA171) generated by reducing the cycle cap from 26 cycles to [redacted] cycles into the ICER calculation. The method for incorporating these savings when switching to the simple discount is also described in Appendix 1, section 2.2.

Since it is not clear what the decision-making incremental NMB was, the discount level required has been calculated [redacted] The associated discount level is [redacted] (Table 2).

Table 2: Multiple myeloma in people who have received one prior therapy (ID667) discount level

Incremental NMB ([redacted], £)	ICER (Rd vs. MP) (£ per QALY)	Discount required [redacted]
[redacted]	[redacted]	[redacted]
Key: MP, melphalan plus prednisolone; NMB, net monetary benefit; Rd, lenalidomide plus dexamethasone; [redacted]		

Indications where lenalidomide has positive NICE Guidance

MDS associated with an isolated deletion 5q cytogenetic abnormality (TA322)

[redacted]

[redacted]

Multiple myeloma in people who have received two or more prior therapies (TA171)

[redacted]

Summary

If a simple discount were to be applied across all indications, the discount level that would result in lenalidomide being cost-effective [redacted]

For the suspended appraisals (ID474 and ID667), this discount level is sufficient to replace the proposed [redacted] cycle cap upon which the committee had based their decisions and produced FADs (see Table 3 below). The ICERs generated by the simple discount level of [redacted] are as follows;

- ID474 Celgene base case: £11,886 per QALY
- ID474 ERG preferred base case: £19,654 per QALY
- ID667 base case: [redacted] per QALY

The simple discount level of [redacted] would come into effect at the point of release of the suspended FADs.

Table 3: Simple discount compared to equivalent discounts offered by the complex PAS (capping scheme)

TA (or ID) number	Indication	Discount offered by the complex PAS in cost-effectiveness modelling	New simple discount offered
TA171	Multiple myeloma in people who have received two or more prior therapies	[redacted]	[redacted]
TA322	Transfusion-dependent anaemia caused by low or intermediate-1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate	[redacted]	[redacted]
ID667***	Patients with multiple myeloma who are ineligible for transplant, unsuitable for thalidomide and have received bortezomib at 1st line	[redacted]	[redacted]
ID474***	Transplant-ineligible newly diagnosed multiple myeloma for patients who are unable to tolerate or have contraindications to thalidomide	[redacted]	[redacted]
Key: TA, Technology Appraisal; * with End of Life criteria met at an ICER of £43,800 per QALY ** [redacted], not matching incremental NMB or discount provided by cycle cap *** cap proposed at [redacted] cycles not at 26 cycles			

Appendix 1 - Methods

[redacted]

[redacted]

[redacted]

[redacted]

References

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The clinical and cost-effectiveness of lenalidomide for people who have received at least one prior therapy with bortezomib (partial review of TA171)

A Single Technology Appraisal

[redacted] Revised - 16th April 2019

Company base case results after replacement of complex PAS with simple PAS

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Any 'commercial in confidence' data provided by companies, and specified as such, is [redacted].

1 Company's implementation of new PAS

The company provided the ERG with detail of the formulae changes within the model required to implement the new PAS. These were provided as part of the document '*The steps to replace the lenalidomide complex patient access scheme (PAS) with a simple discount*'. The ERG has checked and are satisfied that the company has implemented the adjustments as they described. Current ERG researchers have no prior familiarisation with this complex model so are unable to verify the company changes with a full knowledge of its operation.

In order to reflect current and proposed practice the company model lenalidomide at multiple lines and in both the intervention and comparator strategies. Table 1 shows how the new simple PAS has been applied by the company within the model.

[redacted]

Table 1 Simple discount application across treatment arms and lines of therapy

Line of therapy	Intervention arm	Comparator arm
Second-line	[redacted]	[redacted]
Third-line	[redacted]	[redacted]
Fourth-line	[redacted]	[redacted]

Source: Extracted from company addendum: The steps to replace the lenalidomide complex (PAS) with a simple discount'; Appendix 1, Table 5.

2 Revised results

The new simple PAS is a straight discount of [redacted] of the unit cost of lenalidomide. The complex PAS is an arrangement whereby the company meet the cost of lenalidomide beyond the 26th treatment cycle. Table 2 presents the company base case result including the revised PAS arrangement, and a scenario in which the new simple PAS is applied to lenalidomide to [redacted].

Table 2 Base-case result when simple PAS is applied to second-line intervention

Scenario	ICER (£/QALY) LEN+DEX vs MP
Company base case with no PAS(s*)	[redacted]
Company base case with previous complex PAS	[redacted]
Company base case with new simple PAS	[redacted]
Company base case with new simple PAS applied to both strategies	[redacted]

Key: DEX, dexamethasone; LEN, lenalidomide; MP, melphalan plus prednisolone. **Note.** *Of the comparator treatments considered by the model only bortezomib has a PAS, but this is not a base case comparator so this figure represents the removal of the previous complex PAS.

Table 3 details the ERG changes made to the model in addition to those already made by the company to implement the presented scenario.

Table 3 Model formulae changes made by the ERG for scenario analysis

Cell	Formula	Rationale
'Results' sheet, F34	[redacted]	[redacted]
'Results' sheet, E47	[redacted]	[redacted]
'Results' sheet, F34	[redacted]	[redacted]
PF.Comparator, DS17:DS343	[redacted]	[redacted]
Cells containing changes to formulae are colour-coded orange.		