**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Ixazomib citrate for treating relapsed or refractory multiple myeloma [ID807]

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

1. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Takeda
     - ACD response
     - Addendum to ACD response
     - Additional evidence – new analyses with current PAS
   - Myeloma UK
   - UK Myeloma Forum

2. **Comments on the Appraisal Consultation Document received through the NICE website**

3. **Clarification questions related to the additional evidence** provided by the company, Takeda
   - Clarification letter to company
   - Company response to clarification letter

4. **Review of the company additional evidence** provided by the Evidence Review Group, Warwick Evidence
   - ERG review of the company additional evidence
   - Additional analyses by the ERG: Comparison of different survival extrapolations with survival in the UK general population
   - Additional analyses by the ERG: ICERs using different survival extrapolations based on the approved PAS

5. **Statements from the clinical experts who attended the first meeting, in response to questions about the company's additional evidence**

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

# Ixazomib with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma [ID807]: Response to the ACD 20 April 2017 for the consideration of the NICE Appraisal Committee

**Submitted by Takeda UK Ltd.**

***Single Technology Appraisal (STA)***
***National Institute of Health and Care Excellence***

Submitted 19th May 2017

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| ACD | Appraisal committee document |
| BORT | Bortezomib |
| CAA | Commercial Access Agreement |
| CDF | Cancer Drugs Fund |
| CI | Confidence interval |
| CR | Complete response |
| CSR | Clinical study report |
| DEX | Dexamethasone |
| DH | Department of Health |
| EoL | End of life |
| EMA | European Medicines Agency |
| ERG | Evidence Review Group |
| HR | Hazard ratio |
| HRQoL | Health related quality of life |
| IA | Interim analysis |
| ICER | Incremental cost-effectiveness ratio |
| IMW | International Myeloma Workshop |
| ISS | International staging system |
| ITT | Intention to treat |
| IXA | Ixazomib |
| LDH | Lactate dehydrogenase |
| LEN | Lenalidomide |
| NE | Not estimable |
| NHS | National Health Service |
| NICE | National Institute for Health Care and Excellence |
| NSCLC | Non-small cell lung cancer |
| OR | Odds ratio |
| ORR | Overall response rate |
| OS | Overall survival |
| PANO | Panobinostat |
| PAS | Patient access scheme |
| PASLU | Patient access schemes liaison unit |
| PFS | Progression free survival |
| QALY | Quality-adjusted life year |
| RRMM | Relapsing remitting multiple myeloma |
| TTP | Time to progression |
| UKMF | UK Myeloma Forum |
| VGPR | Very good partial response |

# 1. Executive Summary

Takeda agrees with the committee that the main population relevant to the ixazomib appraisal are patients who have had 2 or 3 prior therapies as this reflects the expected use of ixazomib (i.e. as 3rd or 4th line therapy in combination with lenalidomide and dexamethasone as the IXA + LEN +DEX regimen).

At this time, and consistent with comments from the committee in the ACD, Takeda wishes to put on hold further appraisal of ixazomib for use in patients who have had only one prior therapy (i.e. use in 2nd line), pending the resolution by NICE of a number of outstanding issues regarding relevant comparators in this setting. Takeda may decide to revisit at some point in the near future the use of ixazomib at 2nd line, once these issues have been resolved.

Therefore, the current ACD response will be focused only on the issues that are relevant to the use of IXA + LEN + DEX in the key patient population, which is patients who have had 2 or 3 prior therapies.

Takeda agrees with a number of statements and recommendations made by the committee in Sections 3.1, 3.2 and 3.3 of the ACD, related to the value in relapsed/refractory multiple myeloma (RRMM) of a triplet regimen that combines a proteasome inhibitor (ixazomib) and an immunomodulator (lenalidomide); the importance of oral treatment options such as ixazomib for patients, clinicians and the wider NHS; and that progression and progression free survival (PFS) are clinically meaningful outcomes for patients.

Based on the committee's recommendations, Takeda has updated the economic analysis to: (i) use the second interim analysis data from the TOURMALINE MM-1 (TMM-1) trial for key outcomes; (ii) include regular, rather than one-off, costs for post-progression therapies; and (iii) reflect an updated analysis of EQ 5D derived utility data. The cost-effectiveness results using the updated economic model with the current PASLU/DH approved patient access scheme (PAS) for ixazomib (a simple discount of [redacted] on the NHS list price) are presented in Appendix 1.

The company has responded to and challenged the remaining issues raised by the committee by providing additional evidence and analysis on the topics of the positioning of IXA + LEN + DEX in the RRMM pathway, including the relevant comparators; the clinical efficacy of the IXA + LEN + DEX regimen (note the consistency of the results between the first and second interim analyses of TMM-1 in the key 2/3 prior therapy patient population); the appropriate estimation of duration of therapy on ixazomib using the time on treatment (ToT) approach; and the most appropriate estimation of quality of life (QoL) decrement for a progressed multiple myeloma patient.

The committee, clinical experts and Takeda all agree that the IXA + LEN + DEX triplet regimen will be used in the same line of therapy as the LEN + DEX doublet is currently used in the UK. Hence, it is agreed by all parties that the predominant use of IXA + LEN + DEX will be after 2 prior therapies (3rd line) with minor usage after 3 prior therapies (4th line) in a small number of patients who have not received lenalidomide in earlier lines. Therefore, the most robust data on which to base an appraisal of cost-effectiveness is the stratified, balanced sub-group of 2 or 3 prior therapies from the TMM-1 trial. An

exploratory analysis of the unstratified 3rd line only patient sub-group, adjusted for patient characteristics, is presented and shows similar cost-effectiveness results versus LEN + DEX as the stratified 3rd and 4th line sub-group, further supporting the clinical and cost-effectiveness of the IXA + LEN + DEX regimen in this setting.

The company does not agree with the committee's assertion in Section 3.10 of the ACD that panobinostat, given as the panobinostat + bortezomib + dexamethasone (PANO + BORT + DEX) regimen is a relevant comparator for patients who have had 3 prior therapies. Clinical experts opinion is that PANO + BORT + DEX is reserved for later lines of therapy in select patients only and is used after LEN + DEX. Given that PANO + BORT + DEX will always be used later than IXA + LEN + DEX, it would be inconsistent with clinical expert opinion and clinical practice to consider the panobinostat regimen as a direct and relevant comparator to IXA + LEN + DEX. Hence, the company has not included PANO + BORT + DEX as a comparator for IXA+LEN+DEX in either the 3rd or 4th line setting.

Takeda would like to reaffirm its request in the original submission that ixazomib be considered for inclusion with the Cancer Drug Fund (CDF). Takeda agrees with the committee that ixazomib would benefit from additional data maturation in the TMM-1 trial (potentially supplemented by real world evidence from the UK Named Patient Program/NPP), and that this has the potential to reduce the uncertainty about the clinical benefits of ixazomib, thereby meeting the first criterion for entry into the CDF. Takeda also recognises that the ICERs in the current ACD are too high to be considered a cost-effective use of NHS health care resources in England and Wales, or to meet the criterion of plausible cost-effectiveness in order to qualify for consideration for the CDF.

However, based on the information and analyses contained within this ACD response, Takeda request that the committee reconsiders ixazomib's eligibility for both the end of life criteria (applying what we understand are newly revised criteria for combination regimens) and also the CDF.

In order to provide a route through which the committee could recommend ixazomib for inclusion in the CDF, Takeda has been in positive discussions with NHS England regarding the outline of a proposed Commercial Access Agreement (CAA) for ixazomib. The proposed CAA is intended to both address uncertainty regarding the cost effectiveness of ixazomib (via the inclusion of a cycle/time cap for ixazomib at [redacted] cycles/months) and to reduce the ICER to a level that shows plausible potential for cost effectiveness in the 2/3 prior therapies sub-group at the relevant threshold (via the combined effect of the cycle/time cap and a reduced net price of [redacted] per ixazomib capsule, arising from a rebate mechanism which equates to a discount of [redacted] on the NHS list price; this represents an estimated [redacted] price reduction on the costs of bortezomib).

The cost-effectiveness results using the modified economic model and including the proposed CAA are presented in Appendix 2 of this response document.

Takeda is optimistic that the steps we have taken in this response will allow the committee to conclude that there is both clinical uncertainty (which can be addressed via data collection/data maturation) and plausible potential for cost effectiveness (based on the proposed CAA), thus leading to a recommendation that ixazomib be included within the CDF. This would allow Takeda to engage fully with NHS England with a view to

agreeing a mutually acceptable CAA that would allow patients and the NHS to benefit from having early access to an effective and simple all-oral triplet that uniquely combines a proteasome inhibitor and an immunomodulator.

# 2. Introduction

## 2.1 Appraisal committee's preliminary recommendations

On the 20th April 2017, an Appraisal Committee of the National Institute for Health and Care Excellence (NICE) prepared an Appraisal Consultation Document (ACD) summarising the evidence, views and draft recommendations of the committee regarding the use of ixazomib with lenalidomide and dexamethasone (IXA + LEN + DEX) within the National Health Service (NHS) in England for treating relapsed or refractory multiple myeloma (RRMM). The ACD sets out the draft recommendations made by the committee which currently state that:

*'Ixazomib, with lenalidomide and dexamethasone, is not recommended within its marketing authorisation for treating multiple myeloma in adults who have already had at least 1 therapy'.*

## 2.2 Response to the appraisal committee's standard key questions

Following feedback from the NICE Appraisal Committee on page 1 of the NICE ACD, that they are interested in receiving comments to key standard questions (see Section 3), Takeda UK Ltd. are responding to key issues raised in the ACD. We recognise that the NICE Appraisal Committee considered the analysis in patients who have had one previous therapy because it is part of the marketing authorisation, but concluded that the main population relevant to this appraisal are patients who have had 2 or 3 previous therapies as this reflects the expected use of ixazomib in clinical practice i.e. in the same place in the RRMM treatment pathway as lenalidomide plus dexamethasone (LEN+DEX; Section 3.7 of the ACD). The original submission to NICE was based on an expectation that ixazomib would be used mainly for patients who had only 2 previous therapies. However, Takeda have reconsidered the expected use in clinical practice and agree with the conclusion of the committee presented in section 3.7 of the ACD, and seek a recommendation for use in patients who have received 2 or 3 prior therapies (i.e. use in the 3rd line+ patient population). Hence, our focus in this response is on the issues raised relating to this particular patient population.

At this time, and consistent with comments from the committee in the ACD, Takeda no longer wishes to put on hold further appraisal of pursue a recommendation for ixazomib for use in patients who have had one prior therapy (i.e. for use in 2nd line). There are a number of reasons for this which we will summarise here. Firstly, there remains is currently significant uncertainty over the most appropriate comparator after one prior therapy, and as highlighted in the ACD this is dependent on the first treatment received (Section 3.8 of the ACD). Section 3.8 of the ACD states that bortezomib plus dexamethasone (BORT+DEX) is only relevant for patients who have had thalidomide front-line, whereas for people who have had bortezomib front-line then the comparator is a cyclophosphamide-based regimen, although the committee recognised that a comparison with such regimens would not be possible due to lack of data. Secondly the NICE technology appraisal of lenalidomide and

dexamethasone (LEN +DEX) in RRMM (ID667) after one prior therapy (bortezomib) is currently suspended due to number of issues relating to the impact of guidance on the treatment pathway. The current ACD issued in November 2016 for this appraisal has a draft "not recommended" guidance.[1] We await the final outcome of this appraisal, and dependent on this and any new developments in clinical practice, it should be noted that Takeda may decide wish to revisit at some point in the near future the use of ixazomib in at least some of the patients who have received one prior therapy (i.e. use in 2nd line). Takeda would like to emphasise that we do not wish to terminate the appraisal of ixazomib for patients at first relapse – rather we wish to put this part of the appraisal on hold until the issues highlighted above have been resolved.

In this document Takeda have addressed issues raised by the Evidence Review Group (ERG) and Appraisal Committee, and provided what we think is a fair and balanced response which covers the use of an updated economic model and the provision of new analyses to estimate what we believe to be the most plausible base case incremental cost-effectiveness ratio (ICER) for patients who have had 2 or 3 prior therapies. As has been recognised in the ACD, the appropriate comparator based on established clinical practice for this patient population is LEN + DEX (Section 3.5 of the ACD). Takeda recognise that the ICERs against this comparator discussed in the current ACD (Section 3.25 of the ACD) are too high to be considered a cost-effective use of NHS health care resources in England and Wales, or to meet the criterion of plausible cost-effectiveness in order to qualify for consideration for the Cancer Drug Fund (CDF). The committee recognised that additional data collection, relating primarily to more mature overall survival (OS) data from the ongoing TOURMALINE MM-1 trial, has the potential to reduce the uncertainty associated with the magnitude of the clinical benefits with ixazomib (Section 3.30 of the ACD). However, the committee did not yet see any plausible potential for ixazomib to satisfy the relevant cost-effectiveness threshold for routine use at its current price. In order to address this, Takeda are proposing a Commercial Access Agreement (CAA), which is currently the subject of an ongoing positive discussion with NHS England, regarding potential future commercial arrangements if ixazomib were recommended by NICE for inclusion within the CDF. The proposed CAA is intended to both address uncertainty regarding the cost-effectiveness of ixazomib (via the inclusion of a cycle/time cap for ixazomib) and to reduce the ICER to a level that shows plausible potential for cost-effectiveness in the 3rd line+ patient population at the relevant threshold (via the combined effect of the cycle/time cap and a reduced net price arising from a rebate mechanism). The proposed CAA consists of a cycle/time cap at [redacted] cycles/months and a cost that equates to [redacted] per ixazomib capsule (a discount of [redacted] on the NHS list price).

The proposed CAA has been included in a revised economic model that has been modified in response to issues and concerns raised in the ACD. The cost-effectiveness results using the modified economic model with the current PASLU/DH approved patient access scheme (PAS) are presented in Appendix 1, while the results using the modified economic model with the proposed CAA are presented in Appendix 2.

Takeda is optimistic that the steps we have taken in this response will allow the committee to conclude that there is both clinical uncertainty (which can be addressed via data collection/data maturation) and plausible potential for cost-effectiveness (based on the proposed CAA), thus leading to a recommendation that ixazomib be included within the

CDF. This would allow Takeda to engage fully with NHS England with a view to agreeing a mutually acceptable Managed Access Agreement (including the CAA) within the CDF.

# 3. Response to the appraisal committee's key standard questions

Please find below the responses of Takeda to the questions from the Appraisal Committee listed on page 1 of the ACD.

## 3.1 Has all of the relevant evidence been taken into account?

Takeda consider that all of the relevant evidence available at the time of submission has been considered by the AC. The main clinical evidence to support the case for the clinical and cost-effectiveness of IXA + LEN + DEX versus LEN + DEX in the sub-group of patients who have received 2 or 3 prior therapies is from the TOURMALINE MM-1 trial which is ongoing.

In response to issues raised in the ACD, a number of modifications have been made to the economic analysis of IXA + LEN + DEX versus LEN + DEX in the sub-group of patients who have received 2 or 3 prior therapies. The main new analyses conducted are summarised as follows:

- In response to comments in Section 3.15 of the ACD, use of the most mature data available currently for key outcomes in the economic analysis (progression free survival (PFS), OS and time on treatment (ToT)) from the TOURMALINE-MM1 trial (i.e. 2nd interim analysis (IA) dataset of July 2015).

- In response to comments in Section 3.16 of the ACD, use of 2 prior therapy data, with adjustment for baseline characteristics, to perform a scenario analysis to explore cost-effectiveness in the 2 prior therapies sub-group (i.e. 3rd line). To reflect expected use of ixazomib in clinical practice, Takeda are no longer seeking a positioning in just a 2-prior therapy patient population alone. However, this analysis remains useful for supporting the updated base case analysis demonstrating cost-effectiveness across patients receiving 2/3 prior therapies, and also helps justify use of the larger and more robust 2/3 prior therapy sub-group data to support the positioning of IXA + LEN + DEX versus LEN + DEX in patients with 2/3 prior therapies.

- In response to comments in Sections 3.19 and 3.20 of the ACD, new analyses have been conducted on the EQ-5D derived utility data using the 2nd IA data cut.

- In response to comments in Section 3.22 of the ACD, the inclusion of weekly cycle costs have been considered in the economic analysis for costs relating to post-progression treatments.

The modifications to the economic modelling are summarised in our response to Q2 below, with further details of the new analyses and results in Appendix 1 (with original

PASLU/DH approved PAS) and Appendix 2 (with proposed Commercial Access Agreement).

## 3.2 Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?

There are a number of issues raised in the ACD relating to the analysis of the clinical and cost-effectiveness of IXA + LEN + DEX in RRMM patients who have received two or three prior therapies. The Takeda response to these issues is provided below.

### 3.2.1 Discussion on ixazomib as a new treatment option (response to Sections 3.1 to 3.3 of the ACD)

***Company Response:***

In relation to Section 3.1 of the ACD, Takeda agree with the following statements:

> *"The patient and clinical experts emphasised that oral treatment regimens are very important"*
>
> *"The committee concluded that people would welcome new oral treatment options for multiple myeloma."*

With regard to Section 3.2 of the ACD, Takeda concur with the following statements:

> *"clinical experts explained that triple therapy regimens combining a proteasome inhibitor (such as ixazomib) with an immunomodulatory agent (such as lenalidomide) are becoming the standard of care for multiple myeloma."*
>
> *"this is because of the synergistic effect of combining drugs with different mechanisms of action"*
>
> *"the committee concluded that new triple therapy combinations with improved tolerability and more convenient administration would be welcomed"*

In relation to Section 3.3 of the ACD, Takeda agree with the following statements:

> *"The patient expert explained that being progression-free is important to patients, both psychologically and physically. They also explained that a relapse of multiple myeloma, even without symptoms (known as biochemical progression), causes anxiety and affects daily activities"*

In relation to the above statement we would like to clarify that, in our experience, although biochemical relapse often happens before a symptomatic relapse, that doesn't mean that patients are symptom-free. Most patients have constant symptoms due to the underlying impact of the disease but they learn to live with these. The availability of the next treatment is important in helping patients to maintain a decent quality of life.

In relation to Section 3.3 of the ACD, Takeda also agree with the following statements

*"The clinical experts noted that progression-free survival is an important outcome for patients because relapses can be fatal, especially in older people."*

*"The committee concluded that progression-free survival is important to people with multiple myeloma."*

### 3.2.2 Discussion on clinical management: positioning of ixazomib in clinical practice and relevant comparators for patients receiving 2-3 prior therapies (response to sections 3.5, 3.6, 3.7, 3.9, 3.10 of the ACD):

***Company Response:***

**LEN + DEX is a comparator in 3rd and 4th line**

The company agrees with the committee's conclusion that LEN + DEX is established in clinical practice for treating RRMM patients who have had 2/3 prior therapies (Section 3.5 in the ACD). LEN + DEX is therefore the key comparator to IXA + LEN + DEX for RRMM at both 3rd and 4th line (Sections 3.9 and 3.10 in the ACD). This is supported by the latest IMS research found in the company's submission (Table 14; page 57), which showed predominant usage of LEN + DEX in 3rd line (69% market share) with lesser uptake at 4th line (25% market share). In the TOURMALINE MM-1 trial, the 2/3 prior therapies (3rd and 4th line) stratified sub-group of 281 patients consisted of 208 patients treated after 2 prior therapies and 73 patients treated after 3 prior therapies. The 3 prior therapies patients therefore only accounted for 26% of the patients within the combined stratified sub-group. Hence, the efficacy benefits seen in the combined 2/3 prior therapies stratified sub-group have been driven primarily by the 2 prior therapy patients. The breakdown of patients in the stratified sub-group between 2 prior and 3 prior therapies is also consistent with the proportional use of LEN + DEX at 3rd and 4th line in UK clinical practice, as supported by the IMS research referenced above.

In addition, the MM009 and MM010 pivotal trials for LEN + DEX were stratified by 1 versus2 or 3 prior lines of treatment, the same as in TOURMALINE MM-1. In NICE TA171, Celgene modelled the cost-effectiveness of LEN + DEX using the 2 or 3 prior line stratified sub-group.[2] This was reviewed and accepted by NICE and led to the NICE approval of this combination for patients who had received at least 2 prior therapies. As explained in the ERG report for the ixazomib appraisal (page 42), ixazomib is not approved as a single agent – it must be combined with LEN + DEX. Therefore, if ixazomib was to be recommended, the drug would implicitly be used in those situations where LEN + DEX is already used within the UK. Given this case precedent with NICE and the inherent linkage of ixazomib with LEN+ DEX, it is logical to use the same stratified sub-group to model the cost-effectiveness of IXA + LEN + DEX versus LEN + DEX in this submission.

In conclusion, there is both a NICE case precedent and clinical relevance to the company using the 2/3 prior therapy stratified sub-group of patients in TOURMALINE MM-1 to

calculate the cost-effectiveness for IXA + LEN + DEX versus LEN + DEX in RRMM. This is further supported by the benefits from randomisation within this stratified sub-group, which results in an equal distribution of key prognostic factors across the IXA + LEN + DEX and LEN + DEX arms and therefore allows a robust interpretation of the efficacy gains and cost-effectiveness arising from the addition of IXA to LEN + DEX (see Section 3.2.3 below).

**Panobinostat is not a relevant comparator at 3rd or 4th line**

The company does not agree with the committee's assertion in Section 3.10 of the ACD that the panobinostat regimen, given as the panobinostat + bortezomib + dexamethasone (PANO + BORT + DEX)) is a relevant comparator for RRMM patients who have had 3 previous therapies (i.e. at 4th line). The NICE recommendations for LEN + DEX and PANO + BORT + DEX do not restrict usage of these regimens to a particular line of therapy, thus allowing patients to benefit from individualised treatment plans. The committee acknowledge that LEN + DEX is the only relevant comparator in 3rd line (Section 3.9 of the ACD). This demonstrates that the committee agrees that despite similar potential positioning, LEN + DEX will be used earlier than PANO + BORT + DEX, thus placing the panobinostat regimen into a subsequent line of therapy. If a patient enters into a clinical trial and is LEN naïve at the time of their third relapse, then LEN + DEX can be utilised at 4th line, with the option to use PANO + BORT + DEX used at a subsequent relapse. However, we would emphasise that lenalidomide-naïve patients are rare, and increasingly so, at 4th line.

This is consistent with the UK Myeloma Forum (UKMF) clinical experts' opinion that they would use LEN + DEX before panobinostat, with PANO + BORT + DEX sometimes reserved until later in the pathway as an alternative to bendamustine (Section 3.6 ACD). The main reasons why PANO + BORT + DEX is used after LEN + DEX is because this regimen is associated with toxic side-effects and a complicated dosing regimen (Section 3.6 of the ACD). Importantly, ixazomib can be added to LEN + DEX without any clinically significant toxicity and as part of a simple, all oral dosing regimen. Therefore, the IXA + LEN + DEX triplet offers the same simplicity and toxicity profile that has resulted in the LEN + DEX doublet being positioned before PANO + BORT + DEX, but with the additional benefit for patients shown from the results of TMM1 of a statistically and clinically meaningful 9 month extension of PFS and increase in quality responses versus LEN+ DEX (see Table 1 below) in the 2/3 prior therapy sub-group (HR: 0.58, 95% CI 0.40, 0.84, p=0.0033).

In conclusion, if ixazomib was recommended by NICE, then PANO + BORT + DEX would be positioned after relapse on IXA + LEN + DEX. Given that PANO + BORT + DEX will, in effect, always be used later than IXA + LEN + DEX, it would therefore be inconsistent with clinical expert opinion to consider it as a relevant comparator to IXA + LEN + DEX.

### 3.2.3 Discussion on Clinical Effectiveness: *"The clinical benefit of ixazomib is uncertain"* (response to Section 3.11 of the ACD):

***Company Response:***

In Section 3.11 of the ACD, the committee comment that they are concerned that data from the second interim analysis (2nd IA) of TOURMALINE MM-1 showed a reduced PFS difference between the treatment arms, which was no longer statistically significant for the intention-to-treat (ITT) population. As described in Section 3.2.1 of this ACD response, the key sub-group of relevance to this submission (which reflects the current usage of LEN + DEX in the UK) are patients who have received 2/3 prior lines of therapy. Within this stratified sub-group, the key efficacy endpoints of PFS, time to progression (TTP) and overall response rate (ORR) (including very good partial response or better (≥VGPR) and complete response (CR)) are all statistically significant at the 2nd IA. As shown below, the addition of IXA to LEN + DEX resulted in a statistically significant 9-month improvement in PFS, a 42% reduction in the risk of disease progression and an almost three-fold increased likelihood of obtaining a complete remission (as shown in Table 1):

**Table 1: Summary of key efficacy endpoints for IXA+LEN+DEX vs LEN+DEX in the 2/3 prior lines stratified subgroup**

| Endpoint | IXA + LEN + DEX | LEN + DEX | HR/ OR, 95% CI and p value |
|---|---|---|---|
| PFS | 22.0 months | 13.0 months | HR: 0.62; (0.45-0.86) p=0.0033 |
| OS | NE | NE | HR 0.65; (0.409-1.02) p=0.0569 |
| TTP | 28.8 months | 14.1 months | HR 0.58; (0.41-0.83) p=0.002 |
| ORR | 80.4% | 66.4% | OR 2.09; (1.23-3.56) p=0.006 |
| VGPR+CR | 54.1% | 36.2% | OR 2.08; (1.31-3.33) p=0.002 |
| CR rate | 18.2% | 6.7% | OR 3.18; (1.47-6.89) p=0.003 |
| Abbreviations: IXA: ixazomib; LEN: lenalidomide; DEX: dexamethasone; HR/ OR: hazard/ odds ratio; NE: not estimable; PFS: progression free survival; OS: overall survival; TTP: time to progression; ORR: overall response rate; VGPR: very good partial response; CR: complete response<br>Source: Company submission and IA2 CSR | | | |

Due to the robust and statistically significant efficacy results within the 2/3 prior therapy stratified sub-group at the 2nd IA, the only key efficacy endpoint that remains uncertain is the degree of improvement in OS. At the 2nd IA, there was a trend for OS benefit for IXA + LEN + DEX versus LEN + DEX in this sub-group (NE vs NE, HR 0.645; 0.409-1.017, p=0.0569). As highlighted within the ACD, the clinical experts stated that they would expect to see an OS benefit with ixazomib after longer follow-up (Section 3.10 of the ACD). The TOURMALINE MM-1 study remains double-blind to enable collection of mature OS results, with the 3rd IA and final OS analyses expected in 2017 and 2019, respectively. This clinical uncertainty, which can be addressed via combined with the additional planned analyses of OS, combined with the proposed Commercial Access Agreement with NHS England, makes ixazomib IXA + LEN + DEX a suitable candidate for inclusion within funding via the CDF (see Section 3.2.11 of this ACD response for further detail).

### 3.2.4 Discussion on the company's economic model: *"The model should use the most recent clinical data"* (response to Section 3.15 of the ACD)

***Company Response:***

We note the comment in Section 3.15 of the ACD that the committee deemed the economic model using the 1st IA dataset was acceptable for decision making, but would have preferred to see a model informed by the most recent clinical data for ixazomib. The most recent data is that from the 2nd IA (July 2015, 23 month follow up) which was used in a scenario analysis in the company's original submission.

The base case economic model has been updated for the patient population receiving 2/3 prior therapies to use more mature 2nd IA data for OS, PFS, ToT, health related quality of life (HRQoL), response status and resource use. This updated model provides updated results for the combined 2/3 prior therapy population versus LEN + DEX, and enables results for a scenario analysis in patients who have received 2 prior therapies versus LEN + DEX. Details of the updated data used within this model, which are based on the direct TOURMALINE-MM1 data and not from indirect comparisons, and the cost-effectiveness results with the current ixazomib PAS are provided in Appendix 1: "New evidence analyses" (with PAS); while the cost-effectiveness results with the proposed CAA with NHS England are provided in Appendix 2: "New evidence analyses" (with proposed CAA).

In Section 3.15 of the ACD it states that, based on ERG concerns, the committee was not convinced that the analysis (in the original company submission scenario analysis) using data from the 2nd IA was robust; the ERG stated that time constraints meant that they could not examine the robustness of the model submitted using data from the 2nd IA.

The updated model includes both data from the 1st IA and from the 2nd IA, with transparent user functionality to select from which dataset the OS, PFS, ToT or response data are sourced from. In addition to this, Takeda have been transparent in presenting all the survival analysis and goodness of fit statistics associated with the updated data in the Appendices. We believe the updated economic model can be considered a robust basis for the estimation of updated base case ICERs for IXA + LEN + DEX versus LEN + DEX in patients who have received 2/3 prior therapies.

### 3.2.5 Discussion of clinical effectiveness and clinical evidence in the economic model: *"Ixazomib may be more effective after 3 previous therapies than after 2 previous therapies"* (response to Section 3.12 of the ACD); *"Analyses after 3 previous therapies are uncertain"* (response to Section 3.13 of the ACD); and *"It is appropriate to use the data after 2 or 3 previous therapies to compare ixazomib with lenalidomide"* (response to Section 3.16 of the ACD)

***Company Response:***

The company does not agree with the committee's conclusion that it is biologically plausible for IXA + LEN + DEX to be clinically more effective in the sub-group of people who have had

3 previous therapies, compared with those who have had 2 prior therapies (i.e. more effective in 4th line than 3rd line). The committee's hypothesis is that triple therapy regimens are more effective than double therapy regimens in more heavily pre-treated populations. The committee asserts that this may explain the apparently better PFS hazard ratio for IXA + LEN + DEX versus LEN + DEX after 3 prior therapies compared with 2 prior therapies (Sections 3.2 and 3.12 of the ACD). In contrast, we believe it is much more likely that this apparent difference is actually an artefact due to the imbalance of key prognostic factors between the unstratified 3rd line and 4th line sub-groups, as illustrated in Table 2 below derived from the TMM1 study.

**Table 2: Distribution of known key prognostic factors in the unstratified sub-group of patients who had received 2 prior therapies (3rd line) or 3 prior therapies only (4th line patients).**

| | 2 prior therapies (3rd line alone) | | | 3 prior therapies (4th line alone) | |
|---|---|---|---|---|---|
| | **LEN+DEX N=111** | **IXA+LEN+DEX N = 97** | | **LEN+DEX N=34** | **IXA+LEN+DEX N = 39** |
| **Age** | | | | | |
| ≤ 65 years | 52% | 45% | | 41% | 46% |
| >65 and ≤75 | 31% | 39% | | 26% | 44% |
| >75 years | 17% | 15% | | 32% | 10% |
| **Cytogenetic risk** | | | | | |
| Standard | 67% | 53% | | 50% | 67% |
| High risk | 15% | 21% | | 26% | 18% |
| Not available | 18% | 27% | | 24% | 15% |
| **ISS stage** | | | | | |
| I or II | 91% | 89% | | 79% | 85% |
| III | 9% | 11% | | 21% | 15% |

Abbreviations: ISS: international staging system, IXA: ixazomib; LEN: lenalidomide; DEX: dexamethasone
Red (unfavourable) and green (favourable) text indicate imbalances in prognostic variables between arms

Source: IA2 CSR addendum

Randomisation, combined with appropriate stratification, is usually considered the 'gold standard' of clinical trial design as it minimises bias. In Section 3.13 of the ACD, the committee acknowledged the limitations of the ERG's *post-hoc* economic analysis of IXA + LEN + DEX in 3rd line only and therefore recognised the limitations of breaking randomisation/stratification. Limitations include potential imbalances in key prognostic factors between treatment arms which can confound the interpretation of trial results, as well as a reduction in the size of the sub-groups. Table 2 above shows the distribution of age, cytogenetic risk and International Staging System (ISS) stage in the unstratified 2 prior therapies alone and 3 prior therapies alone sub-groups within the TOURMALINE MM-1 trial. Older age, high-risk cytogenetics and ISS stage III disease are key negative prognostic factors in multiple myeloma that consistently predict reduced PFS and OS [3, 4] In the small sub-group of 3 prior therapies alone, it is evident that the LEN + DEX control arm has a much higher proportion of over 75 year olds (32% vs 10%), ISS stage III (21% vs 15%) and high-risk cytogenetics patients (26% vs 18%) compared to the IXA + LEN + DEX arm (Table 2). These negative prognostic factors will negatively impact the efficacy of the control arm and skew the PFS results and hazard ratio in favour of the IXA + LEN + DEX arm. In the 2 prior therapies only sub-group, the LEN + DEX arm has disproportionally more patients <65

years old (52% vs 45%) and with standard risk cytogenetics (67% vs 53%), factors which will positively bias the PFS result in favour of the LEN + DEX control arm. The disproportionate distribution of key prognostic factors that favour the LEN + DEX control arm in 2 prior therapies sub-group and conversely the IXA + LEN + DEX arm in 3 prior therapies sub-group is consistent with the committee's observation that the PFS hazard ratio for IXA + LEN + DEX is more favourable for patients receiving 3 prior therapies than those receiving 2 prior therapies. These *post-hoc*, unstratified results are therefore confounded and do not provide an accurate and unbiased representation of the efficacy gains with IXA + LEN + DEX within these lines of treatment.

In contrast, the benefit of randomisation within the stratified pooled sub-group for patients receiving 2/3 prior therapies has resulted in a more balanced distribution of age, cytogenetic risk and ISS stage across both arms, with no enrichment of negative prognostic factors across a specific arm (Table 3). Other unknown prognostic factors, such as LDH levels and *TP53* mutation status, will also benefit from randomisation within this combined subgroup, but not in the *post-hoc* 2 prior therapies only or 3 prior therapies only sub-groups. The stratified sub-group of patients treated at 3rd or 4th line therefore provides a more accurate and statistically robust determination of the relative efficacy and cost-effectiveness of IXA + LEN + DEX versus LEN + DEX.

**Table 3: Distribution of known key prognostic factors in the stratified sub-group of patients who had received 2/3 prior therapies (3rd and 4th line combined)**

| | 2/3 prior therapies pooled stratified sub-group | |
|---|---|---|
| | **LEN + DEX N = 149** | **IXA + LEN + DEX N = 148** |
| **Age** | | |
| ≤ 65 years | 48% | 46% |
| >65 and ≤75 | 33% | 39% |
| >75 years | 19% | 15% |
| **Cytogenetic risk** | | |
| Standard | 62% | 59% |
| High risk | 19% | 20% |
| Not available | 19% | 20% |
| **ISS stage** | | |
| I or II | 88% | 86% |
| III | 12% | 14% |

Abbreviations: ISS: international staging system, IXA: ixazomib; LEN: lenalidomide; DEX: dexamethasone

Source: IA2 CSR addendum

Finally, the sample size informing the results of the unstratified, *post-hoc* sub-group should be taken into account. The results of the 3 prior therapies only sub-group are informed by 34 and 39 patients in the LEN+DEX and IXA+LEN+DEX arms, respectively. Such small patient numbers result in wide 95% confidence intervals and are highly sensitive to outliers, this could further confound the likelihood of bias introduced by breaking randomisation/stratification. By contrast, the efficacy of the stratified, pooled 2/3 prior therapy sub-group is informed by 297 patients across both arms, thereby providing a more robust data set.

In conclusion, we do not agree that there is biological plausibility for IXA + LEN + DEX to be clinically more effective versus LEN + DEX in patients who were treated after 3 prior therapies compared to those treated after 2 prior therapies. It is evident that the small 3 prior therapies alone sub-group has wide PFS confidence intervals due to its small size and is significantly confounded by imbalances in key prognostic factors. These imbalances provide a clear and more plausible rationale for the apparent difference in PFS hazard ratios between 2 prior and 3 prior patient sub-groups for IXA + LEN + DEX versus LEN + DEX.

The stratified and balanced sub-group of 2/3 prior therapies both reflects the committee's preferred positioning of LEN + DEX in the UK treatment pathway and the company's requested positioning for IXA + LEN + DEX (i.e. for use in both 3rd and 4th line; see Section 3.2.1 of this ACD response), and is also a more statistically robust sub-group in order to model the base case cost-effectiveness of IXA + LEN + DEX versus LEN + DEX.

As Takeda no longer wish to position the use of ixazomib in patients who have received only 2 prior therapies (using the more robust 2/3 pooled pre-specified sub-group data as proxy data for this positioning), but wish to be considered for a recommendation in patients who have received either 2 or 3 prior therapies, the 2/3 prior therapy pooled data represents the appropriate data to support this positioning. However, in Section 3.16 of the ACD in reference to the clinical evidence used in the economic model the committee has expressed a preference for a scenario analysis in patients who have received 2 prior therapies only, adjusting for different baseline characteristics, to *"ensure that the average cost-effectiveness estimates across both subgroups (2 previous and 3 previous therapies) represent the cost-effectiveness estimates within the subgroups".* Although this is no longer an essential analysis for the positioning sought of 2/3 prior therapies, which represents the base case in our updated economic analysis, we have performed a scenario analysis to explore cost-effectiveness of IXA + LEN + DEX versus LEN + DEX in the 2-prior therapy only sub-group, adjusted for differences in baseline characteristics. These results are presented to provide supportive evidence and re-assurance that cost-effectiveness is not worse in this sub-group compared to the 2/3 prior therapy patient population combined. This new analysis also provides supportive evidence for using the more robust 2/3 prior therapy data to evaluate the cost-effectiveness of the ixazomib regimen versus LEN + DEX in patients receiving 2/3 prior therapies. This scenario analysis is covered in the new evidence analyses included in Appendices 1 and 2. Analysis in a 3 prior therapies only patient population would not be meaningful due to the small number of patients in this sub-group of the TOURMALINE-MM1 trial.

### 3.2.6 *"*Discussion on Health-related quality of life: *"It is unreasonable to assume better health-related quality of life after disease progression than for stable disease"* (response to Section 3.19 of the ACD); and

### *"Utility estimates in the model are uncertain"* (response to Section 3.20 of the ACD)

***Company Response:***

We understand the committee's concern that the marginally higher utility value for progressed disease compared to stable disease would seem to lack clinical plausibility (Section 3.19 of the ACD). The committee acknowledged the feedback from clinical experts supporting that they would not expect to see an immediate reduction in HRQoL for people with progressed MM due to disease progression often being diagnosed based on biochemical changes, while people do not show symptoms until later. In the economic model, we applied a utility decrement associated with progressed disease 3 months prior to death; utility was constant in the progressed disease health state before this. However, the committee did not consider that a constant utility value up to this timepoint was plausible, but instead considered that there is a continual quality of life decline from the point at which when a patient has clinical progression.

In response to the committee's concerns, we have now updated the analysis of EQ-5D data used for the estimation of the progression free health state (based on very good partial response/complete response, partial response, stable disease utility) and the progressed disease state using the most mature dataset from TOURMALINE-MM1 (2nd IA). The use of the 2nd IA dataset is also to address the ERG's concern that basing the HRQoL regression analysis on the 1st IA may cause bias (with unknown direction), and that analysis based on the 2nd IA will have more data (based on a longer follow-up period) and should provide more robust estimates, particularly for the progressive disease state (see page 204 of the ERG report).[5] In addition, we have addressed the concerns raised in Section 3.20 of the ACD regarding the robustness of the original EQ-5D regression analysis, by including additional demographic variables such as a patient's age, gender and race, as well as adjusting for a patient's overall response assessment which was recorded at the same time as when the EQ-5D response was measured in the TOURMALINE-MM1 trial, rather than being based on a patient's best overall response.

The new results using the updated EQ-5D data are presented and discussed in Appendix 1: "New evidence analyses" (with PAS) and in Appendix 2: "New evidence analyses" (with proposed CAA). This updated analysis indicates a lower utility associated with progressed disease compared with stable disease (see Appendices).

To provide supportive evidence for the utility values used, we have also looked further into the pattern of HRQoL over time in patients with RRMM by conducting further analysis of the EQ-5D data according to "time to death", as an alternative approach to using markers of response and disease progression for HRQoL/utility estimation. As noted in the ACD, there are limitations with using biochemical disease progression for utility estimation, and in addition one of the reasons why there appears to be relatively high progressive disease utility is that the EQ-5D is measured in TOURMALINE-MM1 at a time point only shortly after disease progression, meaning that it may not reflect HRQoL over time. The analysis of utility according to time to death provides an alternative approach that better takes into account HRQoL changes over time as a patient 'progresses' towards death, and has been used in previous submissions to NICE in cancer (e.g. ipilimumab in malignant melanoma

pembrolizumab in NSCLC)[6, 7]. The analysis we have conducted is supportive of patients experiencing a reasonably stable/slightly declining HRQoL from >12 months until the last 3, at which point, a steeper decline in HRQoL is observed (i.e. in the final 3 months prior to death). This is similar to the pattern found using this approach in the analysis of EQ-5D data by time to death for ipilimumab in malignant melanoma.[8] In addition, a clinical expert advisory board was held by Takeda in May 2017 at which the clinical experts provided support that the HRQoL of patients with RRMM does not usually decline significantly until about 3 months before death because patients would continue to receive active treatments that can relieve symptoms and help maintain a relatively stable HRQoL. Full details of the time to death analyses and the clinical experts feedback are provided in the Appendices of new evidence analyses.

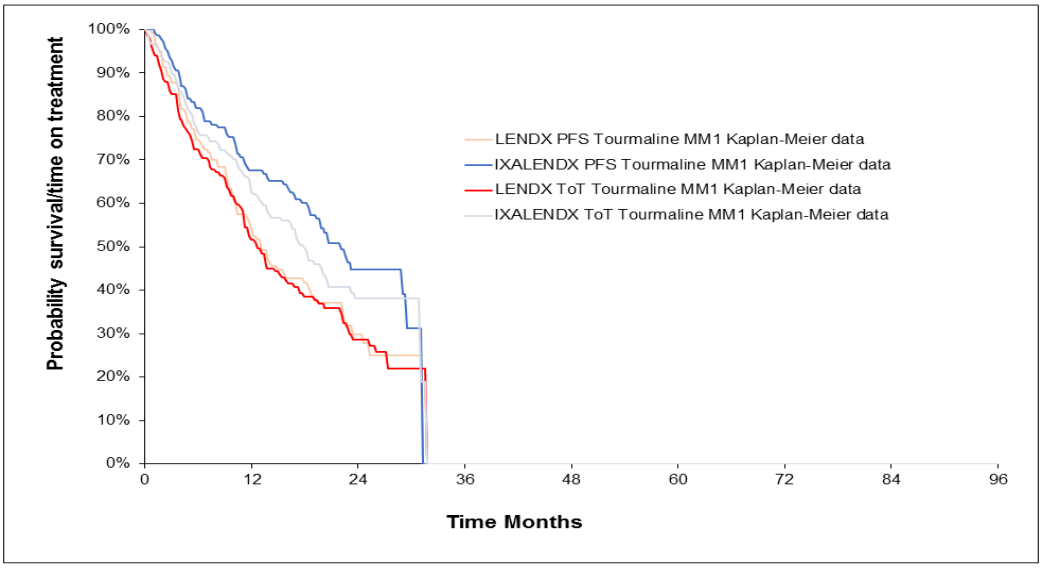
### 3.2.7 Discussion on costs: *"Extrapolating duration of treatment from TOURMALINE-MM1 trial underestimates treatment costs in the model"* (response to Section 3.21 of the ACD)

***Company Response:***

The company disagrees with the committee's conclusion that it is implausible for the ratio of ToT to PFS to be lower for RRMM patients receiving IXA + LEN + DEX than it is for patients receiving LEN + DEX (Section 3.21 of the ACD). Takeda also disagree with the committee's preferred assumption to use the extrapolation of PFS to model treatment costs instead of using ToT (Section 3.25 of the ACD). Treatment with LEN + DEX or IXA + LEN + DEX within the TOURMALINE MM-1 study was until disease progression or unacceptable toxicity. As discussed by the UKMF experts present at the NICE AC meeting on 29th March 2017, although there is the clinical intent to treat until progression, patients can and often will terminate therapy before progression for reasons other than disease progression, including for example patient or clinician choice and intolerance to therapy.[9] To model ToT using PFS is to assume that, without exception, all patients treated with IXA + LEN + DEX will stay on therapy until disease progression and never stop early due to non-progression related factors such as patient choice or adverse events. Based on feedback we have had from a number of clinical experts in multiple myeloma, this is clinically implausible and will significantly overestimate treatment costs for IXA + LEN + DEX. According to the clinical experts we have consulted, it is normal for ToT to be less than PFS for medicines that are used in RRMM. It is well established in multiple myeloma that response to a fixed duration therapy is maintained for a period of time beyond treatment cessation, thereby leading to a treatment-free interval before disease progression [10, 11]

Moreover, within the latest observed data from the TOURMALINE MM-1 trial (2nd IA cut-off), it is evident that even without any extrapolation, the ToT for IXA + LEN + DEX is consistently less than the PFS and that this difference is proportionately greater for IXA + LEN + DEX than it is for the LEN + DEX control arm (Figure 1). The addition of ixazomib to LEN + DEX does therefore result in an observed difference in ToT versus PFS and this is not an implausible result arising from extrapolation.

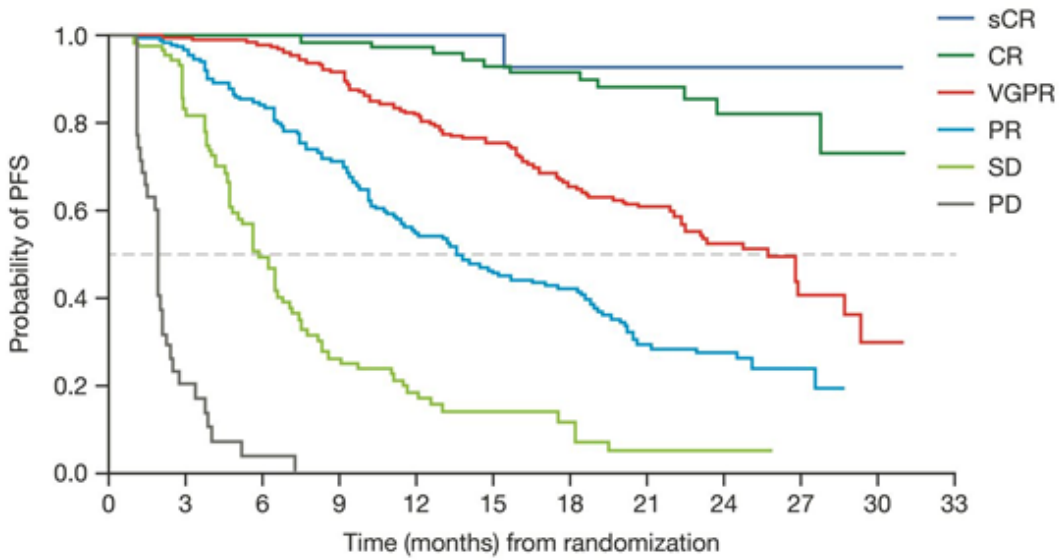
**Figure 1: TOURMALINE MM-1 PFS and ToT relationship in the stratified 2/3 prior therapies sub-group (2nd IA data cut)**




Key: IXALENDX, ixazomib + lenalidomide + dexamethasone; LENDX, lenalidomide + dexamethasone; PFS, progression free survival; ToT, time on treatment

The observed ratio of ToT to PFS being lower for RRMM patients receiving IXA + LEN + DEX than LEN + DEX is likely due to the higher quality (deeper) clinical responses observed on the triplet regimen translating into prolonged remissions, following early treatment cessation. In the TOURMALINE MM-1 trial, the depth of response to therapy was directly correlated with PFS, with a response of ≥VGPR leading to particularly significant remissions (Figure 2). In the stratified sub-group of patients who had received 2/3 prior therapies (3rd and 4th line), the addition of IXA to LEN + DEX was associated with significantly more responses (80.4% versus66.4%, OR: 2.09 (1.23, 3.56), p=0.006), more ≥VGPRs (54.1% versus 36.2%, odds ratio (OR): 2.08 (1.31-3.33), p=0.002) and a three-fold increase in complete responses (18.2% versus6.7%, OR: 3.18 (1.47-6.89), p=0.003). Therefore, if a patient discontinues therapy early due to patient choice or an adverse event, the more frequent and higher quality responses seen with IXA + LEN + DEX will logically lead to a longer treatment-free interval before eventual relapse. This was also observed in the PANORAMA-1 trial where, despite the median duration of therapy for PANO + BORT + DEX being less than the BORT + DEX control arm (5.0 versus 6.1 months, respectively), PANO + BORT + DEX was associated with a significant ~4 month extension of PFS (11.99 versus 8.08 months, p<0·0001).[12] The longer PFS observed in the PANO + BORT + DEX group was likely due to the higher quality of the observed responses in this group, as evidenced by the higher rate of mCR/CR (27.6% versus15.7%).[13]

**Figure 2: Relationship between depth of response and PFS in TOURMALINE MM-1[14]**




Key: CR, complete response; PD, progressive disease; PFS, progression free survival; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response

In conclusion, the increase in time spent off treatment in a progression-free state with the IXA + LEN + DEX triplet combination versus the LEN + DEX control arm was observed directly within the TOURMALINE-MM1 trial data and can be clinically explained by the increased number of high quality responses with IXA + LEN + DEX. The proposal to model ToT using PFS would therefore significantly overestimate treatment costs for IXA + LEN + DEX and directly contradict evidence-based results from the pivotal RCT. We believe it is appropriate to model ToT and PFS independently and we would note that such an approach is consistent with the statement made by the NHS commissioning expert at the NICE AC meeting on 29th March 2017 that *"time on treatment is usually the preferred way to model treatment costs"* (Section 3.21 of the ACD). Due to data immaturity, there is inevitable uncertainty about how this difference will be maintained over time. As discussed further in Section 3.2.12 of this response, an appropriate period of time in the CDF for ixazomib will enable further data collection for ToT to address this key area of clinical uncertainty.

### 3.2.8 Discussion on costs: *"Costs of treatments taken after disease progression should be modelled weekly"* (response to section 3.22 of the ACD)

***Company Response:***

In response to comments in the ACD (Section 3.22), we have updated the way the economic model accounts for post-progression treatment costs. The updated model considers a weekly cycle cost for the duration of time in post-progression, as well as a one-off cost applied to patients upon transition to the post-progression health state. These costs are applied to all patients receiving active subsequent therapy. This approach is in line with suggestions provided by the ERG in the ERG report. Furthermore, the error identified by the ERG associated with the proportion of patients receiving subsequent treatment has been

corrected and updated using the 2nd IA and 2/3 prior therapies data. Further details of the modification to the model are provided in the Appendices of new evidence analyses.

### 3.2.9 Discussion on results: *"Ixazomib is not recommended for people who have had 2 or 3 prior therapies"* (response to Section 3.25 of the ACD)

***Company Response:***

In clinical practice it is expected that IXA + LEN +DEX in the RRMM treatment pathway will be used in patients who have had 2/3 prior therapies as an alternative to LEN +DEX alone. Hence, Takeda wish for ixazomib to be considered for this use in this position rather than in patients who have received only 2 prior therapies, which was the requested positioning in our original submission. The base case in the updated economic model now consists of an assessment of the cost-effectiveness of IXA + LEN +DEX versus LEN + DEX in patients who have had 2/3 prior therapies. A number of modifications and updates have been made to the model which have been summarised above in Section 3.1 of this response. The changes are in response to issues raised in the ACD, such that we now believe we have a model and analysis that provides a robust base for determining the most plausible ICER for ixazomib in the 2/3 prior therapy patient population. The results of the updated economic model are presented in Appendix 1 applying the current PASLU/DH approved PAS for ixazomib (a simple discount of [redacted] on the NHS list price), and in Appendix 2 applying the proposed and significantly enhanced CAA with NHS England (combination of a cycle/time cap at [redacted] cycles/months and a cost that equates to [redacted] per ixazomib capsule which is a price discount of [redacted] on the NHS list price). The updated economic analysis provides a robust base for applying the PAS/CAA. In Appendix 2, it can be seen that the improved commercial offering which this represents results in an ICER that we believe supports a case for ixazomib to be considered plausibly cost-effective (particularly in light of NICE's apparently revised end of life guidance for combination regimens), and therefore justifies its inclusion within the CDF (see Section 3.2.11 and 3.2.12 of this response below).

### 3.2.10 Discussion on results: *"The cost-effectiveness of ixazomib compared with panobinostat, after 3 therapies, is uncertain"* (response to Section 3.26 of the ACD)

***Company Response:***

As discussed in Section 3.2.2 of this ACD response, despite having similar positioning in respect of NICE guidance, LEN + DEX will always be used earlier in the treatment pathway than panobinostat (as the PANO + BORT + DEX regimen), thus placing PANO + BORT + DEX into a subsequent line of therapy

Given that PANO + BORT + DEX will always be used later than IXA + LEN + DEX, it would be inconsistent with clinical expert opinion and somewhat unusual to consider PANO + BORT + DEX as a direct and relevant comparator to IXA + LEN + DEX. In addition, it is expected that any indirect treatment comparison of IXA + LEN + DEX versus PANO + BORT + DEX in patients who have received 3 prior therapies would lack robustness due to the lack

of publicly available data for panobinostat in these patients, and the small number of patients in the 3 prior therapy sub-group for ixazomib (see Section 3.25 of this response). Hence, a comparison would need to be based on 2+ prior therapy data for panobinostat (and also for ixazomib), which would not be representative data for the use of panobinostat in clinical practice, and the NICE preferred analysis in patients with 3 prior therapies.

### 3.2.11 Discussion on End of Life "Ixazomib does not meet the end of life criteria" (response to Sections 3.27 of the ACD)

***Company response:***

To be considered an end-of-life (EoL) therapy by NICE, traditionally a regimen must satisfy the following two criteria:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and

-There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.[15]

Focusing on the RRMM population who have had 2 or 3 previous therapies (i.e. 3rd and 4th line use), in Section 3.27 of the ACD the committee concluded that although ixazomib has the potential to meet the second EoL criterion for extension to life, it was not considered to be an EoL therapy because the first criterion, of short life expectancy, was not met.

Recently, Takeda has become aware that NICE has apparently issued a further qualification to its Appraisal Committee's on the EoL criteria and has given its committees more discretion over the application of these EoL criteria. As we understand it, the qualification relates specifically to combination regimens where a new medicine undergoing a NICE appraisal is used in combination with an existing medicine. This clarification has not yet been published by NICE due to the "purdah" period associated with the upcoming UK General Election which takes place on 8th June 2017; but we understand that it will be published after the purdah is lifted. However, we believe the revised EoL criteria have already been applied during the NICE Appraisal Committee A meeting on May 9th 2017 which discussed the appraisal of perutuzumab in combination with trastuzumab [ID523].[16]

According to the revised criteria for combination regimens, we believe the Appraisal Committee has discretion to apply the EoL criteria to technologies under appraisal if they satisfy the following criteria:

- The treatment is indicated for patients with a life expectancy normally more than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment[15]
- The new treatment is given in combination with an existing treatment and;
- Both treatments are licensed to be administered until disease progression

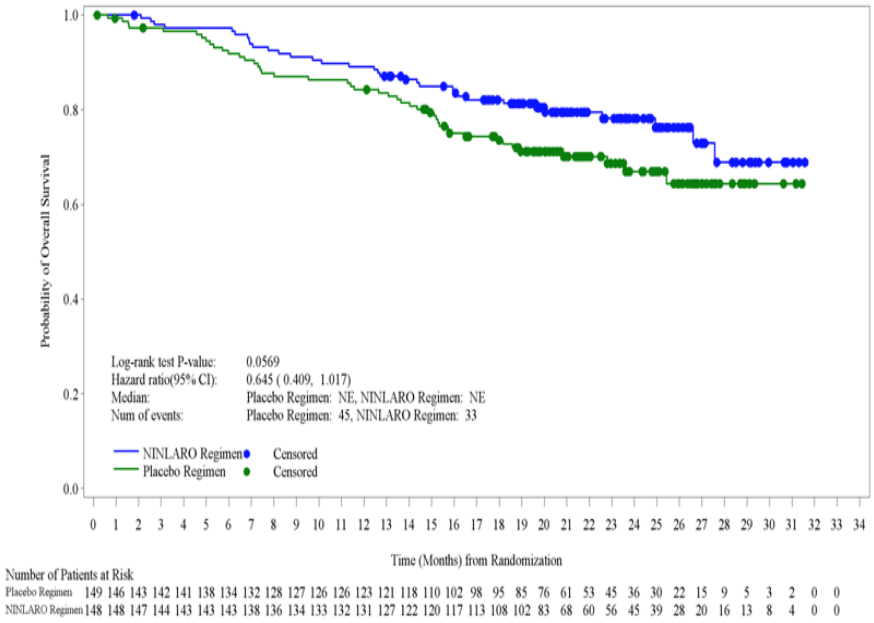
The company would like the Appraisal Committee to consider the IXA+LEN+DEX regimen under the revised EoL criteria for combination regimens. If a new technology meets the revised EoL criteria, then we believe the committee has the discretion to consider £50,000 per quality adjusted life year (QALY) as the cost-effectiveness threshold for the new technology.

In Section 3.27 of the ACD, the committee noted that the modelled OS with LEN + DEX in RRMM patients after two or more prior therapies was 3.6 years and that this was consistent with other NICE technology appraisal guidance for treatments at this stage of RRMM. The company agrees that the normal life expectancy for 3rd and 4th line RRMM patients is more than 24 months, which meets the first of the revised EoL criteria for combination regimens. In Section 3.27 of the ACD, the committee stated that ixazomib has the potential to meet the criterion of extension of life (normally defined as at least 3 additional months), as stipulated in both the original and revised EoL criteria. As stated in Section 3.27 of the ACD, the committee considered that the modelled OS benefit and incremental QALY gain with ixazomib would suggest that it has the potential to extend life, but agreed that these results were uncertain.

The company recognises that the modelling is based on immature data and acknowledges the committee statement that the modelled extension of life benefit is uncertain. However, the company firmly believes that the modelled OS benefit in the 2/3 prior therapies sub-group will be realised with the maturation of the OS data from the TOURMALINE-MM1 trial.

The latest follow-up data in the 2nd IA of TOURMALINE-MM1 demonstrated a strong trend towards an OS benefit for IXA + LEN + DEX in patients who have had 2 or 3 previous therapies, which is the relevant sub-group for the EoL consideration as stated in Section 3.27 of the ACD. The Kaplan-Meier curve demonstrating the latest analysis of OS at the 2nd IA for the population under consideration is shown in Figure 3. The OS hazard ratio for IXA + LEN + DEX compared to LEN + DEX was 0.645, with a 95% confidence interval of 0.409 to 1.017. Although the company recognises that these results are immature and the OS benefit has not yet reached statistical significance, we would like to highlight that the top end of the 95% confidence internal is only slightly above 1 and thus is very close to reaching statistical significance. It is therefore highly plausible that a statistically significant OS benefit will emerge as the data matures (3rd IA estimated to become available in Q4 2017, with the final analysis of OS before the end of 2019).

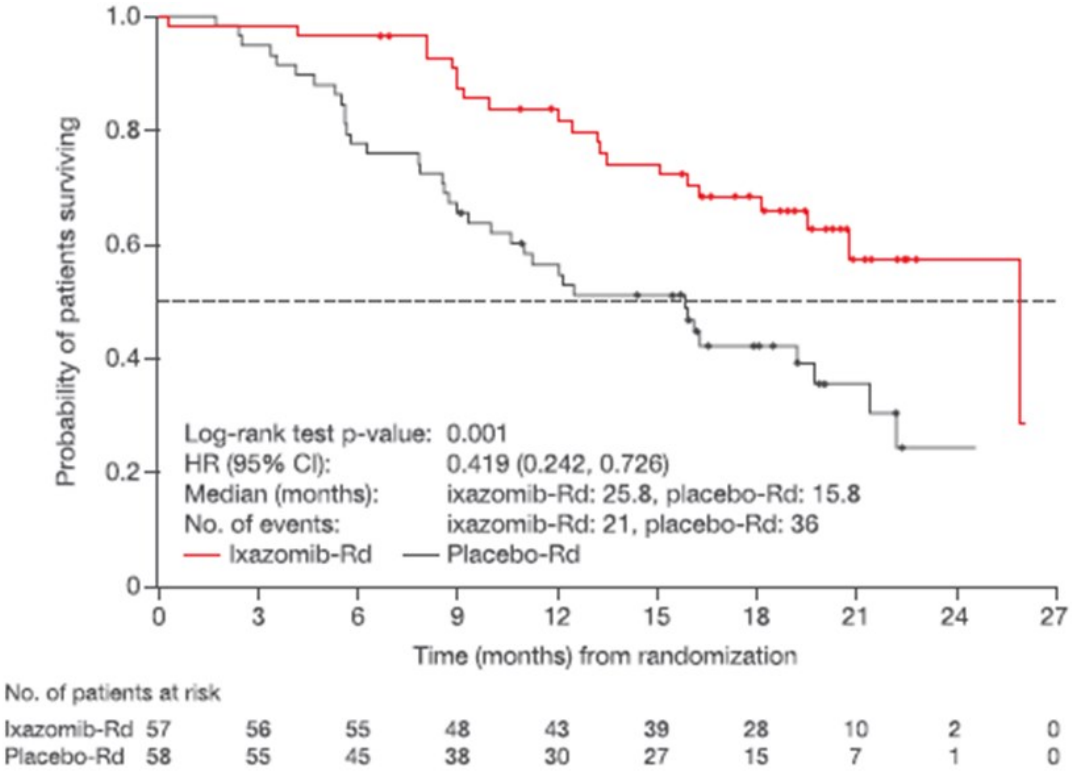
**Figure 3: TOURMALINE MM-1: OS (2nd IA) in the stratified sub-group of patients who had received 2/3 prior lines (3rd and 4th line)**




Key: CI, confidence interval; NE, not estimable

To further support that the currently modelled OS benefit of ixazomib can plausibly be realised, we would point to the recently presented OS results from the China Continuation Study. This study (included within Appendix 4 of the original company submission in December 2016) was a regional extension of the TOURMALINE-MM1 study (n=115) that evaluated the safety and efficacy of IXA + LEN + DEX versus LEN + DEX in adult RRMM patients from China.[17] The results of the China Continuation Study showed an OS benefit for IXA + LEN + DEX compared with LEN + DEX in patients who have received more than 1 previous therapy (i.e. the ITT population). The results shown below in Figure 4 are based on mature data and demonstrate a median OS of 25.8 months for IXA + LEN + DEX versus15.8 months for LEN + DEX (HR=0.419, 95% CI 0.242, 0.726, p=0.001) for the ITT population. The absolute life extension demonstrated in the China Continuation Study is approximately 10 months, which meets and exceeds the 3-month life extension criterion included as part of NICE's EoL criteria. Furthermore, a 10-month life extension is a clinically meaningful benefit that would be recognised as such by the clinical community and, most importantly, by patients and their families.

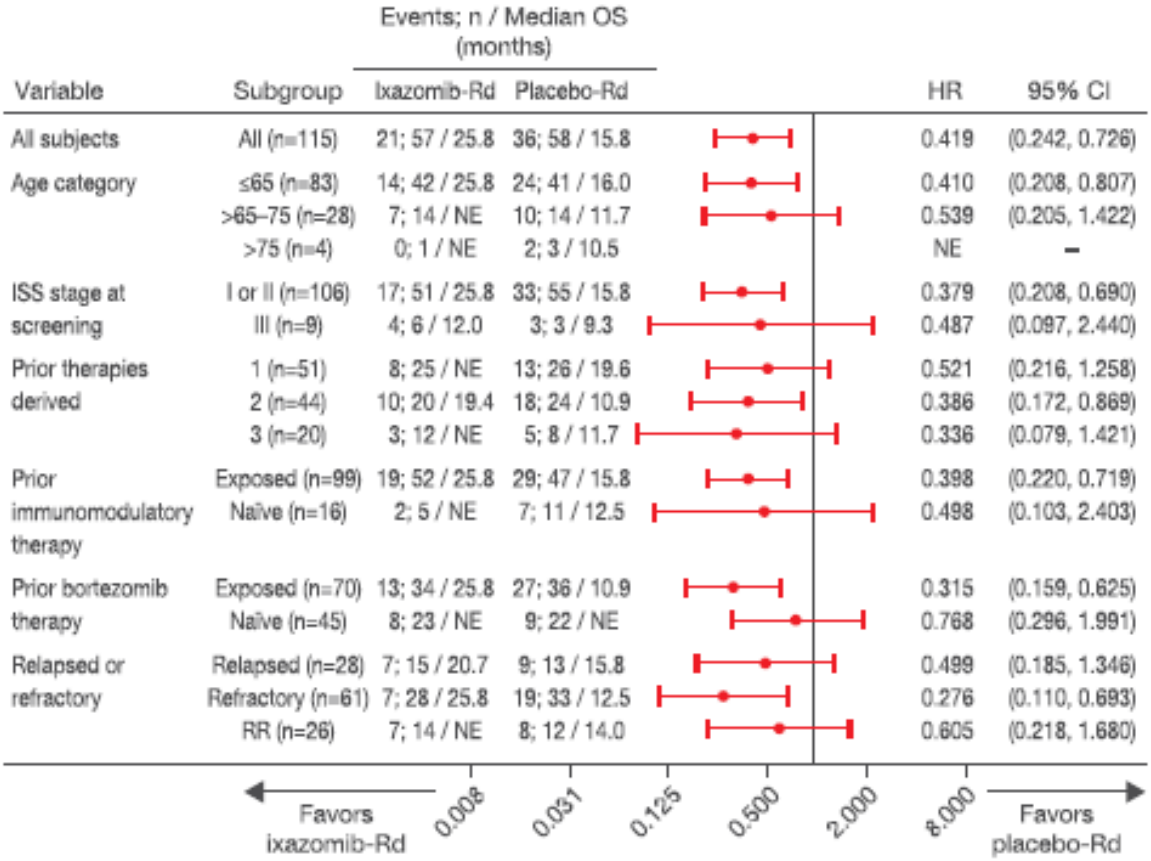
**Figure 4: China Continuation Study final OS analysis (ITT population)**




Key: CI, confidence interval; HR, hazard ratio; No., number; Rd, revlimid + dexamethasone

The OS benefit demonstrated in the ITT population of the China Continuation Study for RRMM patients who have received more than 1 previous treatment is also seen in patients who have received 2 or 3 prior therapies. The forest plot in Figure 5, shows that IXA + LEN + DEX had a median OS benefit of 19.4 months versus10.9 months (HR 0.386, 95% CI 0.172-0.869) for patients with 2 prior therapies and NE versus 11.7 months (HR 0.336, 95% CI 0.079-1.421) for patients with 3 prior therapies compared to LEN + DEX. We would like to point out to the committee that the sample size of the unstratified sub-groups or 2 or 3 prior therapies when considered alone is small and subject to uncertainty, particularly the 3 prior therapies unstratified sub-group which included only 20 patients.

**Figure 5: The China Continuation Study OS Forest Plot**




Key: CI, confidence interval; HR, hazard ratio; ISS, international staging system; n, number; NE, not estimable; OS, overall survival; Rd, revlimid + dexamethasone; RR, relapsed refractory

The company recognises that the patient characteristics differ between the China Continuation Study and the TOURMALINE-MM1 trial and that the studies are therefore not likely to yield identical results. However, the company felt it would be relevant for the committee to be aware of the final results of the China Continuation Study as it was cited in Section 3.28 of the ACD as a potential source of data to address the uncertainty of the OS benefit with ixazomib. The final results of the China Continuation Study demonstrated a statistically significant OS benefit for IXA + LEN + DEX for the ITT population, with patients living approximately 10 months longer. This final data set supports that it is clinically plausible that the trend towards an OS benefit seen in the 2nd IA of TOURMALINE-MM1 is likely to become statistically significant over time.

IXA+LEN+DEX is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. The marketing authorisation for the IXA + LEN + DEX regimen granted by European Medicines Agency states that treatment should be continued until disease progression or unacceptable toxicity.[18] The marketing authorisation of ixazomib therefore satisfies the third and fourth criteria of what we understand are the revised EoL guidance whereby a new treatment must be used in combination with an existing treatment, and both treatments should be continued until disease progression.

Based on all of the above, the company would like to request that the committee considers the IXA + LEN + DEX regimen for the recently revised EoL criteria for combination regimens. Takeda believes that three of the four EoL criteria (i.e. criteria 1, 3 and 4 on life expectancy, combination medicines and treatment to progression) are already objectively met and/or agreed upon. In the ACD, the committee suggests that ixazomib has the potential to meet the second criterion, requiring the regimen to extend life by three months. The company strongly believes that a statistically significant OS benefit will be demonstrated in the 2/3 prior therapies sub-group (i.e. the population where ixazomib would be used), on further maturation of the OS data from the ongoing TOURMALINE-MM1 trial. As discussed, the latest analysis of TOURMALINE-MM1 (i.e. the 2nd IA) showed a strong trend towards an OS benefit in this sub-group, with the top end of the 95% confidence interval being just slightly above 1. The plausibility for further follow-up demonstrating a statistically significant OS benefit in TOURMALINE-MM1 is further supported by the statistically significant OS benefit recently seen in the China Continuation Study, where the IXA + LEN + DEX triplet regimen extended life by approximately 10 months in the ITT population. A period of time in the CDF would allow patients in England to access ixazomib while the OS data from the TOURMALINE-MM1 trial matures.

### 3.2.12 Discussion on Cancer Drugs Fund: *"Ixazomib does not meet the criteria to be included in Cancer Drugs Fund"* (response to Sections 3.28 to 3.30 of the ACD)

***Company Response:***

In the initial company submission, Takeda requested that ixazomib (as the IXA + LEN + DEX triplet regimen) be considered for the CDF because some of the key data from the TOURMALINE-MM1 trial that drives the cost-effectiveness analysis, namely OS and ToT, are both immature. In Section 3.28 of the ACD, the committee *"agreed that there is uncertainty about the clinical benefits of ixazomib, particularly for overall survival"*. The committee further *"recognised that the survival data are immature and that median survival with ixazomib has not been reached in the TOURMALINE-MM1 trial"*. The committee also noted that *"additional survival analysis from TOURMALINE-MM1 will be available by 2019 and that the final survival analyses from another study (the China continuation study) will be available in 2017"*. Consequently, in Section 3.30 of the ACD, the committee agreed with Takeda that *"additional data collection has the potential to reduce the uncertainty about the clinical benefits of ixazomib"*.

As discussed in Section 3.2.11 of this ACD Response, the latest follow-up data in the 2nd IA of TOURMALINE-MM1 demonstrated a strong trend towards an OS benefit for IXA + LEN + DEX in patients who have had 2/3 previous therapies. We reiterate that Takeda feel it is highly plausible that a statistically significant OS benefit will emerge as the TOURMALINE-MM1 data matures (3rd IA estimated to become available in Q4 2017, with the final analysis of OS before the end of 2019). The impact of a positive OS benefit could be very significant in terms of both reducing the size of the ICER and also increasing the robustness of the ICER estimate.

In addition, we would also note that the OS results from the China Continuation Study were recently presented at the 16th International Myeloma Workshop (IMW) in March 2017 (these

have been included in this ACD response in Section 3.2.11 ). The results of the China Continuation Study showed a clinically meaningful OS benefit of approximately 10 months for IXA + LEN + DEX compared with LEN + DEX in patients who have received more than 1 previous therapy (median OS of 25.8 months versus15.8 months, respectively; HR=0.419, 95% CI 0.242, 0.726, p=0.001). The China Continuation Study therefore provides supportive evidence that a significant OS benefit is likely to emerge over time in the ongoing TOURMALINE-MM1 trial.

Takeda agrees with the committee that ixazomib would benefit from additional data collection/data maturation in the TOURMALINE-MM1 trial, and that this has the potential to reduce the uncertainty about the clinical benefits of ixazomib, thereby meeting the first criterion for entry into the CDF. However, the committee noted in Section 3.30 of the ACD that the cost-effectiveness estimates for ixazomib that were originally submitted by the company are *"substantially above the range normally considered to be a cost-effective use of NHS resources, and did not consider it likely that reducing the clinical uncertainty would sufficiently reduce the ICERs"*. The committee did not see any *"plausible potential for ixazomib to satisfy the criteria for routine use at its current price"*, thus failing the second criterion for the CDF. Hence, the committee concluded in Section 3.31 of the ACD that *"ixazomib does not meet the criteria to be included in the CDF"*.

In order to address this issue and to provide a route through which the committee could recommend ixazomib for inclusion in the CDF, Takeda has been in positive discussions with NHS England regarding the outline of a proposed CAA for ixazomib which would become active if ixazomib is recommended by NICE for inclusion within the CDF. The proposed CAA is intended to both address uncertainty regarding the cost-effectiveness of ixazomib (via the inclusion of a cycle/time cap for ixazomib) and to reduce the ICER to a level that shows plausible potential for cost-effectiveness in the 2/3 prior therapies sub-group at the relevant threshold (via the combined effect of the cycle/time cap and a reduced net price arising from a rebate mechanism). As stated, the inclusion of a cycle/time cap not only improves the ICER but it also reduces uncertainty regarding the duration of therapy, a concern that was discussed by the committee in Section 3.21 of the ACD and is addressed further by Takeda in Section 3.2.6 of this response document. The impact of the proposed CAA on the cost-effectiveness of ixazomib is described in Appendix 2 of this response document.

Based on the above, Takeda would like the committee to reconsider ixazomib for inclusion in the CDF. The proposed CAA reduces the ICER to a level that is plausibly cost effective (see Appendix 2), particularly if the revised EoL criteria for combination regimens (see Section 3.2.10 of this response) are applied (i.e. at a £50,000/QALY threshold), thus meeting the second criterion for the CDF. In addition, based on the current trend towards a significant OS benefit for IXA + LEN + DEX in the population under consideration (i.e. RRMM patients who have had 2 or 3 prior therapies), Takeda believes strongly that the level and certainty of the ICER for ixazomib will improve further as this survival data matures. By the end of the CDF period, it is likely that the cost-effectiveness of ixazomib will be firmly below the threshold that is considered a cost-effective use of NHS resources. A recommendation for inclusion within the CDF would permit Takeda and NHS England to complete their discussions and reach a mutually acceptable CAA that would allow patients and the NHS in England to benefit from having early access to an effective and simple all-oral triplet that uniquely combines a proteasome inhibitor and an immunomodulatory agent.

## 3.3 Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

***Company response:***

In conclusion, Takeda disagrees that the committee's provisional negative recommendation for ixazomib is sound and a suitable basis for guidance to the NHS (Section 3.35 of the ACD), particularly in relation to the CDF where we believe the ixazomib regimen is a strong fit.

Takeda agrees with the committee that the main population relevant to the ixazomib appraisal are RRMM patients who have had 2 or 3 prior therapies as this reflects the expected use of ixazomib (i.e. as 3rd or 4th line therapy in combination with lenalidomide and dexamethasone as the IXA + LEN +DEX regimen). The company has therefore focused its ACD response and all new analyses on this patient population.

- The committee, clinical experts and Takeda all agree that the IXA + LEN + DEX triplet regimen will be used in the same line of therapy as the LEN + DEX doublet is currently used in the UK. Hence, it is agreed by all parties that the predominant use of IXA + LEN + DEX will be after 2 prior therapies (3rd line) with minor usage after 3 prior therapies (4th line) in a small number of patients who have not received lenalidomide in earlier lines. Therefore, the most robust data on which to base an appraisal of cost-effectiveness is the stratified, balanced sub-group of 2 or 3 prior therapies from the TMM-1 trial. The addition of IXA to LEN + DEX resulted in a statistically significant 9 month improvement in PFS (HR: 0.62, 95% CI 0.45-0.86) compared to LEN+DEX in patients with 2/3 prior lines of therapy in the 2nd IA, a result which is consistent with that seen in the 1st IA. An exploratory analysis of the unstratified 3rd line only patient sub-group, adjusted for patient characteristics, shows similar cost-effectiveness results versus LEN + DEX as the stratified 3rd and 4th line sub-group, further supporting the clinical and cost-effectiveness of the IXA + LEN + DEX regimen in this setting.

- The company does not agree with the committee's assertion in Section 3.10 of the ACD that panobinostat, given as the panobinostat + bortezomib + dexamethasone (PANO + BORT + DEX) regimen is a relevant comparator for patients who have had 3 prior therapies. Clinical experts opinion is that PANO + BORT + DEX is reserved for later lines of therapy in select patients only and is used after LEN + DEX. Given that PANO + BORT + DEX will always be used later than IXA + LEN + DEX, it would be inconsistent with clinical expert opinion and clinical practice to consider the panobinostat regimen as a direct and relevant comparator to IXA + LEN + DEX. Hence, the company has not included PANO + BORT + DEX as a comparator for IXA+LEN+DEX in either the 3rd or 4th line setting.
- Takeda agrees with NHS England that the most appropriate method to analyse duration of therapy on ixazomib is the time on treatment (ToT) approach. Although the clinical intent is for treatment until disease progression, this is not often achieved in clinical practice due to factors such as patient or clinician choice or intolerance to therapy. This trend is seen in the TMM-1 trial where ToT was

consistently less than PFS in the observed data for IXA + LEN + DEX and LEN+DEX; although the difference was proportionally greater in the ixazomib arm due to the achievement of a deeper response with a triplet versus a doublet which induces a longer progression free state after termination of treatment.

- In response of the committee's request, the most mature data available from the TMM-1 trial (i.e. 2nd IA) was used in the updated economic analysis presented in this response. The cost-effectiveness results using the 2nd IA in this setting was similar to the results using the 1st IA, which further supports the certainty of the ICERs presented. The 2nd IA data demonstrated a maintained 9 month improvement in PFS for IXA + LEN + DEX compared to LEN + DEX in the 2/3 prior therapies group. There was also a strong trend towards an overall survival benefit, nearly reaching statistical significance at the 2nd IA. An abstract submitted to the European Haematology Association, reporting on the experience of 30 Named Patient Program (NPP) patients from UCH London who have received IXA + LEN + DEX as 3rd or 4th line treatment, showed an overall response rate of 70.8% [19]. This early analysis of the UK real world experience with ixazomib through the NPP demonstrated similar results to the TMM-1 trial, challenging the committee's conclusion that the clinical benefit of ixazomib is uncertain.
- The need for an all-oral, effective novel treatment option for RRMM is evident through the significant number of patients in the UK who have been enrolled on the NPP. In Section 3.34 of the ACD, the patient expert and committee recognised the benefit of an oral regimen for patients; however the further benefit as a resource advantage to the NHS (with minimal implementation burden to an already stretched system) should also be noted.
- Takeda reaffirms its request in the original submission that ixazomib be considered for inclusion with the Cancer Drug Fund (CDF). Takeda agrees with the committee that ixazomib would benefit from additional data collection/data maturation in the TMM-1 trial, and that this has the potential to reduce the uncertainty about the clinical benefits of ixazomib, thereby meeting the first criterion for entry into the CDF. Takeda also recognises that the ICERs in the current ACD are too high to be considered a cost-effective use of NHS health care resources in England and Wales, or to meet the criterion of plausible cost-effectiveness in order to qualify for consideration for the CDF.

- However, based on the information and analyses contained within this ACD response, Takeda request that the committee reconsiders ixazomib's eligibility for both the end of life criteria (applying what we understand are newly revised criteria for combination regimens) and also the CDF.

- In order to provide a route through which the committee could recommend ixazomib for inclusion in the CDF, Takeda has been in positive discussions with NHS England regarding the outline of a proposed Commercial Access Agreement (CAA) for ixazomib. The proposed CAA is intended to both address uncertainty regarding the cost effectiveness of ixazomib (via the inclusion of a cycle/time cap for ixazomib at [redacted] cycles/months) and to reduce the ICER to a level that shows

plausible potential for cost effectiveness in the 2/3 prior therapies sub-group at the relevant threshold (via the combined effect of the cycle/time cap and a reduced net price of [redacted] per ixazomib capsule, arising from a rebate mechanism which equates to a discount of [redacted] on the NHS list price; this represents an estimated [redacted] price reduction on the costs of bortezomib)

- The cost-effectiveness results using the updated economic model and including the proposed CAA are presented in Appendix 2 of this response document.

- Takeda is optimistic that the steps we have taken in this response will allow the committee to conclude that there is both clinical uncertainty (which can be addressed via data collection/data maturation) and plausible potential for cost effectiveness (based on the proposed CAA), thus leading to a recommendation that ixazomib be included within the CDF. This would allow Takeda to engage fully with NHS England with a view to agreeing a mutually acceptable CAA that would allow patients and the NHS to benefit from having early access to an effective and simple all-oral triplet that uniquely combines a proteasome inhibitor and an immunomodulator.

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# Addendum to ACD response of 19/5/2017 (submitted on 31/5/2017)

## 1.1.1 Handling of time on treatment in the model

Table 1 presents the definition of the PFS and ToT outcomes used in the statistical analysis of data from the TOURMALINE-MM1 clinical trial.

**Table 1: Definition of censoring/ events for PFS and ToT**

| PFS | | ToT | |
|---|---|---|---|
| Event | Censoring | Event | Censoring |
| • Progression<br>• Death | • Alternative therapy<br>• Dying or progressing after more than 1 missed visit<br>• No baseline/post baseline<br>• No documented death or progression<br>• Lost to follow up<br>• Withdrawal of consent | Discontinuing treatment due to:<br>• Progression<br>• Adverse event<br>• Protocol violation<br>• Study termination by sponsor<br>• Withdrawal of consent<br>• Lost to follow up<br>• Other | Continue on treatment at the time of data cut-off |

As per the email from NICE dated 10th May 2017, the ERG has requested further detail around the response to Clarification Question B7c in four areas. Takeda's response in each of these four areas is provided below. Please note that this response provides additional information to that already provided in Section 2.1.4 of Appendix 1 and Appendix 2 to our ACD response document that was submitted on 19th May 2017.

*NICE Committee request 1: Present the different events that contribute to the events in columns E and Y for "Disc Treatments" of the Lifetable (ToT) worksheet.*

Table 2 presents the different events that contribute to the events in column E and Y for "Disc Treatments" of the Lifetable (ToT) worksheet for the primary and secondary data cuts in the 2/3 prior lines population. The patient level data for IXA+LEN+DEX and LEN+DEX for both data cuts are provided in separate documents, named:

- "2017 05 17LENDEX ToT KM Disc Treatments IA1"
- "2017 05 17LENDEX ToT KM Disc Treatments IA2"
- "2017 05 17IXALENDEX ToT KM Disc Treatments IA1"
- "2017 05 17IXALENDEX ToT KM Disc Treatments IA2"

These are the data that were used in the original model (1st IA analysis) and the updated model (2nd IA analysis).

**Table 2: Patient level data for reasons for treatment discontinuation for primary and secondary data cuts**

| Data cut | Arm | N | Discontinuation Event | | | | | | | Censor |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | All | Progression | AE | Withdrawal | Study Termination | Protocol Violation | Other | |
| 1st IA | LEN+DEX | 149 | 76 | 39 | 23 | 11 | 1 | 1 | 1 | 73 |
| | IXA+LEN+DEX | 148 | 61 | 30 | 18 | 10 | 1 | 0 | 2 | 87 |
| 2nd IA | LEN+DEX | 149 | 103 | 57 | 30 | 13 | 1 | 1 | 1 | 46 |
| | IXA+LEN+DEX | 148 | 88 | 46 | 24 | 14 | 1 | 0 | 3 | 60 |
| Key: AE, adverse event; DEX, dexamethasone; IA, interim analysis; IXA, ixazomib; LEN, lenalidomide; N, number | | | | | | | | | | |

*NICE Committee request 2: Present the different events that contribute to the events in columns F and Z for "Censored" of the Lifetable (ToT) worksheet*

Columns F and Z present the number of patients censored for the ToT outcome for LEN+DEX and IXA+LEN+DEX, respectively.

The only event that causes a patient to be "censored" for this outcome is if the patients are still on treatment at time of cut-off. Therefore, the patient numbers within the model present the numbers for this event. Even though there is a fixed cut-off date (i.e. 2nd IA: July 2015), patients start the study at various time points, so the follow-up time for each patient is highly variable. For example, the first censor in the ITT population for the 1st IA cut was randomised on the 27th May 2014 and as such would be censored at 22 weeks and as such the 30-week censor in the 2/3 prior line population is reasonable in this context.

*NICE Committee request 3: Align these definitions as closely as possible to those of the company response to clarification question B7b, in order to permit a read across between the PFS curve and the ToT curve events and the PFS curve censoring events and the ToT curve censoring events, even if this requires the response to clarification B7b to be revised and/or expanded.*

Table 1 defines the PFS and ToT variables, which was discussed for PFS in clarification question B7b. Patients were only censored for ToT if patients were still on treatment at time of cut-off. Patients were censored for PFS if patients were receiving an alternative therapy, dying or progressing after more than 1 missed visit, had no baseline/post baseline, had no documented death or progression at time of cut-off, were lost to follow up or who withdrew their consent. Therefore, in theory, a patient may have been censored for the PFS outcome and not censored in the ToT outcome and vice versa.

Table 3 presents the number of patients censored for each different reason for the PFS outcome (independent review) in the 2/3 prior lines population using the 2nd interim analysis dataset; the majority of patients were censored due to no documented death or disease progression at time of cut-off (n=60 and n=37 for IXA+LEN+DEX and LEN+DEX arms, respectively). Table 3 shows that the number of patients who were censored for the PFS outcome who would not have been censored for the ToT outcome under the aforementioned definitions were similar across the treatment arms; 19.46% (n=20; calculated as 80 - 60 = 20) and 13.51% (n=29; calculated as 66 - 37 = 29) of IXA+LEN+DEX and LEN+DEX patients in the 2/3 prior lines population, respectively. Although similar, any potential bias is likely to be in favour of the LEN+DEX arm in the cost-effectiveness model; a higher proportion of patients that are censored in the PFS outcome still accrue the cost of treatment in the IXA+LEN+DEX arm meaning that there is potential for overestimation in the costs accruing to the IXA+LEN+DEX arm given the PFS outcomes.

**Table 3: Reasons for censoring in the PFS independent review outcome**

| Reason for censor | IXA+LEN+DEX | LEN+DEX |
|---|---|---|
| Alternate therapies | 9 | 14 |
| Death or progressed disease after more than 1 missed visit | 3 | 6 |
| Lost to follow up | 1 | 0 |
| No baseline/no post baseline | 3 | 4 |
| No documented death or disease progression at time of cut-off | 60 | 37 |
| Withdrawal of consent | 4 | 5 |
| Total censors | 80 | 66 |
| Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide | | |

It should also be noted that the timing between the ToT and PFS Kaplan-Meier data are not comparable. The ToT measures the time from first dose date to last dose date, which may be before or after the date of disease progression. At the decision to stop treatment it is recorded whether a patient has discontinued due to progression or another reason. The PFS data measures time from randomisation to the date of progression, which is determined based on the disease assessment schedule. These data are not aligned in terms of time. The ToT data therefore describes the duration over which a patient is actively receiving treatment, whereas the PFS data describes the duration over which a patient is in the pre-progression health state. Therefore, from a costing perspective using the ToT data is a more accurate representation of the costs accrued from treatment.

*NICE Committee request 4: Clarify whether the definition of the ToT curve (its events and its censoring events) was pre-specified in the trial's statistical analysis plan. If it was, please highlight where to find this.*

The definition of the ToT curve was not defined in the statistical analysis plan. This variable was defined within the statistical code and is defined in Table 1.

# Ixazomib with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma [ID807]:
# Appendix 1: New evidence analyses (with current PAS) - updated results in response to the ACD 20 April 2017 for the consideration of the NICE Appraisal Committee

**Submitted by Takeda UK Ltd.**

***Single Technology Appraisal (STA)***
***National Institute of Health and Care Excellence***

Submitted 17th May 2017

# Table of Contents

# List of Abbreviations

| | |
|---|---|
| ACD | Appraisal Consultation Document |
| AE | Adverse event |
| AFT | Accelerated failure time |
| AIC | Akaike Information Criterion |
| BIC | Bayes Information Criterion |
| CAA | Commercial access agreement |
| CEAC | Cost-effectiveness acceptability curve |
| CEP | Cost-effectiveness plane |
| DEX | Dexamethasone |
| DSU | Decision Support Unit |
| EOL | End of life |
| ERG | Evidence Review Group |
| HRQL | Health related quality of life |
| IA | Interim analysis |
| ICU | Intensive care unit |
| IXA | Ixazomib |
| LCHP | Log cumulative hazard plot |
| LEN | Lenalidomide |
| ORR | Overall response rate |
| OS | Overall survival |
| OWSA | One way sensitivity analysis |
| PAS | Price access scheme |
| PD | Progressive disease |
| PFS | Progression free survival |
| PR | Partial response |
| PSA | Probabilistic sensitivity analysis |
| SD | Stable disease |
| ToT | Time on treatment |
| TTD | Time to death |
| VGPR | Very good partial response |

# 1. Introduction

This appendix provides new evidence analyses in response to comments raised in the ACD on the clinical and cost-effectiveness of ixazomib. This analysis uses a modified and updated economic model to produce updated base case and scenario analysis results for the cost-effectiveness of ixazomib plus lenalidomide plus dexamethasone (IXA+LEN+DEX) vs. lenalidomide plus dexamethasone (LEN+DEX) in patients who have received 2 or 3 previous therapies.

The results in this appendix are based on the original price access scheme (PAS) accepted by PASLU consisting of a [redacted] price discount on the listed price of ixazomib. Appendix 2 provides the results applying the proposed Commercial Access Agreement (CAA) with NHS England.

This document first outlines the updates to the economic model (Section 2) and then presents the results associated with the new model and base case (Section 3).

# 2. Updated data and methods

### 2.1.1 Overview

In response to issues raised in the ACD, a number of modifications have been made to the economic analysis of IXA + LEN + DEX versus LEN + DEX in the sub-group of patients who have received 2 or 3 prior therapies. The main new analyses conducted are summarised as follows:

- In response to comments in Section 3.15 of the ACD, use of the most mature data available currently for key outcomes in the economic analysis (progression free survival (PFS), OS and time on treatment (ToT)) from the TOURMALINE-MM1 trial (i.e. 2nd interim analysis (IA) dataset of July 2015).
- In response to comments in Section 3.16 of the ACD, use of 2 prior therapy data, with adjustment for baseline characteristics, to perform a scenario analysis to explore cost-effectiveness in the 2 prior therapies sub-group (i.e. 3rd line). To reflect expected use of ixazomib in clinical practice, Takeda are no longer seeking a positioning in just a 2-prior therapy patient population alone. However, this analysis remains useful for supporting the updated base case analysis demonstrating cost-effectiveness across patients receiving 2/3 prior therapies, and also helps justify use of the larger and more robust 2/3 prior therapy sub-group data to support the positioning of IXA + LEN + DEX versus LEN + DEX in patients with 2/3 prior therapies.
- In response to comments in Sections 3.19 and 3.20 of the ACD, new analyses have been conducted on the EQ-5D derived utility data using the 2nd IA data cut.
- In response to comments in Section 3.22 of the ACD, the inclusion of weekly cycle costs has been considered in the economic analysis for costs relating to post-progression treatments.

Each of these modifications to the economic modelling and the results of the new analyses run using it based on the original PAS for ixazomib are covered in this appendix. The purpose of this appendix is to show the impact of the updated model and analyses on the ICER, so that this can be compared to the impact on the ICER associated with the proposed Commercial Access Agreement (CAA) which is covered in Appendix 2.

### 2.1.2 Use of the most mature clinical data in the model 2nd IA data cut

In line with the Evidence Review Group (ERG) feedback, the model has been updated with the second interim analysis (2nd IA), recording outcomes up to July 2015 (23 months of follow up). This represents the most recent clinical data available. Updated inputs include:

- Overall survival (OS)
- Progression free survival (PFS)
- Time on treatment (ToT)
- Health related quality of life (HRQL)
- Overall response rates (ORR)
- Subsequent therapies

- Number of hospitalisations
- Adverse event (AE) data
- Concomitant medications

These are discussed in detail below.

#### *2.1.2.1* Updated survival analysis

The methods used in the survival analysis with the updated clinical data are the same as those outlined in the original submission for the first interim analysis (1st IA). Updated survival analysis is presented in this Section for the 2+ prior lines population only. A summary of methods is provided below.

Covariate adjustment

Log-rank tests were used to detect evidence of significant differences in clinical endpoints between the two treatment arms in the 2+ prior therapies subgroups based on observed data for PFS, OS and ToT. These tests indicated that in addition to treatment, there were several patient risk factors that appeared to be associated with differences in clinical endpoints. Therefore, covariate adjustment was used to account for potential imbalances between the two treatment arms. This is implemented within the economic model using the mean of covariates method.

The data for covariate adjustment were obtained from the TOURMALINE-MM1 trial, see Section 5.2 of the original submission. Variables from the 2nd IA sub-grouped data were assessed for collinearity and significance in a multivariable Cox regression model using backwards stepwise regression techniques. The covariates included in the economic model are presented in Table 1. A scenario analysis considers the impact on results of using unadjusted estimates.

**Table 1: Covariate data for 2+ prior lines population**

| | **2+ prior lines covariates** |
|---|---|
| PFS | Light chain myeloma = Yes |
| OS | ISS =Stage 3<br>Age > 65 years |
| ToT | ISS = stage 3<br>Light chain myeloma = Yes |
| Key: ISS, international staging system; OS, overall survival; PFS, progression free survival; ToT, time on treatment | |

Overview of extrapolation

In line with the NICE Decision Support Unit (DSU) [1] guidance the applicability of a single parametric model or a Cox proportional hazards model was determined using visual inspection of the Kaplan-Meier curves, the log cumulative hazard plots (LCHPs) and the Q-Q curves. LCHPs were assessed to determine the suitability of using a single parametric model for the two treatment arms in terms of the underlying hazard and in assessing the suitability of projecting using exponential, Weibull and Gompertz curves. Q-Q plots were assessed to determine the suitability of the use of accelerated failure time (AFT) models.

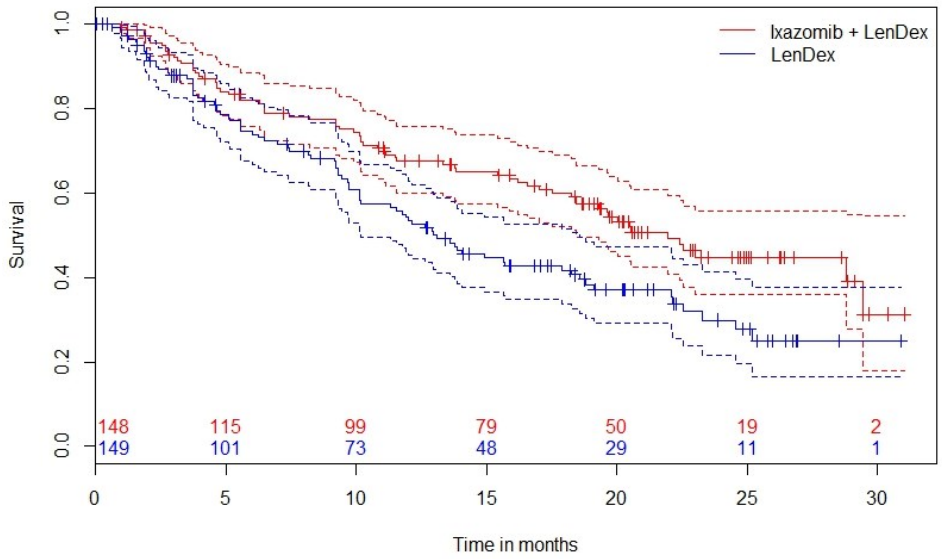
Six parametric distributions (exponential, log-normal, log-logistic, Gompertz, generalised gamma and Weibull) were examined for each clinical outcome (OS, PFS and ToT), in line with the NICE DSU guidance. The fit of each parametric model to the covariate adjusted survival data was explored using visual inspection, LCHPs, Schoenfeld residual plots, Q-Q plots, Akaike information criterion (AIC) and Bayesian information criterion (BIC) goodness of fit statistics and clinical plausibility. AIC and BIC provide an estimated relative fit of the alternative parametric models to the observed trial data. All curves were fitted using statistical software package R.

Progression free survival (PFS)

The Kaplan-Meier curves, the LCHPs, the Schoenfeld residual plots, the Q-Q plots and the AIC and BIC estimates for the covariate adjusted PFS associated with LEN+DEX are presented in Figure 1 to Figure 4 for the 2+ prior lines population. These methods suggest that the generalised gamma provides the most appropriate choice of model; the data satisfy the AFT assumption required when fitting a generalised gamma curve and this curve has relatively low AIC/BIC (

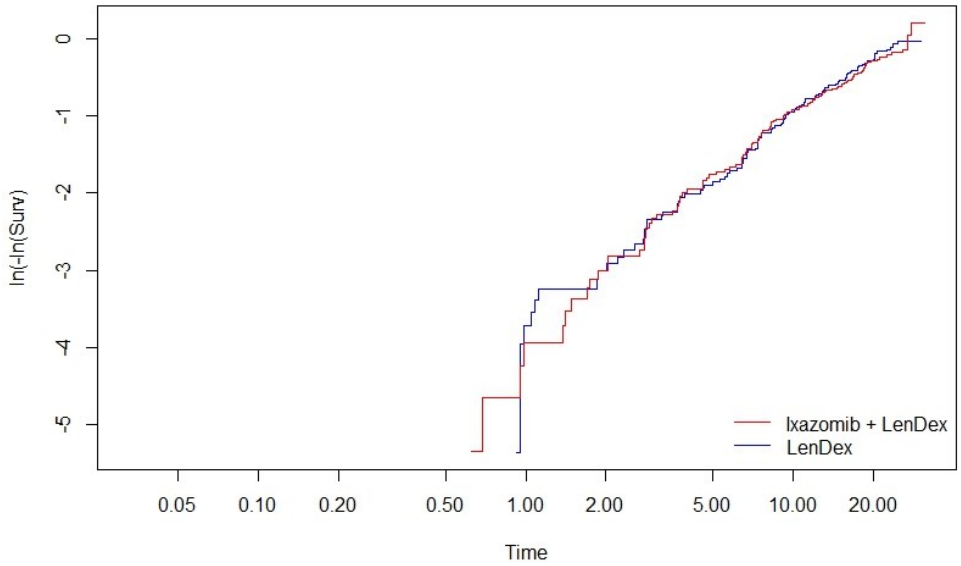
Table 2).

**Figure 1: Kaplan-Meier plot for PFS, 2+ prior lines population**



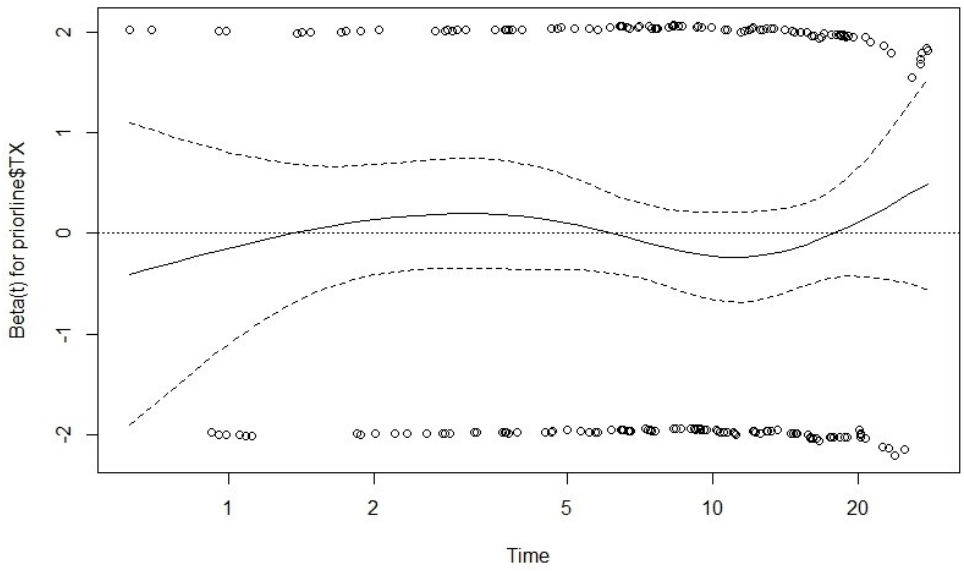

Key: LenDex, lenalidomide plus dexamethasone; PFS, progression free survival

**Figure 2: LCHP plot for PFS, 2+ prior lines population**



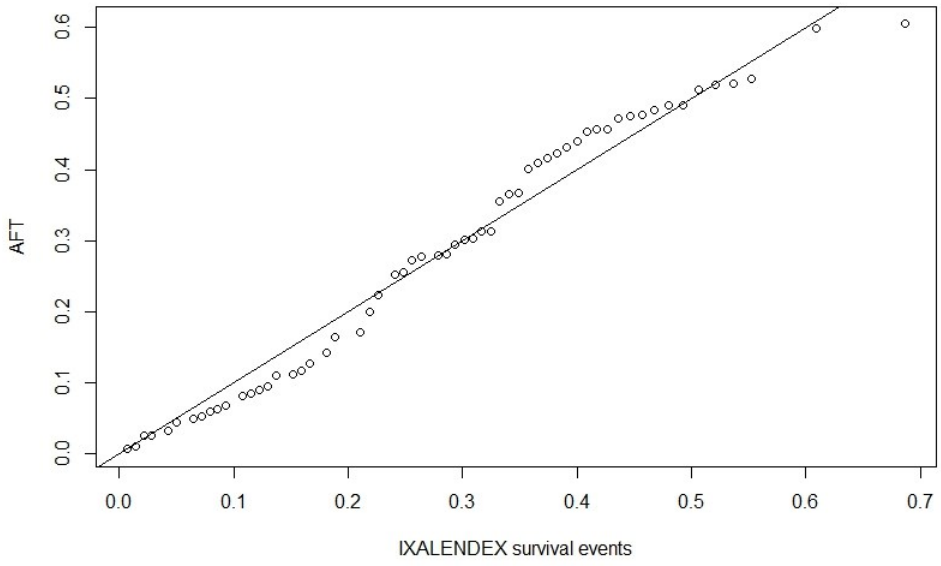

Key: LCHP, log cumulative hazard plot; LenDex, lenalidomide plus dexamethasone; PFS, progression free survival

**Figure 3: Schoenfeld residuals for PFS, 2+ prior lines population**




Key: PFS, progression free survival

**Figure 4: Q-Q curves for PFS, 2+ prior lines population**




Key: AFT, accelerated failure time; IXALENDEX, ixazomib plus lenalidomide plus dexamethasone; PFS, progression free survival

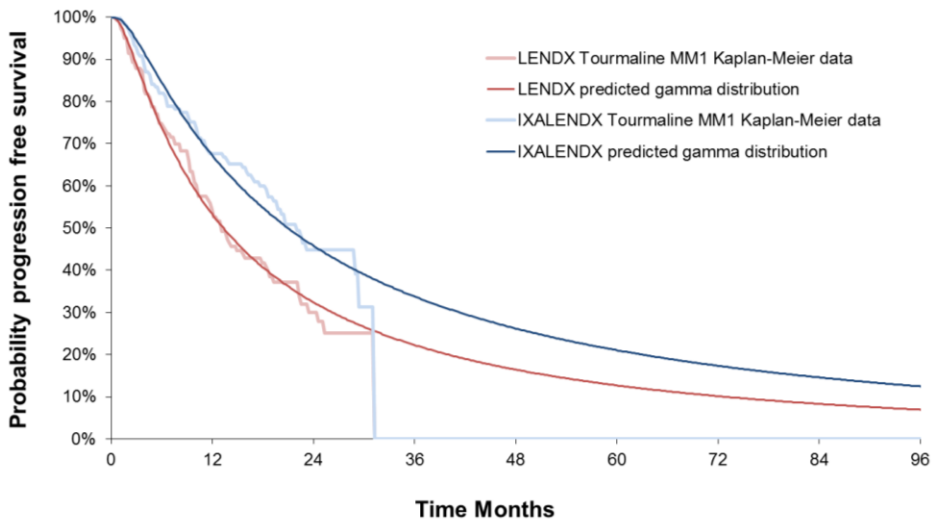
**Table 2: AIC and BIC estimates for covariate adjusted curves for PFS, 2+ prior lines population**

| | Model | N | ll(null) | ll(model) | df | AIC | BIC |
|---|---|---|---|---|---|---|---|
| 1 | Exponential | 297 | -639.5079224 | -633.8738443 | 3 | 1273.747689 | 1284.828885 |
| 2 | Weibull | 297 | -638.2264386 | -632.0577242 | 4 | 1272.115448 | 1286.890377 |
| 3 | Gompertz | 297 | -639.3386697 | -633.4616298 | 4 | 1274.92326 | 1289.698188 |
| 4 | Lognormal | 297 | -634.4455465 | -626.9326332 | 4 | 1261.865266 | 1276.640195 |
| 5 | Log logistic | 297 | -636.6533927 | -629.245471 | 4 | 1266.490942 | 1281.265871 |
| 6 | Gamma | 297 | -634.4383267 | -626.7982493 | 5 | 1263.596499 | 1282.065159 |
| Key: AIC, Akaike information criteria; BIC, Bayesian information criteria; df, degrees of freedom; PFS, progression free survival | | | | | | | |

The applicability of using unstratified models for the comparison of IXA+LEN+DEX with LEN+DEX for PFS was determined using the LCHP plots, the Q-Q plots and visual inspection. The LCHP and the Q-Q curves support the assumption of proportional hazards and AFT functionality, respectively, and as such a treatment effect was estimated for IXA+LEN+DEX compared with LEN+DEX [treatment effect: 0.63 related to LEN+DEX, 95% CI: 0.46-0.87] and applied to the LEN+DEX fitted generalised gamma covariate-adjusted PFS curve. Treatment with IXA+LEN+DEX is shown to result in a significant improvement in PFS compared with LEN+DEX for the 2+ prior therapies subgroup.

Figure 5 compares the modelled IXA+LEN+DEX curves with the original IXA+LEN+DEX data, this indicates a reasonably good visual fit.

**Figure 5: Comparison of fitted covariate adjusted PFS curves (generalised gamma) with unadjusted Kaplan-Meier curves for IXA+LEN+DEX in the 2+ prior lines subgroup**



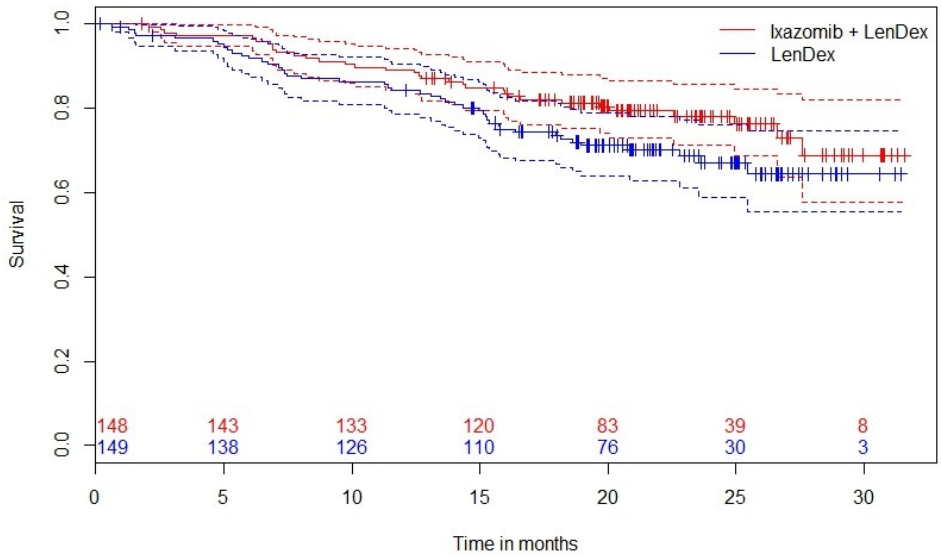

Key: DEX, dexamethasone; IXA, ixazomib; IXALENDX, ixazomib, lenalidomide and dexamethasone; LEN, lenalidomide; LENDX, lenalidomide and dexamethasone; PFS, progression free survival

Overall survival (OS)

The Kaplan-Meier curves, the LCHPs, the Schoenfeld residual plots, the Q-Q plots and the AIC and BIC estimates for the covariate adjusted OS associated with LEN+DEX are presented in Figure 6 to Figure 9 for the 2+ prior lines population. These methods suggest that the Weibull provides the most appropriate choice of model; the data satisfy the AFT assumption required when fitting a Weibull curve and this curve has relatively low AIC/BIC (

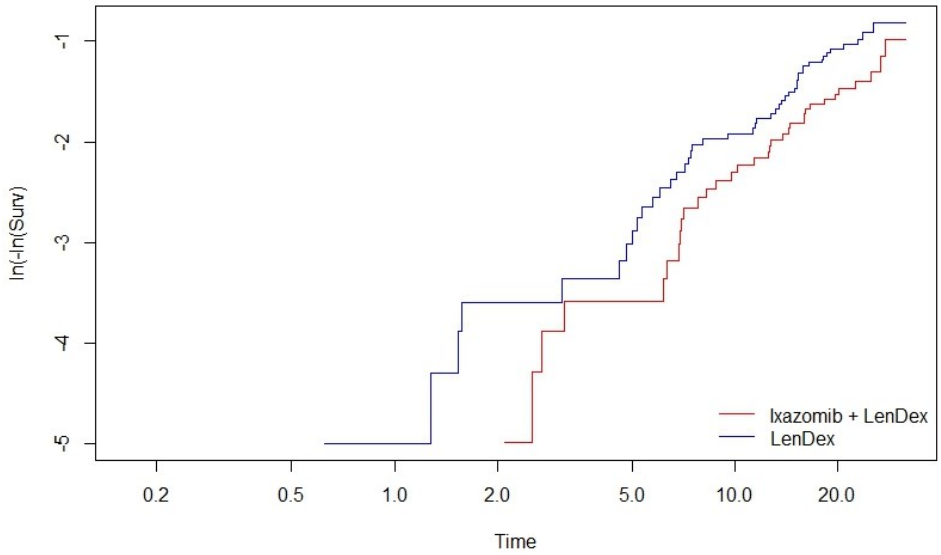
Table 3).

**Figure 6: Kaplan-Meier plot for OS, 2+ prior lines population**



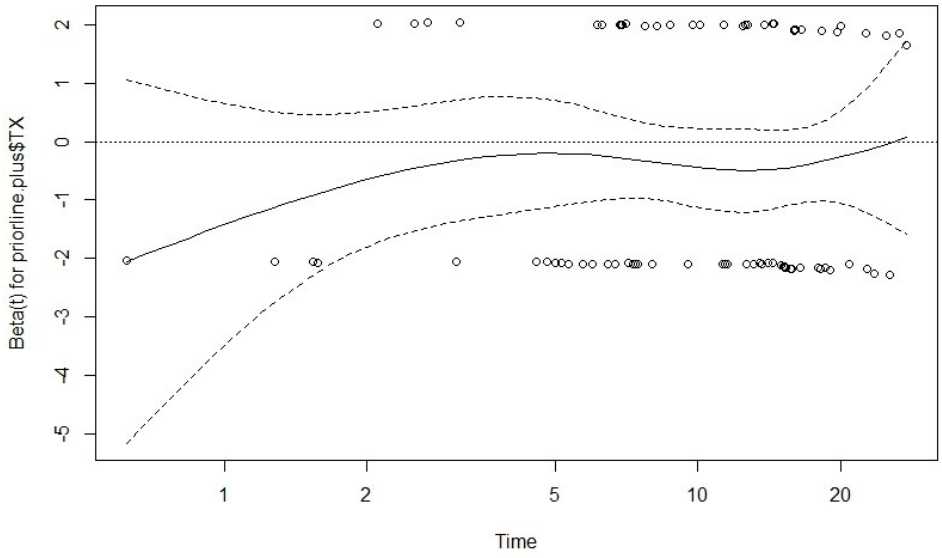

Key: LenDex, lenalidomide plus dexamethasone; OS, overall survival

**Figure 7: LCHP plot for OS, 2+ prior lines population**



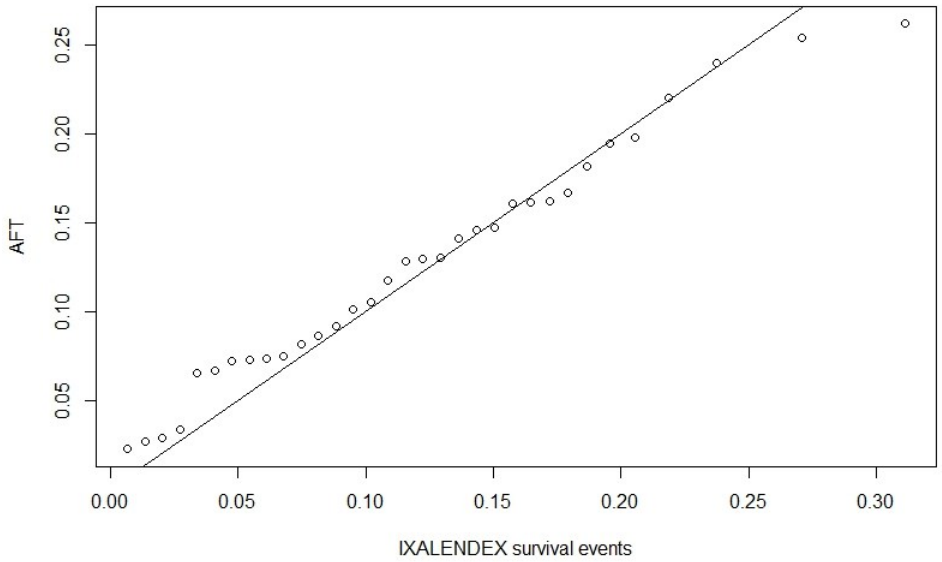

Key: LCHP, log cumulative hazard plot; LenDex, lenalidomide plus dexamethasone; OS, overall survival

**Figure 8: Schoenfeld residuals plot for OS, 2+ prior lines population**




Key: OS, overall survival

**Figure 9: Q-Q curve for OS, 2+ prior lines population**




Key: AFT, accelerated failure time; IXALENDEX, ixazomib, lenalidomide plus dexamethasone; OS, overall survival

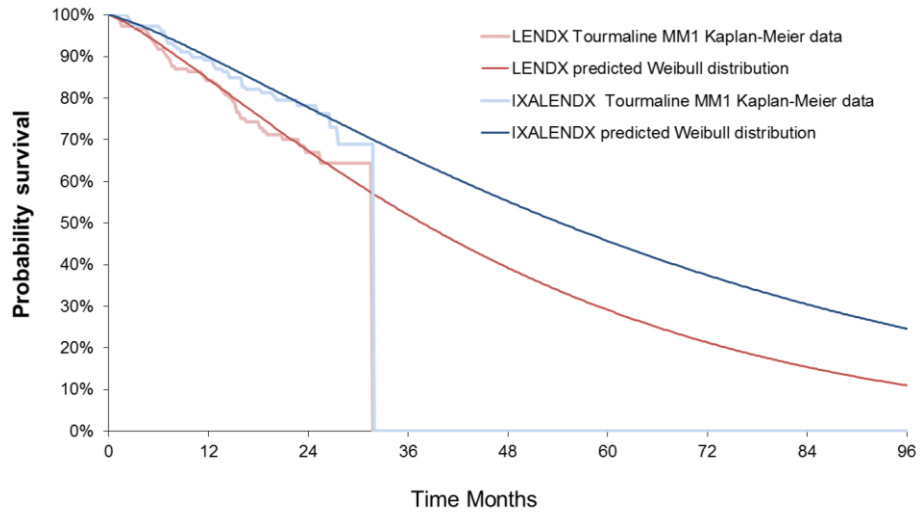
**Table 3: AIC and BIC estimates for covariate adjusted curves for OS, 2+ prior lines population**

| | Model | N | ll(null) | ll(model) | df | AIC | BIC |
|---|---|---|---|---|---|---|---|
| 1 | Exponential | 297 | -413.6863259 | -406.4962944 | 4 | 820.9925888 | 835.7675174 |
| 2 | Weibull | 297 | -412.1170569 | -404.5684433 | 5 | 819.1368866 | 837.6055473 |
| 3 | Gompertz | 297 | -413.2224561 | -405.7945471 | 5 | 821.5890941 | 840.0577548 |
| 4 | Lognormal | 297 | -411.2384505 | -404.6174319 | 5 | 819.2348639 | 837.7035246 |
| 5 | Log logistic | 297 | -411.6246937 | -404.3390253 | 5 | 818.6780506 | 837.1467113 |
| 6 | Gamma | 297 | -411.1864381 | -404.2043749 | 6 | 820.4087499 | 842.5711427 |
| Key: AIC, Akaike information criteria; BIC, Bayesian information criteria; df, degrees of freedom; N, number' OS, overall survival | | | | | | | |

The applicability of using unstratified models for the comparison of IXA+LEN+DEX with LEN+DEX for OS was determined using the LCHP plots, the Q-Q plots and visual inspection. The LCHP and the Q-Q curves support the assumption of proportional hazards and AFT functionality, respectively, and as such a treatment effect was estimated for IXA+LEN+DEX compared with LEN+DEX [treatment effect: 0.69 related to LEN+DEX, 95% CI: 0.48-1.00] and applied to the LEN+DEX fitted Weibull covariate-adjusted OS curve.

Figure 10 compares the modelled IXA+LEN+DEX curves with the original IXA+LEN+DEX data, this indicates a reasonably good visual fit.

**Figure 10: Comparison of fitted covariate adjusted OS curves (Weibull) with unadjusted Kaplan-Meier curves for IXA+LEN+DEX in the 2+ prior lines subgroup**



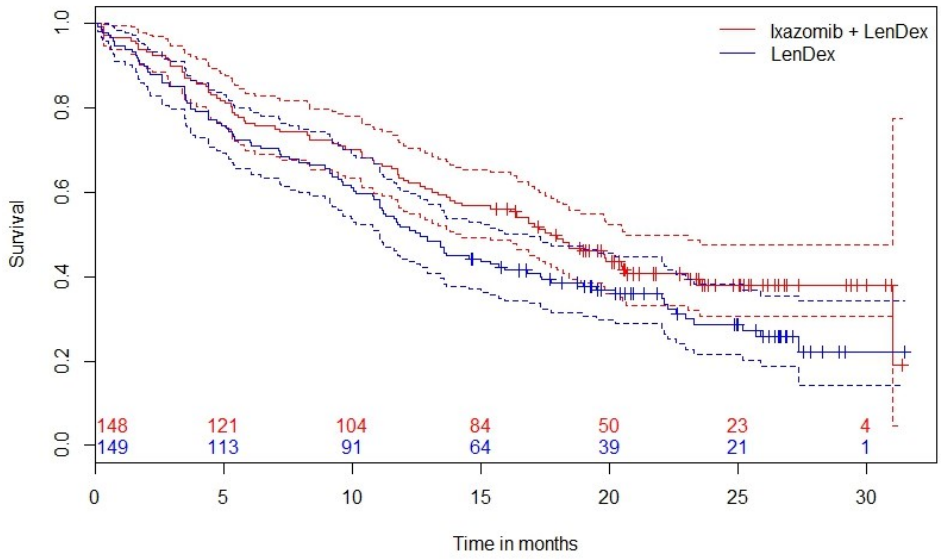

Key: DEX, dexamethasone; IXA, ixazomib; IXALENDX, ixazomib, lenalidomide and dexamethasone; LEN, lenalidomide; LENDX, lenalidomide and dexamethasone; OS, overall survival

Time on treatment (ToT)

The Kaplan-Meier curves, the LCHPs, the Schoenfeld residual plots, the Q-Q plots and the AIC and BIC estimates for the covariate adjusted ToT associated with LEN+DEX are presented in Figure 11 to Figure 14 for the 2+ prior lines population. These methods suggest that the exponential provides the most appropriate choice of model; the data satisfy the proportional hazards assumption required when fitting an exponential curve and this curve has relatively low AIC/BIC (

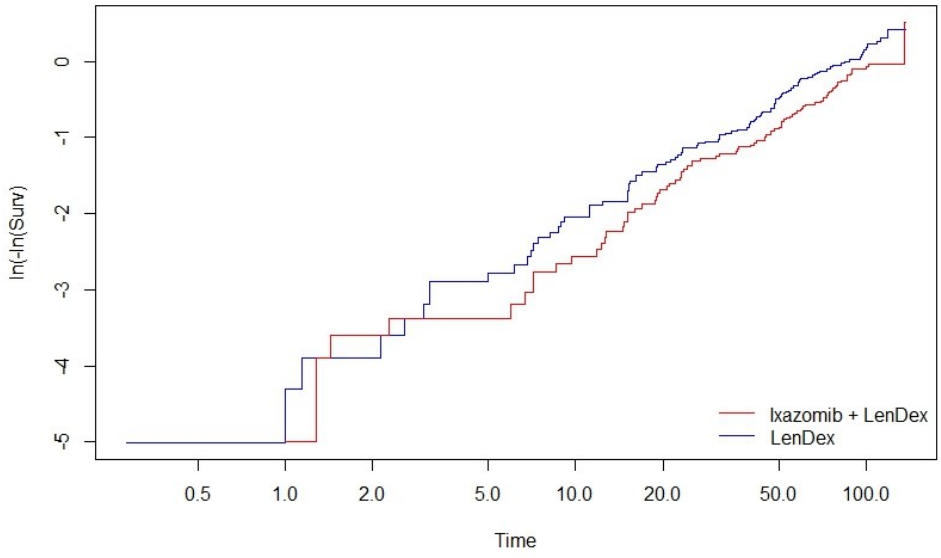
Table 4).

**Figure 11 Kaplan-Meier plot for ToT, 2+ prior lines population**



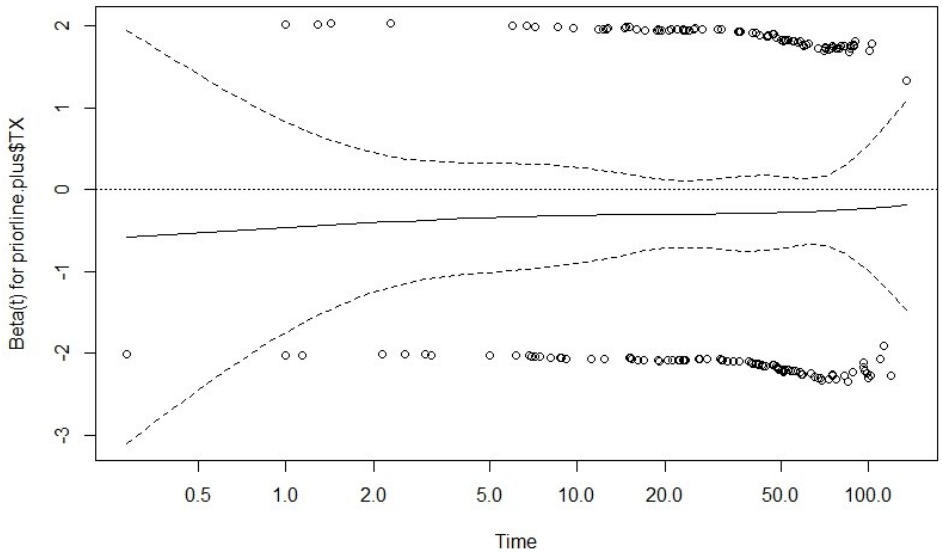

Key: LenDex, lenalidomide plus dexamethasone; ToT, time on treatment

**Figure 12: LCHP plot for ToT, 2+ prior lines population**



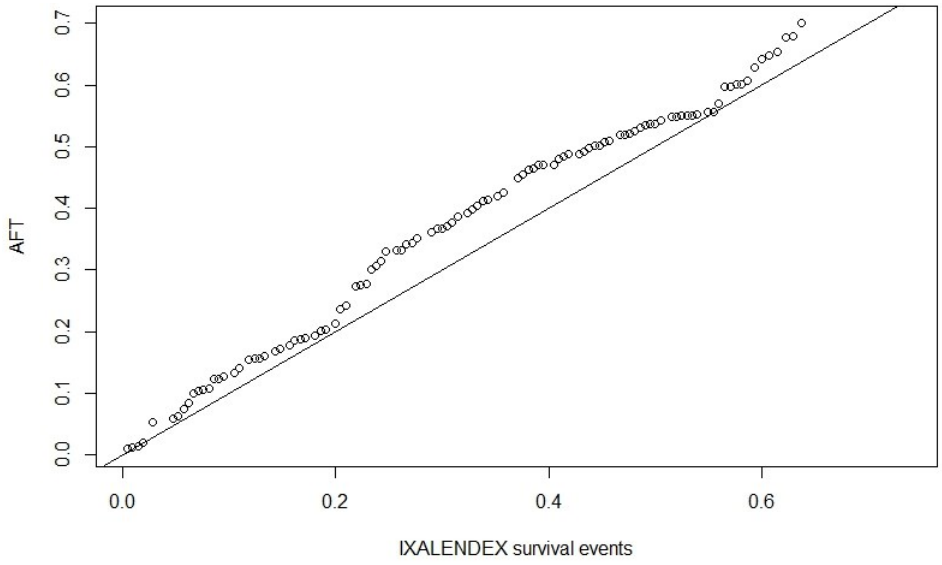

Key: LCHP, log cumulative hazard plot; LenDex, lenalidomide plus dexamethasone; ToT, time on treatment

**Figure 13: Schoenfeld residuals plot for ToT, 2+ prior lines population**




Key: ToT, time on treatment

**Figure 14: Q-Q curve for ToT, 2+ prior lines population**




Key: AFT, accelerated failure time; IXALENDEX, ixazomib, lenalidomide and dexamethasone; ToT, time on treatment

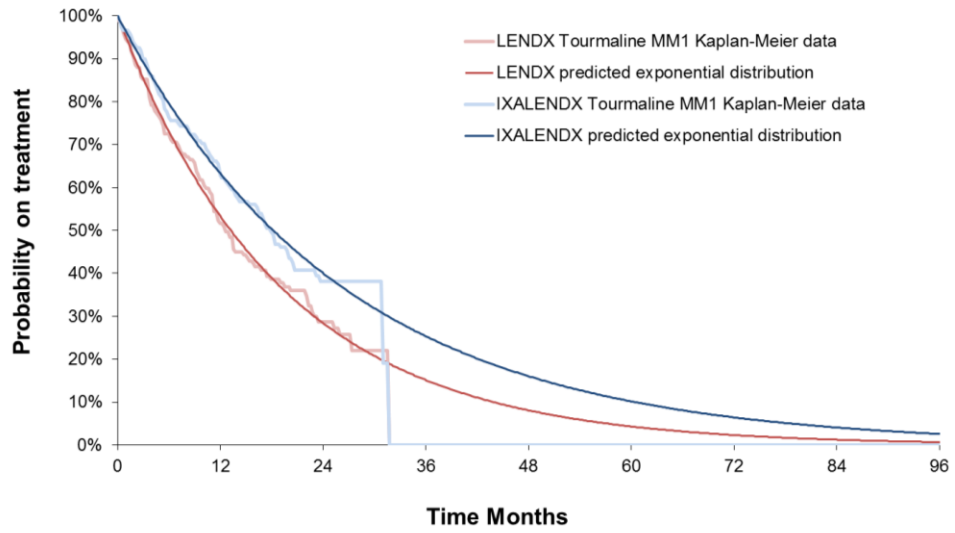
**Table 4: AIC and BIC estimates for covariate adjusted curves for ToT, 2+ prior lines population**

| | Model | N | ll(null) | ll(model) | df | AIC | BIC |
|---|---|---|---|---|---|---|---|
| 1 | Exponential | 297 | -1064.604777 | -1056.77381 | 4 | 2121.54762 | 2136.322549 |
| 2 | Weibull | 297 | -1064.598953 | -1056.761784 | 5 | 2123.523568 | 2141.992228 |
| 3 | Gompertz | 297 | -1064.566646 | -1056.773698 | 5 | 2123.547395 | 2142.016056 |
| 4 | Lognormal | 297 | -1070.773937 | -1063.277336 | 5 | 2136.554673 | 2155.023334 |
| 5 | Log logistic | 297 | -1066.058925 | -1058.181929 | 5 | 2126.363859 | 2144.832519 |
| 6 | Gamma | 297 | -1064.538939 | -1056.624148 | 6 | 2125.248296 | 2147.410689 |
| Key: AIC, Akaike information criteria; BIC, Bayesian information criteria; df, degrees of freedom; N, number; ToT, time on treatment | | | | | | | |

The applicability of using unstratified models for the comparison of IXA+LEN+DEX with LEN+DEX for ToT was determined using the LCHP plots, the Q-Q plots and visual inspection. The LCHP and the Q-Q curves support the assumption of proportional hazards and AFT functionality, respectively, and as such a treatment effect was estimated for IXA+LEN+DEX compared with LEN+DEX [treatment effect: 0.73 related to LEN+DEX, 95% CI: 0.55-0.97] and applied to the LEN+DEX fitted exponential covariate-adjusted ToT curve.

Figure 15 compares the modelled IXA+LEN+DEX curves with the original IXA+LEN+DEX data, this indicates a reasonably good visual fit.

**Figure 15: Comparison of fitted covariate adjusted ToT curves (exponential) with unadjusted Kaplan-Meier curves for IXA+LEN+DEX in the 2+ prior lines subgroup**




Key: DEX, dexamethasone; IXA, ixazomib; IXALENDEX, ixazomib, lenalidomide and dexamethasone; LEN, lenalidomide; LENDEX, lenalidomide and dexamethasone; ToT, time on treatment

### *2.1.2.2* Updated HRQL inputs

An updated utility analysis was performed on the 2nd IA data cut from the TOURMALINE-MM1 trial, this is explained in detail in Section 2.1.2.

### *2.1.2.3* Updated overall response rates (ORR) inputs

The number of patients achieving each response status was updated using the patient level data from the 2nd IA data cut of the TOURMALINE-MM1 study for the 2+ prior lines population. Table 5 presents the number of patients experiencing each response status from these data.

**Table 5: Updated response status from the TOURMALINE-MM1 trial**

| Population | Therapy | Missing | PD | SD | PR | VGPR+ |
|---|---|---|---|---|---|---|
| 2+ prior line patients only (n=297) | IXA+LEN+DEX | 11 | 7 | 11 | 39 | 80 |
| | LEN+DEX | 16 | 8 | 26 | 45 | 54 |
| | Total | 27 | 15 | 37 | 84 | 134 |
| Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; PD, progressed disease; PR, partial response; SD, stable disease; VGPR+, very good partial response | | | | | | |

### *2.1.2.4* Updated subsequent therapies inputs

The inputs associated with subsequent therapies were updated in line with the second interim analysis (2nd IA). As in the original model, inputs associated with subsequent therapies were pooled for IXA+LEN+DEX and LEN+DEX. Table 6 presents the number of patients progressing, the number of patients receiving at least one subsequent therapy and the number of patients receiving each subsequent therapy.

**Table 6: Updated inputs for subsequent therapy**

| TOURMALINE-MM1 DATA | 2+ prior lines |
|---|---|
| Sample size | 297 |
| Number of patients progressing at 2nd interim analysis | 151 |
| Proportion progressed | 50.84% |
| Number of patients receiving at least 1 subsequent therapy | 99 |
| Proportion of patients who have progressed receiving therapy | 65.56% |
| **Therapy** | |
| Bendamustine + Prednisolone | 11 |
| Cyclophosphamide | 41 |
| Doxorubicin | 9 |
| Bortezomib | 53 |
| Carfilzomib | 6 |
| Lenalidomide | 21 |
| Melphalan | 18 |
| Pomalidomide | 20 |
| Thalidomide | 12 |

The methods used to summate the costs of subsequent therapy were updated based on feedback from the NICE Committee and the ERG. These methods are described in detail in Section 2.1.4.

#### *2.1.2.5* Updated hospitalisation inputs

The inputs associated with number of hospitalisations were updated in line with the second interim analysis. As in the original model, the number of hospitalisations are provided for the four types of inpatient care: acute care unit, palliative care unit, intensive care unit (ICU) and hospice admissions. Due to observed differences between treatment arms and progression status, the number of hospitalisations are stratified based on treatment and progression status. Table 7 presents the updated inputs associated with number of hospitalisations and the resulting probability of hospitalisation per patient cycle.

**Table 7: Updated rate of hospitalisation for pre- and post- progression**

| Description | Number of Events | Rate | Probability per patient cycle |
|---|---|---|---|
| Pre-progression – IXA+LEN+DEX | | | |
| Acute care unit admission | 98 | 0.4772 | 0.0091 |
| Palliative care unit admission | 7 | 0.0341 | 0.0007 |
| ICU admissions | 1 | 0.0049 | 0.0001 |
| Hospice admission | 0 | 0.0000 | 0.0000 |
| Pre-progression – LEN+DEX | | | |
| Acute care unit admission | 89 | 0.5274 | 0.0101 |
| Palliative care unit admission | 11 | 0.0652 | 0.0012 |
| ICU admissions | 4 | 0.0237 | 0.0005 |
| Hospice admission | 5 | 0.0296 | 0.0006 |
| Post-progression – IXA+LEN+DEX | | | |
| Acute care unit admission | 21 | 0.4732 | 0.0090 |
| Palliative care unit admission | 11 | 0.2479 | 0.0047 |

| | | | |
|---|---|---|---|
| ICU admissions | 3 | 0.0676 | 0.0013 |
| Hospice admission | 0 | 0.0000 | 0.0000 |
| Post-progression – LEN+DEX | | | |
| Acute care unit admission | 38 | 0.6096 | 0.0116 |
| Palliative care unit admission | 13 | 0.2085 | 0.0040 |
| ICU admissions | 3 | 0.0481 | 0.0009 |
| Hospice admission | 1 | 0.0160 | 0.0003 |
| Key: DEX, dexamethasone; ICU, intensive care unit; IXA, ixazomib; LEN, lenalidomide | | | |

#### *2.1.2.6* Updated adverse event (AE) inputs

The method used to calculate the costs and utility decrements associated with AEs is the same as in the original submission. However, the number of AEs and the duration of each AE was updated in line with the second interim analysis. As in the original model, 17 different AEs were included in the analysis. Table 8 presents the reported proportion of AEs for IXA+LEN+DEX and LEN+DEX and the calculated relative risk for IXA+LEN+DEX compared with LEN+DEX used within the model.

Table 9 presents the probabilities applied per cycle for LEN+DEX and IXA+LEN+DEX.

**Table 8: Calculation of AE rates for IXA+LEN+DEX**

| Grade 3+ treatment emergent AEs | Reported % of AEs | | Calculated RR vs. LEN+DEX |
|---|---|---|---|
| | LEN+DEX | IXA+LEN+DEX | IXA+LEN+DEX |
| Anaemia | 29.55% | 16.89% | 0.45 |
| Cardiac failure | 1.81% | 2.03% | 0.88 |
| Deep vein thrombosis | 1.21% | 0.68% | 0.44 |
| Diarrhoea | 1.21% | 12.84% | 8.34 |
| Fatigue | 4.22% | 5.41% | 1.00 |
| Upper respiratory tract infection/Pulmonary-related | 1.21% | 2.03% | 1.32 |
| Ischaemic heart disease | 1.21% | 0.00% | 0.00 |
| Nausea | 0.15% | 2.03% | 10.53 |
| Neutropenia | 41.01% | 38.51% | 0.74 |
| Peripheral neuropathy | 0.60% | 0.68% | 0.88 |
| Pneumonia | 16.89% | 12.16% | 0.56 |
| Pulmonary embolism | 2.41% | 3.38% | 1.10 |
| Rash-related | 0.60% | 8.78% | 11.41 |
| Renal failure | 6.03% | 2.03% | 0.26 |
| Thrombocytopaenia | 5.43% | 30.41% | 4.39 |
| Vomiting | 1.21% | 0.68% | 0.44 |
| New primary malignancy | 0.60% | 0.68% | 0.88 |
| Key: AEs, adverse events; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; RR, relative risk | | | |

**Table 9: Cycle probabilities associated with AEs**

| Grade 3+ treatment emergent AEs | Average duration of AEs (days) | LEN+DEX | | | IXA+LEN+DEX cycle probability |
|---|---|---|---|---|---|
| | | No of events* | Rate | Cycle Probability | |
| Anaemia | 42.08 | 25 | 0.2955 | 0.0056 | 0.0025 |
| Cardiac failure | 11.31 | 3 | 0.0181 | 0.0003 | 0.0003 |
| Deep vein thrombosis | 11.40 | 1 | 0.0121 | 0.0002 | 0.0001 |
| Diarrhoea | 31.44 | 19 | 0.0121 | 0.0002 | 0.0019 |
| Fatigue | 63.33 | 8 | 0.0422 | 0.0008 | 0.0008 |
| Upper respiratory tract infection/Pulmonary-related | 15.40 | 3 | 0.0121 | 0.0002 | 0.0003 |
| Ischaemic heart disease | 4.20 | 0 | 0.0121 | 0.0002 | 0.0000 |
| Nausea | 20.60 | 3 | 0.0015 | 0.0000 | 0.0003 |
| Neutropenia | 15.08 | 57 | 0.4101 | 0.0078 | 0.0058 |
| Peripheral neuropathy | 50.00 | 1 | 0.0060 | 0.0001 | 0.0001 |
| Pneumonia | 19.59 | 18 | 0.1689 | 0.0032 | 0.0018 |
| Pulmonary embolism | 56.53 | 5 | 0.0241 | 0.0005 | 0.0005 |
| Rash-related | 26.14 | 13 | 0.0060 | 0.0001 | 0.0013 |
| Renal failure | 37.05 | 3 | 0.0603 | 0.0012 | 0.0003 |
| Thrombocytopaenia | 21.13 | 45 | 0.0543 | 0.0010 | 0.0046 |
| Vomiting | 4.75 | 1 | 0.0121 | 0.0002 | 0.0001 |
| New primary malignancy | 40.33 | 1 | 0.0060 | 0.0001 | 0.0001 |
| Key: AEs, adverse events; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide | | | | | |

#### *2.1.2.7* Updated concomitant medication inputs

The inputs associated with concomitant medications were updated based on population and based on the 2nd IA. The original model considered data from the 1+ prior ITT population and from the first interim analysis (1st IA). The updated model considers data from the 2+ prior lines population and the 2nd IA data cut.

As in the original model, no significant difference was found between the IXA+LEN+DEX and LEN+DEX treatment arms for concomitant medication. Therefore, the model used the pooled data for concomitant medications where at least 7.5% of patients received the medication. Table 10 provides a summary of the inputs associated with concomitant medications based on 2nd IA data.

**Table 10: Overview of concomitant medications**

| Treatment | Description | Cost / pack (£)* | Units cycle) | Drug cost cycle (£) | N | Proportion of patients from the TOURMALINE-MM1 study | Total cost /wk. (£) |
|---|---|---|---|---|---|---|---|
| **ACETYLSALICYLIC ACID** | Tablets, aspirin 300 mg, 32-tab pack, 75 mg daily | 3.35 | 7 | 0.73 | 226 | 76.09% | £0.56 |
| **ACICLOVIR** | Tablets, aciclovir 200 mg, 56-tab pack 4 times daily | 3.02 | 14 | 0.76 | 137 | 46.13% | £0.35 |
| **ALLOPURINOL** | Tablets, allopurinol 100 mg, 28-tab pack, once daily | 0.87 | 7 | 0.22 | 71 | 23.91% | £0.05 |
| **AMLODIPINE** | Tablets amlodipine 5 mg, 28-tab pack, 5 mg once daily | 0.73 | 7 | 0.18 | 41 | 13.80% | £0.03 |
| **BACTRIM (CO-TRIMOXAZOLE)** | Tablets co-trimoxazole 960 mg, 100 tab-pack, 960 mg every 12 hours | 2.29 | 7 | 0.57 | 95 | 31.99% | £0.18 |
| **CALCIUM CARBONATE** | Tablet calcium carbonate 1.25 g (calcium 500 mg or Ca2+ 12.5 mmol); WHO DDD A12AA04 = 3g | 9.46 | 21 | 1.99 | 36 | 12.12% | £0.24 |
| **COLECALCIFEROL** | Tablets 20 mcg, 30-tab pack= £3.60; WHO DDD A11CC05 = 20 mcg | 3.60 | 7 | 0.84 | 29 | 9.76% | £0.08 |
| **ENOXAPARIN** | Injection, enoxaparin sodium 100 mg/mL, 40 mg (4000 units) every 24 hours | 30.27 | 7 | 21.19 | 70 | 23.57% | £4.99 |
| **ESOMEPRAZOLE** | Capsules, enclosing e/c pellets, esomeprazole, 20 mg 28-cap pack, 20 mg daily when required | 2.97 | 7 | 0.74 | 28 | 9.43% | £0.07 |
| **FENTANYL** | Tablet (sublingual) fentanyl (as citrate) 100 micrograms, 10-tab pack, 100 micrograms, repeat if necessary after 15-30 minutes | 57.86 | 2.33 | 27.00 | 40 | 13.47% | £3.64 |
| **FUROSEMIDE** | Tablets furosemide 20 mg, 28-tab pack, 20-40 mg daily | 0.74 | 7 | 0.19 | 63 | 21.21% | £0.04 |

| Treatment | Description | Cost / pack (£)* | Units cycle) | Drug cost cycle (£) | N | Proportion of patients from the TOURMALINE-MM1 study | Total cost /wk. (£) |
|---|---|---|---|---|---|---|---|
| **IBUPROFEN** | Tablets, ibuprofen 200 mg 84-tab pack, maintenance dose of 0.6–1.2 g daily may be adequate | 3.40 | 21 | 0.85 | 33 | 11.11% | £0.09 |
| **LANSOPRAZOLE** | For acid-related dyspepsia: 15-30mg daily for 2-4 wks; caps encl e/c granules 30 mg, 28-cap pack | 1.26 | 0.06 | 0.00 | 28 | 9.43% | £0.00 |
| **LEVOTHYROXINE** | Tablets, levothyroxine sodium 50 micrograms, 28-tab pack, usual maintenance dose 50–200 micrograms once daily | 1.65 | 7 | 0.41 | 23 | 7.74% | £0.03 |
| **METFORMIN** | Tablets, coated metformin hydrochloride 500 mg 28-tab pack, 500 mg with breakfast, lunch and evening meal | 0.86 | 21 | 0.65 | 18 | 6.06% | £0.04 |
| **METOPROLOL** | Tablets, metoprolol tartrate 50 mg, 28-tab pack, 50 mg 2-3 times daily | 1.25 | 14 | 0.63 | 33 | 11.11% | £0.07 |
| **MORPHINE** | Tablets, morphine sulphate 5 mg, 60-tab pack, 5 mg every 4 hours adjusted per response | 3.29 | 42 | 2.30 | 51 | 17.17% | £0.40 |
| **NADROPARIN** | Injection, enoxaparin sodium 100 mg/mL, 40 mg (4000 units) every 24 hours | 3.03 | 7 | 21.21 | 23 | 7.74% | £1.64 |
| **OMEPRAZOLE** | Capsules, omeprazole 10 mg, 28-cap-pack, 10 mg daily | 5.96 | 7 | 1.49 | 128 | 43.10% | £0.64 |
| **ONDANSETRON** | Tablets, ondansetron 8 mg, 10-tab pack, 8 mg 1-2 hours before treatment | 2.28 | 1 | 0.23 | 45 | 15.15% | £0.03 |
| **OXYCODONE** | Capsules, oxycodone hydrochloride 5 mg, 56-cap pack | 6.26 | 28 | 6.74 | 50 | 16.84% | £1.13 |
| **PAMIDRONIC ACID** | IV infusion, powder for reconstitution, pamidronate disodium, 90 mg vial, 90 mg every four weeks | 170.45 | 0.25 | 42.61 | 75 | 25.25% | £10.76 |

| Treatment | Description | Cost / pack (£)* | Units cycle) | Drug cost cycle (£) | N | Proportion of patients from the TOURMALINE-MM1 study | Total cost /wk. (£) |
|---|---|---|---|---|---|---|---|
| **PANTOPRAZOLE** | Tablets pantoprazole 20 mg, 28-tab pack, 20 mg daily | 0.99 | 7 | 0.25 | 47 | 15.82% | £0.04 |
| **PARACETAMOL** | Tablets, paracetamol 500 mg, 32-tab pack | 0.73 | 56 | 1.28 | 167 | 56.23% | £0.72 |
| **POTASSIUM** | Tablets, diclofenac potassium 25 mg, 28-tab pack; Rheumatic disease, musculoskeletal disorders, acute gout, 75–150 mg daily in 2–3 divided doses | 3.23 | 35 | 4.04 | 72 | 24.24% | £0.98 |
| **SIMVASTATIN** | Prevention of cardiovascular events, initially 20-40mg once daily at night 20mg, 28-tab pack | 66.00 | 14 | 33.00 | 16 | 5.39% | £1.78 |
| **TRAMADOL** | Capsules, tramadol hydrochloride 50 mg 30-cap pack, 50 mg every 4-6 hours, adjust per response | 1.20 | 28 | 1.12 | 58 | 19.53% | £0.22 |
| **VALACICLOVIR** | Tablets, valaciclovir 500 mg, 10-tab pack, 500 mg twice daily for 3-5 days | 3.18 | 1.5 | 0.48 | 49 | 16.50% | £0.08 |
| **ZOLEDRONIC ACID** | Concentrate for IV infusion, zoledronic acid, 800 micrograms/mL, 5 ml (4 mg) vial, 4 mg over at least 15 minutes every 3-4 weeks | 174.17 | 0.25 | 43.54 | 48 | 16.16% | £7.04 |
| | | | | | | **Total cost (£) per patient week** | £35.92 |

Key: cap, capsule; encl, enclosure; e/c, enteric coating; IV, intravenous; mg, milligram; mL, millilitre; N, number; tab, tablet; Tx, treatment; wk, week
* BNF accessed November 2016

### 2.1.3 Handling of updated utility analysis based on 2ND IA data cut

An updated utility analysis was performed on the 2nd IA data cut from the TOURMALINE-MM1 trial which attempts to address the ERG's concerns regarding the transparency and robustness of the results. Additionally, a sensitivity analysis is presented which may be considered as a time to death analysis, which aims to explore whether a patients' HRQL declines more notably in the final months before death rather than upon or shortly after progression.

#### *2.1.3.1* Updated utility analysis

An updated utility analysis was performed in order to address the ERG's concerns regarding the transparency and robustness of the results presented in the original submission. The updated analysis uses the EQ-5D data from the relatively mature 2ND IA data cut of the TOURMALINE-MM1 trial. The EQ-5D questionnaire contained five questions about a patient's concerns around mobility, self-care, usual activities, pain and anxiety/depression. Three response options were available for each question (EQ-5D-3L) and an algorithm converting each combination of responses obtained by patients was used to estimate an overall HRQL utility value. Patients completed the EQ-5D questionnaire at various time points including on screening and on day 1 of each cycle of treatment completed (data were available for up to a maximum of 34 cycles per patient). The mean number of measurements per patient was 14 (median=15), i.e. on average patients completed 14 EQ-5D questionnaires.

The explanatory variables included in the statistical regression model are presented in Table 11, which were deemed to be relevant to a patient's HRQL, following feedback from clinicians. Three additional covariates (age, race and gender) were included in the updated regression model and overall response assessments recorded at the time of the EQ-5D measurement superseded the best overall response assessment variable previously included. Multicollinearity was assessed between each of the variables to ensure that sufficient independence was observed; inclusion of highly correlated parameters can affect the robustness of the regression results. Weak correlation was observed between all variables under observation and were therefore taken forward to inclusion within the statistical model.

**Table 11: Summary of explanatory variables**

| Parameter | Format | Levels |
|---|---|---|
| Overall response assessment | Categorical | VGPR+<br>PR<br>SD<br>PD |
| Total number of hospitalisations | Binary | 0<br>≥1 |
| Grade 3/4 AE | Binary | 0<br>≥1 |
| New prior malignancy | Binary | 0<br>≥1 |

| | | |
|---|---|---|
| Age | Continuous | Years |
| Gender | Binary | Female<br>Male |
| Race | Binary | Non-white<br>White |
| Death within 3 months* | Binary | No<br>Yes |
| Key: AE, adverse event; CR, complete response; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response; * includes patients across the overall response assessment states.<br>Notes: VGPR+ includes sCR and CR. | | |

A longitudinal mixed-effects regression model was fitted to the data, which accounted for the repeated measures structure of the data. The model was used to predict EQ-5D utility values, whereby EQ-5D data were converted into utilities using the EQ-5D UK Tariff values.[2] The utility scores were then used as dependent variables in the regression model adjusting for all explanatory variable specified in Table 11. A total of 9,234 records across 651 unique patients were included in the statistical regression model (one patient had no EQ-5D records, 29 patients had no overall response assessments and a further 41 patients had incomplete covariate data). A stepwise selection approach was then applied, using forward selection and backward elimination algorithms to yield the most parsimonious model which identified the final list of predictors. The results from the regression model are presented in Table 12, which show that grade 3/4 AEs, gender, race, hospitalisations, overall response and whether a patient is ≤3 months prior to death were associated with a statistically significant effect on utility. The presence of at least one grade 3/4 AE and at least one hospitalisation both yield a reduction in a patient's HRQL. Death within 3 months from the date of a patients' utility measurement also negatively impacted HRQL and had the greatest magnitude of effect of all variables included in the model. Male patients were associated with higher utility scores vs. females. The variable representing the occurrence of new prior malignancies was dropped during the stepwise selection process; this is likely due to the limited number of new prior malignancy cases observed.

**Table 12: Utility coefficients for parameters obtained using the EQ-5D from the TOURMALINE-MM1 trial (2nd IA)**

| Parameter | Coefficient | Standard Error | 95% Lower Confidence Limit | 95% Upper Confidence Limit | Abs(t-value) | p-value |
|---|---|---|---|---|---|---|
| Intercept | 0.806 | 0.066 | 0.677 | 0.935 | 12.22 | <0.001* |
| Grade 3/4 AE (ref=0)<br>≥1 | -0.031 | 0.006 | -0.043 | -0.019 | 5.301 | <0.001* |
| Age (years) | -0.001 | 0.001 | -0.003 | 0.001 | 0.880 | 0.379 |
| Gender (ref=female)<br>Male | 0.055 | 0.018 | 0.020 | 0.090 | 3.080 | 0.002* |
| Race (ref=non-white)<br>White | -0.059 | 0.026 | -0.110 | -0.008 | 2.234 | 0.026* |

| | | | | | | |
|---|---|---|---|---|---|---|
| Total number of hospitalisations (ref=0)<br>≥1 | -0.091 | 0.018 | -0.126 | -0.056 | 4.995 | <0.001* |
| Death within 3 months (ref=No)<br>Yes | -0.106 | 0.016 | -0.137 | -0.075 | 6.580 | <0.001* |
| Overall response assessment (ref=VGPR+)<br>PR<br>SD<br>PD | 0.001<br>-0.011<br>-0.038 | 0.005<br>0.008<br>0.007 | -0.009<br>-0.027<br>-0.052 | 0.011<br>0.005<br>-0.024 | 0.274<br>1.375<br>5.737 | <0.001*<br>(0.784)<br>(0.169)<br>(<0.001*) |
| Key: Abs, absolute; AE, adverse event; PD, progressive disease; PR, partial response; ref, reference; SD, stable disease; SE, standard error; VGPR+, very good partial response; * statistically significant at 5% level.<br>Notes: VGPR+ includes CR, PR, sCR and VGPR. | | | | | | |

There was very minimal difference in the resulting utility scores between partial response (PR) and very good partial response (VGPR)+ responses (this result was statistically non-significant). The results showed a trend in declining utility scores for stable disease (SD) and progressive disease (PD) overall response assessments (vs. VGPR+), with a statistically significant difference observed between PD and VGPR+. Using the 2nd IA EQ-5D data shows PD no longer yields a utility score that is virtually the same as SD which was the case with the 1st IA analysis. This is likely due to the analysis of the 2nd IA data cut with additional follow-up measurements and consequently more subsequent PD measurements, and improvements made in the robustness of the regression analysis for example, adjusted for overall response assessments recorded at the same time as the EQ-5D questionnaire instead of using a patients' best overall response assessment. The mean number of measurements available per patient across the different overall response assessments for 2nd IA are 11.6, 6.5, 3.0 and 3.0 for VGPR+, PR, SD and PD respectively. The equivalent mean number of measurements for 1st IA are 8.3, 5.3, 2.8 and 2.7 for VGPR+, PR, SD and PD respectively. The average number of measurements per patient is lower for 1st IA; the estimated utility value for PD is expected to be lower in the updated regression analyses, as a longer follow-up of data were available where a patient's HRQL estimates are likely to decrease as their follow-up time increases, particularly once progression has been reached. Resulting utility values by response status (based on the mean of covariates approach) are:

- VGPR+: 0.689
- PR: 0.690
- SD: 0.678
- PD: 0.650

Death within 3 months then is associated with a further significant reduction in utility (table 2). This difference and the difference between SD and PD above represents a more intuitive comparative result than the previous EQ-5D analysis based on the 1st interim analysis dataset. The new utility values were presented to an advisory board of 7 clinical experts held by Takeda on May 16th 2017. The feedback from the clinical experts was that the relative utility values appear plausible and al agreed that MM patients would not be

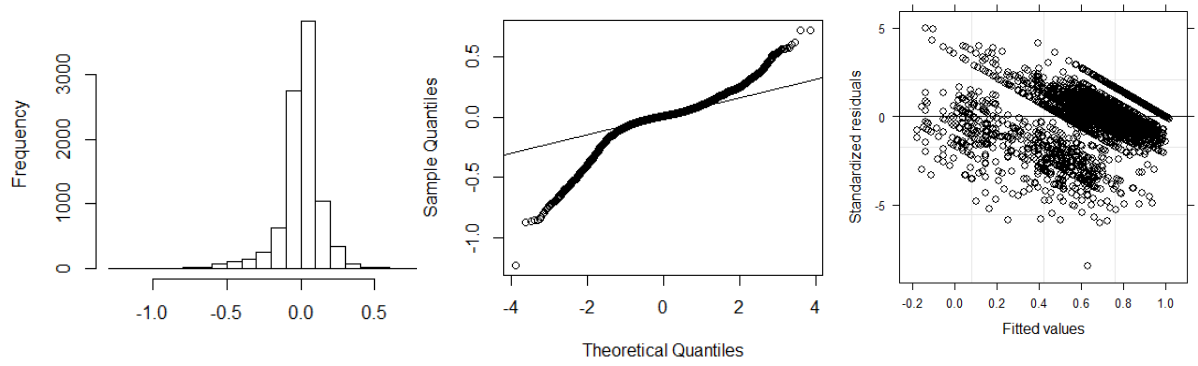
expected to experience a dramatic change in quality of life at or just beyond progression. The consensus was that as progression is a biomedical response and patients are quickly move to another treatment before clinical impact HRQL would not be majorly impacted further until the last few months before death, when there could be a significant drop-off. This provides support for the base case utility values we use in the updated economic model.

Based on this updated utility regression the mean utility associated with the PFS health state is 0.7861 and 0.7876 for LEN+DEX and IXA+LEN+DEX, respectively. These estimates consider response status, age, gender, race and number of hospitalisations required in the PFS health state. Therefore, the estimates vary based on treatment arm. Please note these estimates do not include the utility decrement associated with AEs or end of life.

Based on the updated utility regression the mean utility associated with the PD health state is 0.7491 and 0.7493 for LEN+DEX and IXA+LEN+DEX, respectively. These estimates consider age, gender, race and number of hospitalisations required in the PD health state. Therefore, the estimates vary based on treatment arm.

Model goodness of fit was assessed; comparatively, the stepwise selection procedure improved model fit according to the AIC (vs. the saturated model). Overall model fit was assessed using model diagnostics as presented in Figure 16. The histogram of residuals appears Normally distributed; however, the Q-Q-plot shows some deviation away from the straight line. The shape of the line in the Q-Q-plot suggests a heavy tailed distribution meaning that the utility values are likely to be more extreme than would be expected if they truly came from a Normal distribution. The fitted values vs standardised residuals do not appear ‘cloud-like’ in the upper part of the plot; some systematic patterns appear suggesting that there may be some dependency between the fitted values and residuals. Analyses of HRQL scores frequently suffer from ceiling effects since utility scores are bounded.

**Figure 16: Model diagnostic plots**




This updated regression equation is used within the model to estimate HRQL. Utilities are estimated as a function of overall response status, number of hospitalisations, AEs, age, gender, race and whether a patient is within 3 months of death. The inputs associated with each of these covariates is discussed in Section 2.1.2.2.

Table 13 presents the utility values by health state using the updated utility analysis compared with TA171 and TA338.[3, 4]

**Table 13: Utility values by health state**

| | Updated utility analysis | TA171[5] | TA338[4] |
|---|---|---|---|
| **VGPR+ (pre-progression health state)** | | | |
| VGPR+ | 0.806 [95% CI: 0.798-0.815] | 0.810 | 0.750 |
| Adverse event | 0.775 [95% CI: 0.775-0.775] | 0.779 | 0.719 |
| Age +1 year from baseline | 0.806 [95% CI: 0.805-0.806] | 0.809 | 0.749 |
| Gender=male | 0.862 [95% CI: 0.861-0.862] | 0.865 | 0.805 |
| Race=white | 0.748 [95% CI: 0.747-0.749] | 0.751 | 0.691 |
| Hospitalisation | 0.716 [95% CI: 0.715-0.716] | 0.719 | 0.659 |
| ≤3 months until end of life | 0.701 [95% CI: 0.701-0.701] | 0.704 | 0.644 |
| **PR (pre-progression health state)** | | | |
| PR | 0.808 [95% CI: 0.808-0.808] | 0.810 | 0.750 |
| Adverse event | 0.777 [95% CI: 0.777-0.777] | 0.779 | 0.719 |
| Age +1 year from baseline | 0.807 [95% CI: 0.807-0.807] | 0.809 | 0.749 |
| Gender=male | 0.863 [95% CI: 0.863-0.863] | 0.865 | 0.805 |
| Race=white | 0.749 [95% CI: 0.748-0.750] | 0.751 | 0.691 |
| Hospitalisation | 0.717 [95% CI: 0.717-0.717] | 0.719 | 0.659 |
| ≤3 months until end of life | 0.702 [95% CI: 0.702-0.702] | 0.704 | 0.644 |
| **SD (pre-progression health state)** | | | |
| SD | 0.796 [95% CI: 0.796-0.796] | 0.810 | 0.650 |
| Adverse event | 0.765 [95% CI: 0.765-0.765] | 0.779 | 0.619 |
| Age +1 year from baseline | 0.795 [95% CI: 0.795-0.795] | 0.809 | 0.649 |
| Gender=male | 0.851 [95% CI: 0.851-0.851] | 0.865 | 0.705 |
| Race=white | 0.737 [95% CI: 0.738-0.736] | 0.751 | 0.591 |
| Hospitalisation | 0.705 [95% CI: 0.705-0.705] | 0.719 | 0.559 |

| | | | |
|---|---|---|---|
| ≤3 months until end of life | 0.690 [95% CI: 0.690-0.690] | 0.704 | 0.544 |
| **PD (post-progression health state)** | | | |
| PD | 0.768 [95% CI: 0.768-0.768] | 0.640 | 0.610 |
| Age +1 year from baseline | 0.767 [95% CI: 0.767-0.767] | 0.639 | 0.609 |
| Gender=male | 0.823 [95% CI: 0.823-0.823] | 0.695 | 0.665 |
| Race=white | 0.709 [95% CI: 0.709-0.710] | 0.581 | 0.551 |
| Hospitalisation | 0.677 [95% CI: 0.677-0.677] | 0.549 | 0.519 |
| ≤3 months until end of life | 0.662 [95% CI: 0.662-0.662] | 0.534 | 0.504 |
| Key: CI, confidence interval; PD, progressed disease; PR, partial response; SD, stable disease; TA, technology appraisal; VGPR, very good partial disease | | | |

A limitation of the conventional approach to utility analysis by assessing overall response states is that it is believed that a patients' HRQL may not decline upon progression, but instead utility scores may be relatively stable until around three months before death, when a substantial decrease in HRQL is observed. Whilst expected to yield the lowest utility value out of the four response states, the utility value for PD may be overestimated within the statistical regression model. Therefore, a time to death analysis (TTD) may provide an alternative approach when estimating HRQL over time – see Section 2.1.2.1.

### *2.1.3.2* Utility regression model inputs

Response status

The application of the coefficients associated with response status are applied the same as in the original model.

Age

Age at baseline was included as a continuous variable within the utility regression analysis. The coefficient associated with this variable described the impact of an additional year on utility (i.e. for every year increase in age the utility decreased by 0.001). Each cycle the number of years forgone in the model was multiplied by the coefficient associated with age to estimate the utility decrement associated with increasing age.

Gender

Gender was included as a dichotomous variable within the utility regression analysis. The coefficient associated with this variable described the impact of being male (i.e. male patients were associated with a relative increase in utility of 0.055). The proportion of male patients was obtained from the secondary interim analysis (56.23% for the 2+ prior lines population).

The utility decrement associated with being male is multiplied by the proportion of male patients and applied to the overall utility estimate each cycle.

Race

Whether a patient was white was found to be a significant predictor of utility. Therefore, this was included as a dichotomous variable within the utility regression analysis. The coefficient associated with the variable described the impact of being white (i.e. white patients were associated with a relative decrease in utility of 0.059 compared to non-white patients). The proportion of white patients was obtained from the secondary interim analysis (82.49% for the 2+ prior lines population).

The utility decrement associated with white patients is multiplied by the proportion of white patients and applied to the overall utility estimate each cycle.

Hospitalisations

The application of the coefficients associated with hospitalisations are applied the same as in the original model.

End of life

The application of the coefficients associated with end of life are applied the same as in the original model.

AEs

The application of the coefficients associated with AEs are applied the same as in the original model.

#### *2.1.3.1* Supportive time to death utility analysis

As an alternative to the conventional approach of assessing HRQL (utilities) by response and progression status, we have also looked further into the pattern of HRQL over time in patients with RRMM by conducting further analysis of the EQ-5D data from the 2nd IA dataset according to time to death (TTD). This represents an alternative approach to using markers of response and disease progression for quality of life/utility estimation that potentially fits better to evaluation of HRQL patterns over time in patients with advanced cancer. The clinical experts attending the Takeda advisory board of 16th May 2017 supported the notion that most RRMM patients HRQL will be stable or slowly declining and deteriorate closer to death, with agreement that the time point at which HRQL would reduce most is at 3 months prior to death.

The analysis of utility according to TTD has been used in previous HTA submissions to NICE in cancer (ipilimumab in myeloma, pembrolizumab in NSCLC). The TTD analysis we have conducted for RRMM is supportive of patients experiencing a reasonably stable, quality of life up to 12 months prior to death, and remaining stable to slightly declining between less than 12 months before death and 3 months prior to death, but a larger decrease for the final 3 months. The time to death analysis has been used in previous HTA submissions to NICE in cancer (ipilimumab in myeloma, pembrolizumab in NSCLC), with

similar patterns emerging. This is similar to the pattern found using this approach in analysis of EQ-5D data by time to death for ipilumumab in malignant melanoma. [6]

As a sensitivity analysis (qualitative assessment only), the regression model was fitted to the data but the inclusion of TTD superseded both the overall response assessment states and death occurring within three months' covariates. TTD was categorised into four time periods and these were determined based on the clinical expert feedback at the advisory board of 16th May. An identical approach was taken as for the conventional framework (i.e. a mixed-effects model applied to longitudinal data, utilising a stepwise selection procedure). Results from the TTD analysis are presented in Table 14.

**Table 14: Utility coefficients for parameters obtained using the EQ-5D from the TOURMALINE-MM1 trial (2nd IA) from a time to death analysis**

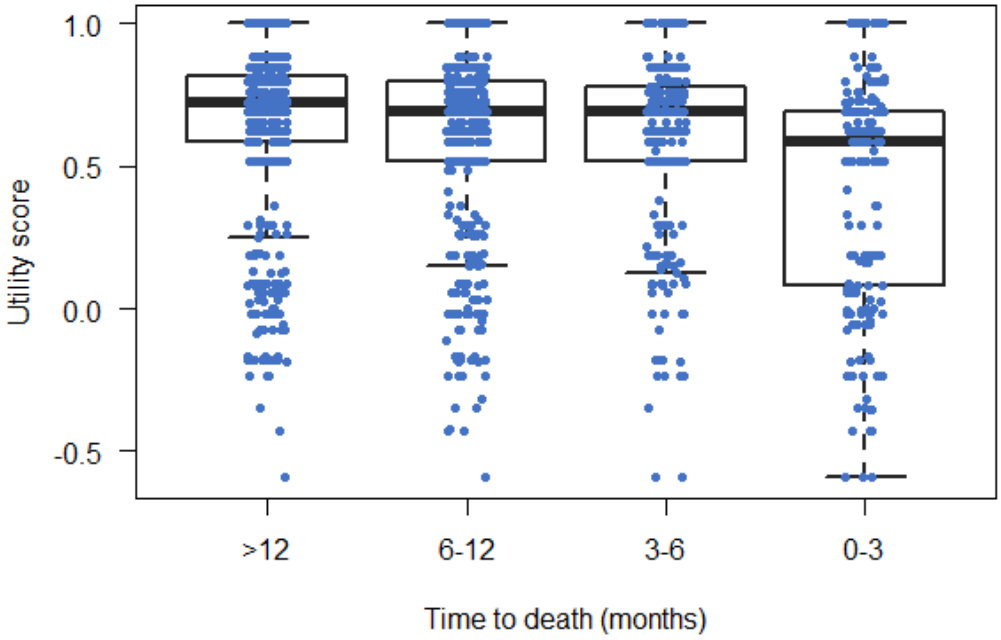
| Parameter | Coefficient | Standard Error | 95% Lower CI | 95% Upper CI | Abs(t-value) | p-value |
|---|---|---|---|---|---|---|
| Intercept | 0.800 | 0.063 | 0.677 | 0.923 | 12.798 | <0.001* |
| Grade 3/4 AE (ref=0) | | | | | | |
| ≥1 | -0.040 | 0.008 | -0.056 | -0.024 | 5.107 | <0.001* |
| Age (years) | -0.001 | <0.001 | -0.003 | 0.001 | 0.778 | 0.437 |
| Gender (ref=female) | | | | | | |
| Male | 0.055 | 0.017 | 0.022 | 0.088 | 3.235 | 0.001* |
| Race (ref=non-white) | | | | | | |
| White | -0.071 | 0.026 | -0.122 | -0.020 | 2.749 | 0.006* |
| Total number of hospitalisations (ref=0) | | | | | | |
| ≥1 | -0.086 | 0.017 | -0.119 | -0.053 | 4.967 | <0.001* |
| Time to death (months) (ref=12+) | | | | | | <0.001* |
| 6-12 months | -0.010 | 0.011 | -0.032 | 0.012 | 0.979 | (0.328) |
| 3-6 months | -0.031 | 0.014 | -0.058 | -0.004 | 2.272 | (0.023) |
| ≤3 months | -0.172 | 0.016 | -0.203 | -0.141 | 10.758 | (<0.001*) |

Key: Abs, absolute; AE, adverse event; CI, confidence interval; EQ-5D, EuroQol 5-dimensions; IA, interim analysis; ref, reference;
* statistically significant at 5% level.
Notes: Censored patients who provided HRQL record(s) at least 12 months before censoring were included in the reference category for the time to death variable.

The regression model results for the TTD analysis show similar trends as those observed when adopting a conventional approach (based on overall response states); grade 3/4 AEs, sex, race, hospitalisations and time to death were associated with a statistically significant effect on utility. The presence of at least one grade 3/4 AE and at least one hospitalisation reduced a patient's HRQL. Male patients were associated with higher utility scores vs females. The TTD variable showed that utility scores decline over time; there was a non-significant difference between 6-12 months' vs 12+ months, but there was a statistically significant difference between both 3-6 months and less than 3 months' vs 12+ months (i.e. it is expected that utility scores are significantly lower as TTD decreases). The variable representing the occurrence of new prior malignancies was dropped during the stepwise selection process; this is likely due to the limited number of new prior malignancy cases observed. A plot of the utility values over time (for patients who died) is presented in

Figure 17**Error! Reference source not found.** which shows the decreasing trend as the time to death approaches zero. Whilst decreasing slightly, the average (median) utility values remain fairly stable for the three time categories 12+, 6-12 and 3-6 months, suggesting that utility values may not substantially differ when TTD is greater than 3 months, with the largest decrement observed in the last time category (less than 3 months). In addition, the range of utility values is much wider when TTD is less than three months, with a higher proportion of patients recording lower utility values (compared with the other time categories).

**Figure 17: Utility values over time**




Resulting utility values for each TTD category (based on the mean of covariates approach) are:

- 12+ months: 0.679
- 6-12 months: 0.669
- 3-6 months: 0.648
- ≤3 months: 0.507

This shows a clearer drop in in utility values when the TTD is 3 months or less, which supports the clinicians' feedback that HRQL reduces substantially in the last few months of life, rather than upon progression. The results from the TTD analyses support the utility estimates obtained from adopting a conventional approach (inclusion of overall response assessments) and moreover, the first approach also included a dichotomous variable indicating whether a patient's record was within 3 months of death, which is where the largest drop in utility is observed in the TTD analysis and so TTD is captured to some extent in the original regression model.

### 2.1.4 Handling of time on treatment in the model

Table 15 presents the definition of the PFS and ToT outcomes from the TOURMALINE-MM1 clinical trial.

**Table 15: Definition of censoring/ events for PFS and ToT**

| PFS | | ToT | |
|---|---|---|---|
| Event | Censoring | Event | Censoring |
| • Progression<br>• Death | • Alternative therapy<br>• Dying or progressing after more than 1 missed visit<br>• No baseline/post baseline<br>• No documented death or progression<br>• Lost to follow up<br>• Withdrawal of consent | Discontinuing treatment due to:<br>• Progression<br>• Adverse event<br>• Protocol violation<br>• Study termination by sponsor<br>• Withdrawal of consent<br>• Lost to follow up<br>• Other | Continue on treatment at the time of data cut-off |

As per the email from NICE dated 10th May 2017, the ERG has requested further detail around the response to clarification question B7c.

*NICE Committee request: Present the different events that contribute to the events in columns E and Y for "Disc Treatments" of the Lifetable (ToT) worksheet.*

Table 16 presents the different events that contribute to the events in column E and Y for "Disc Treatments" of the Lifetable (ToT) worksheet for the primary and secondary data cuts in the 2+ prior lines population. The patient level data for IXA+LEN+DEX and LEN+DEX for both data cuts are provided in separate documents, named:

- "2017 05 17LENDEX ToT KM Disc Treatments IA1"
- "2017 05 17LENDEX ToT KM Disc Treatments IA2"
- "2017 05 17IXALENDEX ToT KM Disc Treatments IA1"
- "2017 05 17IXALENDEX ToT KM Disc Treatments IA2"

These are the data that were used in the original model (1st IA analysis) and the updated model (2nd IA analysis).

**Table 16: Patient level data for reasons for treatment discontinuation for primary and secondary data cuts**

| Data cut | Arm | N | Discontinuation Event | | | | | | | Censor |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | All | Progression | AE | Withdrawal | Study Termination | Protocol Violation | Other | |
| 1st IA | LEN+DEX | 149 | 76 | 39 | 23 | 11 | 1 | 1 | 1 | 73 |
| | IXA+LEN+DEX | 148 | 61 | 30 | 18 | 10 | 1 | 0 | 2 | 87 |
| 2nd IA | LEN+DEX | 149 | 103 | 57 | 30 | 13 | 1 | 1 | 1 | 46 |
| | IXA+LEN+DEX | 148 | 88 | 46 | 24 | 14 | 1 | 0 | 3 | 60 |
| Key: AE, adverse event; DEX, dexamethasone; IA, interim analysis; IXA, ixazomib; LEN, lenalidomide; N, number | | | | | | | | | | |

*NICE Committee request: Present the different events that contribute to the events in columns F and Z for "Censored" of the Lifetable (ToT) worksheet*

Columns F and Z present the number of patients censored for the ToT outcome for LEN+DEX and IXA+LEN+DEX, respectively.

The only event that causes a patient to be "censored" for this outcome is if the patients are still on treatment at time of cut-off. Therefore, the patient numbers within the model present the numbers for this event. Even though there is a fixed cut-off date (i.e. 2nd IA: July 2015), patients start the study at various time points, so the follow-up time for each patient is highly variable. For example, the first censor in the ITT population for the 1st IA cut was randomised on the 27th May 2014 and as such would be censored at 22 weeks and as such the 30-week censor in the 2+ prior line population is reasonable in this context.

The NICE Committee further requested that we align these definitions with the company response to clarification question B7b, in order to permit a read across between the PFS curve and the ToT curve events. As there are likely differences between the number of events due to the ToT being measured using investigator response and PFS being measured using the IRC response, Takeda are sourcing the investigator led response PFS data to allow for this comparison. Takeda will present these data to NICE in due course.

### 2.1.5 Update in method used to cost treatments taken after progression

In line with the feedback from the ERG, the company have updated the method used to cost treatments taken after progression. Both the NICE committee and the ERG concluded that treatments taken after progression should be modelled weekly.

The ERG suggested that "it may be more reasonable to apply an incident cost of £1,081 and an ongoing weekly treatment cost. Based upon the information in the electronic model this can be crudely calculated as a weekly treatment costs for those receiving active treatment of £1,561. This estimate is for illustrative purposes. The ERG is not arguing that it is a realistic estimate and it may be too high given the complex lenalidomide and bortezomib PASs. The company should be free to come up with its own estimate.[7]

Based on this feedback, an incident cost of £1,081 was applied to patients upon entry to the progression health state. However, it was considered that applying a weekly cost of £1,561 would overestimate the costs of subsequent therapy; the weekly cost would be applied over the entire duration of time spent in the post-progression health state, rather than applied over the duration of treatment. This would result in an overestimation of subsequent therapy costs.

The method used by the model takes account of the weekly costs of each individual subsequent treatment and weights this by the proportion of time spent in the post-progression health state the treatment is anticipated to be received for; this is calculated by dividing the duration of treatment in weeks by the average number of weeks spent in post-progression. These weighted weekly costs are then summed to provide a weekly cost. As

the time spent in the post-progression health state varies between treatment arm, separate weighted weekly costs were calculated for IXA+LEN+DEX and LEN+DEX. In the base case, the average number of weeks spent in post-progression was:

- 110.98 for IXA+LEN+DEX
- 84.83 for LEN+DEX

The total costs associated with each subsequent treatment are as presented in the original submission dossier. Table 17 presents these total costs, the weekly costs, the proportion of time spent in post-progression receiving treatment and the weighted weekly costs for IXA+LEN+DEX and LEN+DEX. This results in a total weekly cost of:

- £708.28 for IXA+LEN+DEX
- £926.68 for LEN+DEX

The weekly cost associated with IXA+LEN+DEX is found to be lower. This is consistent with what we would expect given the data; the number of subsequent therapies were not different between the treatment arms yet the duration of time spent in the post-progression health state was longer for IXA+LEN+DEX. Therefore, lower costs are spread over a longer time.

**Table 17: Weekly costs associated with subsequent therapy**

| | | | | IXA+LEN+DEX | | LEN+DEX | |
|---|---|---|---|---|---|---|---|
| **Therapy** | **Duration of treatment in weeks** | **Total** | **Weekly cost** | **Proportion of time spent in post-progression receiving treatment** | **Weighted weekly costs** | **Proportion of time spent in post-progression receiving treatment** | **Weighted weekly costs** |
| Bendamustine + Prednisolone | 15.91 | £981.93 | 61.74 | 14.33% | £8.85 | 18.75% | £11.58 |
| Cyclophosphamide | 58.06 | £11,035.06 | 190.06 | 52.32% | £99.43 | 68.45% | £130.09 |
| Doxorubicin | 15.00 | £2,216.73 | 147.78 | 13.52% | £19.97 | 17.68% | £26.13 |
| Lenalidomide + dexamethasone | 58.06 | £14,447.47 | 248.83 | 52.32% | £130.18 | 68.45% | £170.32 |
| Melphalan + Prednisolone | 48.00 | £1,566.42 | 32.63 | 43.25% | £14.11 | 56.59% | £18.47 |
| Thalidomide + dexamethasone | 17.39 | £1,222.29 | 70.28 | 15.67% | £11.01 | 20.50% | £14.41 |
| Panobinostat+bortezomib+dexamethasone | 21.74 | £47,137.60 | 2168.14 | 19.59% | £424.73 | 25.63% | £555.69 |
| **Total weekly costs** | | | | | **£780.28** | | **£926.68** |
| Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide | | | | | | | |

### 2.1.6 New scenario analysis: use of adjusted 2-prior data

#### *2.1.6.1* Exploring cost-effectiveness in the 2-prior therapy sub-group

This Section summarises the survival analysis conducted using the 2-prior subgroup secondary analysis (2ND IA) data. The methods are in line with those used in the original submission and for the updated 2+ prior lines population.

Additional inputs associated with overall response, number of hospitalisations, concomitant medication use, subsequent therapy and AEs were also updated with 2-prior lines specific data in this scenario analysis. These inputs are available at request or can be found within the updated model "2017 05 19Ixazomib CEA Model – UK adaptation_Updatev2."

Covariate adjustment

Log-rank tests were used to detect evidence of significant differences in clinical endpoints between the two treatment arms in the 2 prior therapies subgroup based on observed data for PFS, OS and ToT. These tests indicated that in addition to treatment, there were several patient risk factors that appeared to be associated with differences in clinical endpoints. Therefore, covariate adjustment was used to account for potential imbalances between the two treatment arms. This is implemented within the economic model using the mean of covariates method.

The data for covariate adjustment were obtained from the TOURMALINE-MM1 trial. Patient characteristics for the 2-prior subgroup are presented in Table 18.

**Table 18: Patient characteristics in the 2-prior lines population from TOURMALINE-MM1**

| Risk Factor | IXA+LEN+DEX (n) | IXA+LEN+DEX (%) | LEN+DEX (n) | LEN+DEX (%) |
|---|---|---|---|---|
| High risk cytogenetics (del(17), t(4:14), t(14:16)) | 20 | 54.05% | 17 | 45.95% |
| ISS Stage III | 11 | 52.38% | 10 | 47.62% |
| Age > 65 years | 53 | 50.00% | 53 | 50.00% |
| Light chain myeloma = Yes | 16 | 42.11% | 22 | 57.89% |
| Relapsed and refractory = Yes | 23 | 47.92% | 25 | 52.08% |

| | | | | |
|---|---|---|---|---|
| Primary refractory = Yes | 8 | 47.06% | 9 | 52.94% |
| Proteasome inhibitor = Yes | 76 | 46.91% | 86 | 53.09% |
| Immunomodulation agent = Yes | 63 | 45.32% | 76 | 54.68% |
| ECOG performance score = 2 | 7 | 38.89% | 11 | 61.11% |
| ASCT undertaken = Yes | 56 | 45.16% | 68 | 54.84% |
| History of bone lesions = Yes | 78 | 49.37% | 80 | 50.63% |
| Renal dysfunction = Yes | 10 | 45.45% | 12 | 54.55% |
| Asian = Yes | 6 | 35.29% | 11 | 64.71% |
| Key: ASCT, allogenic stem cell transplant; ECOG, Eastern Cooperative Oncology Group; ISS, international staging system; IXALENDEX, ixazomib + lenalidomide + dexamethasone; LENDEX, lenalidomide + dexamethasone; n, number | | | | |

Variables from the 2nd IA sub-grouped data were assessed for collinearity and significance in a multivariable Cox regression model using backwards stepwise regression techniques. The covariates included in the economic model are presented in Table 19.

**Table 19: Covariate data for the 2-prior lines population**

| | 2-prior lines covariates |
|---|---|
| PFS | Light chain myeloma = Yes |
| OS | ISS =Stage 3<br>Age > 65 years<br>History of bone lesions |
| ToT | ISS = stage 3<br>Renal dysfunction = Yes |
| Key: ISS, international staging system; OS, overall survival; PFS, progression free survival; ToT, time on treatment | |

Overview of extrapolation

In line with the NICE DSU [1] guidance the applicability of a single parametric model or a Cox proportional hazards model was determined using visual inspection of the KM curves, the

LCHPs and the Q-Q curves. LCHPs were assessed to determine the suitability of using a single parametric model for the two treatment arms in terms of the underlying hazard and in assessing the suitability of projecting using exponential, Weibull and Gompertz curves. Q-Q plots were assessed to determine the suitability of the use of AFT models.

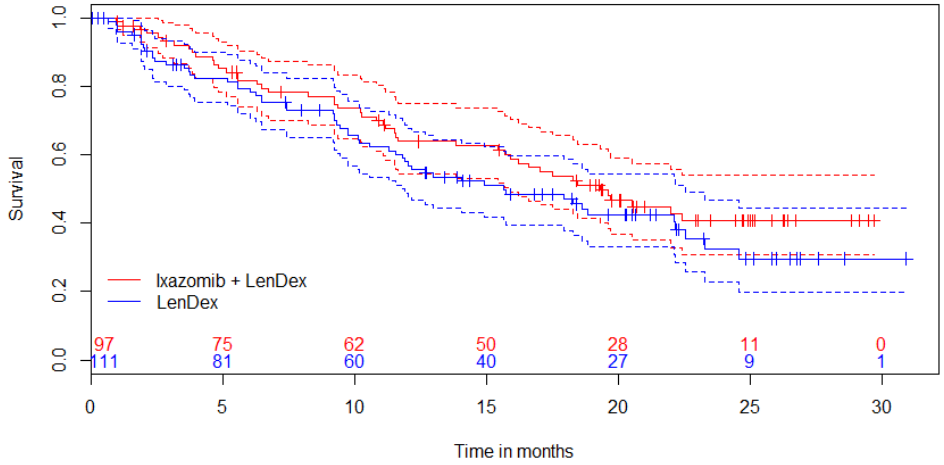
Six parametric distributions (exponential, log-normal, log-logistic, Gompertz, generalised gamma and Weibull) were examined for each clinical outcome (OS, PFS and ToT), in line with the NICE DSU guidance. The fit of each parametric model to the covariate adjusted survival data was explored using visual inspection, LCHPs, Schoenfeld residual plots, Q-Q plots, AIC and BIC goodness of fit statistics and clinical plausibility. AIC and BIC provide an estimated relative fit of the alternative parametric models to the observed trial data. All curves were fitted using statistical software package R.

Progression free survival (PFS)

The Kaplan-Meier curves, the LCHPs, the Schoenfeld residual plots, the Q-Q plots and the AIC and BIC estimates for the covariate adjusted PFS associated with LEN+DEX are presented in Figure 18 to Figure 21 for the 2-prior lines population. These methods suggest that the exponential provides the most appropriate choice of model; the data satisfy the proportional hazards assumption required when fitting an exponential curve and this curve has relatively low AIC/BIC (

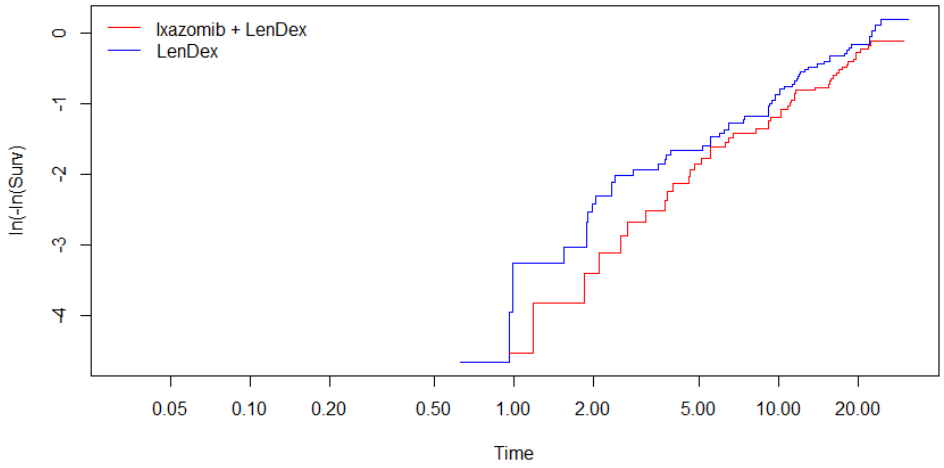
Table 20).

**Figure 18: Kaplan-Meier plot for PFS, 2-prior lines population**



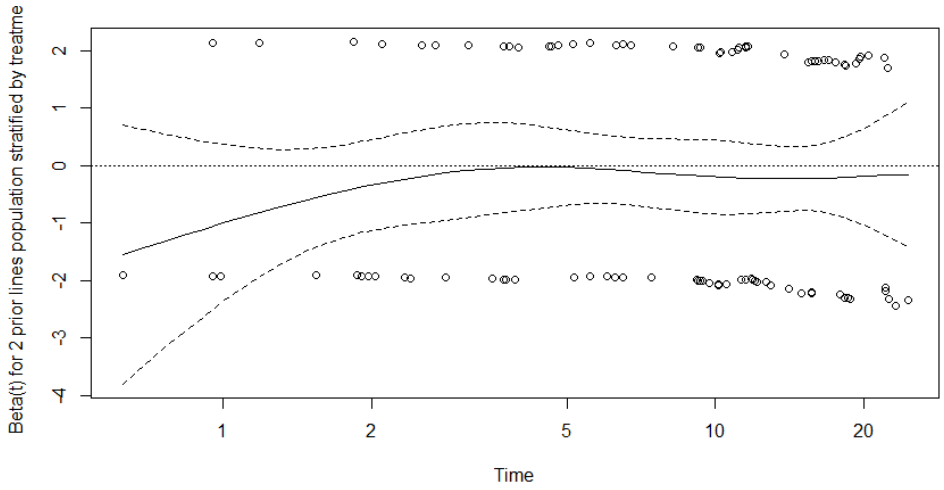

Key: LenDex, lenalidomide and dexamethasone; PFS, progression free survival

**Figure 19: LCHP plot for PFS, 2-prior lines population**



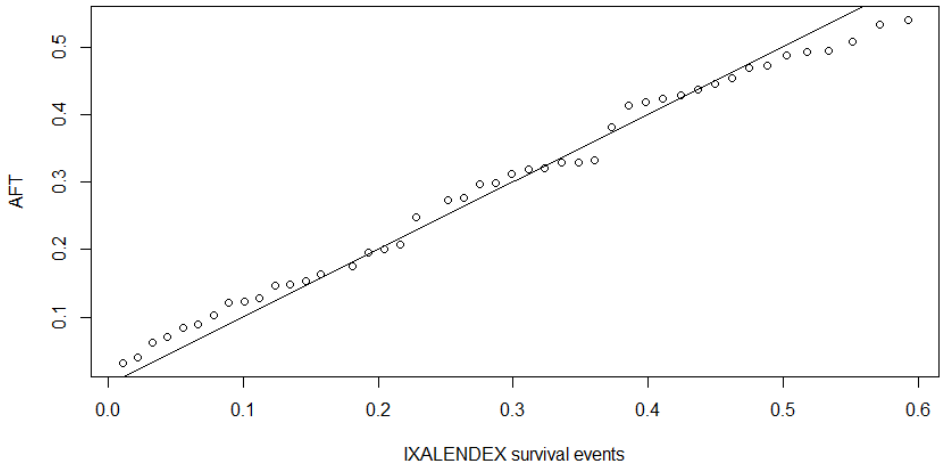

Key: LCHP, log cumulative hazard plot; LenDex, lenalidomide and dexamethasone; PFS, progression free survival

**Figure 20: Schoenfeld residuals for PFS, 2-prior lines population**




Key: PFS, progression free survival

**Figure 21: Q-Q curves for PFS, 2-prior lines population**



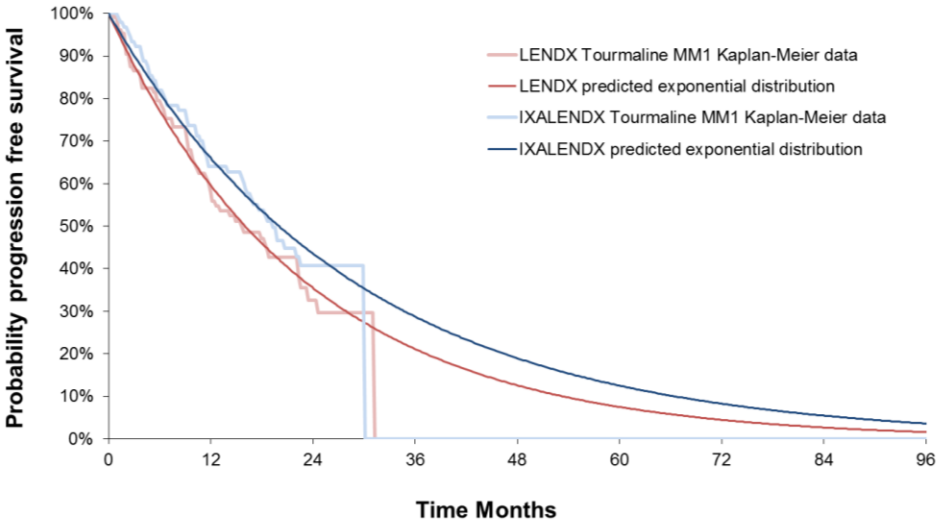

Key: AFT, accelerated failure time; IXALENDEX, ixazomib, lenalidomide and dexamethasone; PFS, progression free survival

**Table 20: AIC and BIC estimates for covariate adjusted curves for PFS, 2-prior lines population**

| | Model | N | ll(null) | ll(model) | df | AIC | BIC |
|---|---|---|---|---|---|---|---|
| 1 | Exponential | 208 | -445.6927044 | -442.810102 | 2 | 891.620204 | 896.2952802 |
| 2 | Weibull | 208 | -444.7269631 | -441.6034449 | 3 | 891.2068898 | 899.219504 |
| 3 | Gompertz | 208 | -445.5252209 | -442.5319707 | 3 | 893.0639414 | 901.0765556 |
| 4 | Lognormal | 208 | -443.3616891 | -439.3440167 | 3 | 886.6880335 | 894.7006477 |
| 5 | Log logistic | 208 | -443.9553741 | -439.828777 | 3 | 887.6575539 | 895.6701682 |
| 6 | Gamma | 208 | -443.2130367 | -439.2827066 | 4 | 888.5654132 | 899.9155655 |
| Key: AIC, Akaike information criteria; BIC, Bayesian information criteria; df, degrees of freedom; N, number; PFS, progression free survival | | | | | | | |

The applicability of using unstratified models for the comparison of IXA+LEN+DEX with LEN+DEX for PFS was determined using the LCHP plots, the Q-Q plots and visual inspection. The LCHP and the Q-Q curves support the assumption of proportional hazards and AFT functionality, respectively, and as such a treatment effect was estimated for IXA+LEN+DEX compared with LEN+DEX [treatment effect: 0.80 related to LEN+DEX, 95% CI: 0.55-1.18] and applied to the LEN+DEX fitted exponential covariate-adjusted PFS curve. Figure 22 compares the modelled IXA+LEN+DEX curves with the original IXA+LEN+DEX data, this indicates a reasonably good visual fit.

**Figure 22: Comparison of fitted covariate adjusted PFS curves (exponential) with unadjusted Kaplan-Meier curves for IXA+LEN+DEX in the 2-prior lines subgroup**



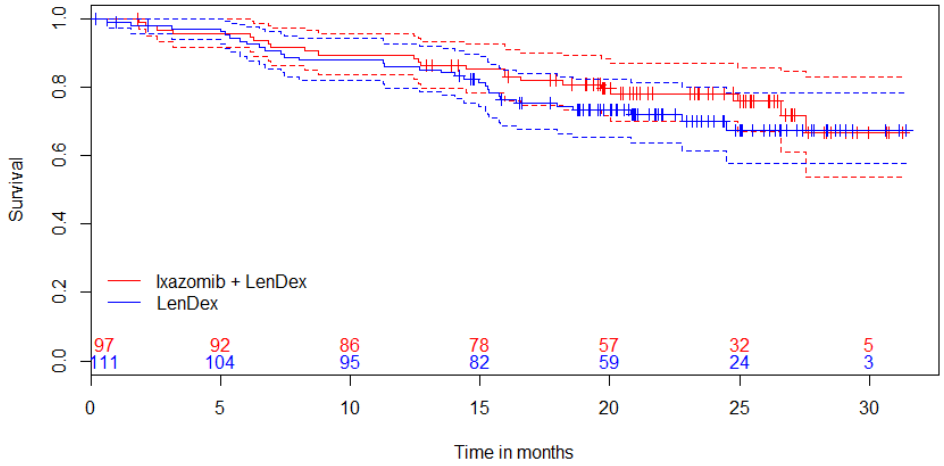

Key: DEX, dexamethasone; IXA, ixazomib; IXALENDX, ixazomib, lenalidomide and dexamethasone; LEN, lenalidomide; LENDX, lenalidomide and dexamethasone; PFS, progression free survival

Overall survival (OS)

The Kaplan-Meier curves, the LCHPs, the Schoenfeld residual plots, the Q-Q plots and the AIC and BIC estimates for the covariate adjusted OS associated with LEN+DEX are presented in Figure 23 to Figure 26 for the 2-prior lines population. These methods suggest that the exponential provides the most appropriate choice of model; the data satisfy the proportional hazards assumption required when fitting an exponential curve and this curve has relatively low AIC/BIC (

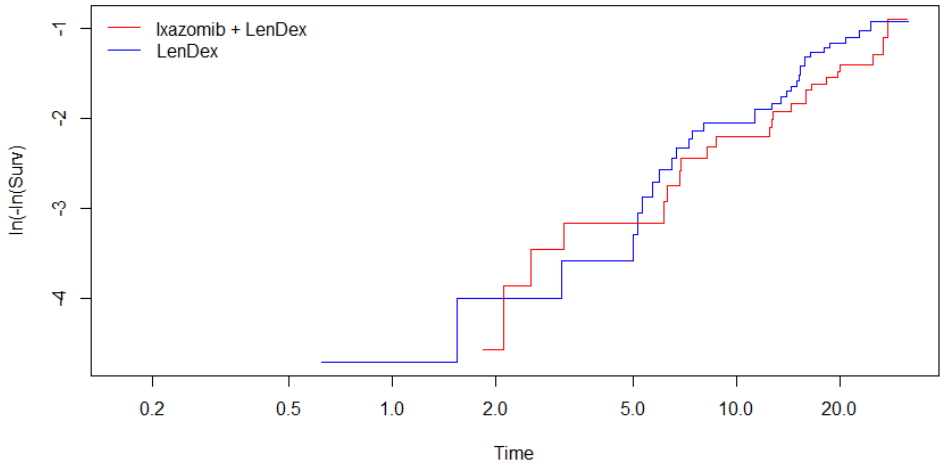
Table 21).

**Figure 23: Kaplan-Meier plot for OS, 2-prior lines population**



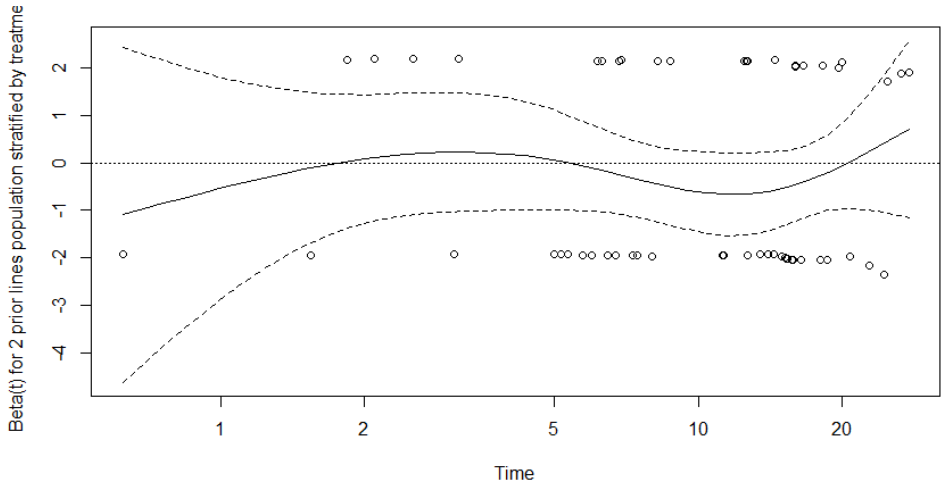

Key: LenDex, lenalidomide and dexamethasone; OS, overall survival

**Figure 24: LCHP plot for OS, 2-prior lines population**



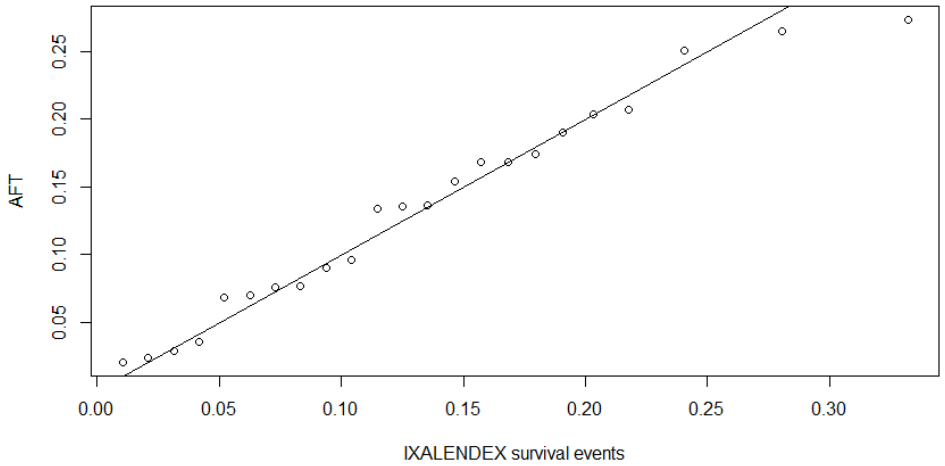

Key: LCHP, log cumulative hazard plot; LenDex, lenalidomide and dexamethasone; OS, overall survival

**Figure 25: Schoenfeld residuals plot for OS, 2-prior lines population**




Key: OS, overall survival

**Figure 26: Q-Q curve for OS, 2-prior lines population**




Key: AFT, accelerated failure time; IXALENDEX, ixazomib, lenalidomide and dexamethasone; OS, overall survival

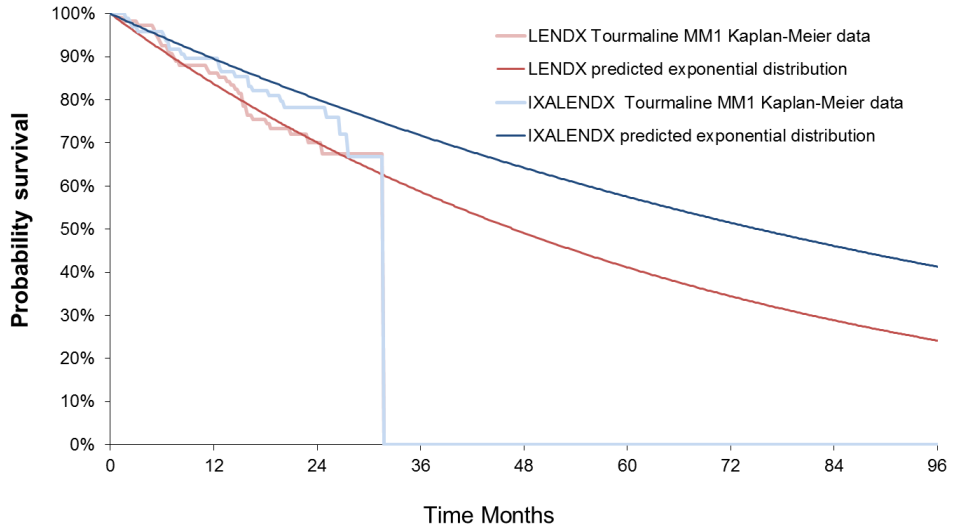
**Table 21: AIC and BIC estimates for covariate adjusted curves for OS, 2-prior lines population**

| | Model | N | ll(null) | ll(model) | df | AIC | BIC |
|---|---|---|---|---|---|---|---|
| 1 | Exponential | 208 | -287.6662361 | -278.8494794 | 2 | 567.6989588 | 568.3740349 |
| 2 | Weibull | 208 | -286.7665997 | -277.5599047 | 3 | 567.1198093 | 571.1324236 |
| 3 | Gompertz | 208 | -287.3482553 | -278.2806296 | 3 | 568.5612591 | 572.5738734 |
| 4 | Lognormal | 208 | -286.4146397 | -277.3835698 | 3 | 566.7671396 | 570.7797538 |
| 5 | Log logistic | 208 | -286.5324839 | -277.5131816 | 3 | 567.0263632 | 571.0389774 |
| 6 | Gamma | 208 | -286.3258565 | -277.2147924 | 4 | 568.4295848 | 575.7797371 |
| Key: AIC, Akaike information criteria; BIC, Bayesian information criteria; df, degrees of freedom; N, number; OS, overall survival | | | | | | | |

The applicability of using unstratified models for the comparison of IXA+LEN+DEX with LEN+DEX for OS was determined using the LCHP plots, the Q-Q plots and visual inspection. The LCHP and the Q-Q curves support the assumption of proportional hazards and AFT functionality, respectively, and as such a treatment effect was estimated for IXA+LEN+DEX compared with LEN+DEX [treatment effect: 0.62 related to LEN+DEX, 95% CI: 0.36-1.09] and applied to the LEN+DEX fitted exponential covariate-adjusted OS curve.

Figure 27 compares the modelled IXA+LEN+DEX curves with the original IXA+LEN+DEX data, this indicates a reasonably good visual fit.

**Figure 27: Comparison of fitted covariate adjusted OS curves (exponential) with unadjusted Kaplan-Meier curves for IXA+LEN+DEX in the 2-prior lines subgroup**



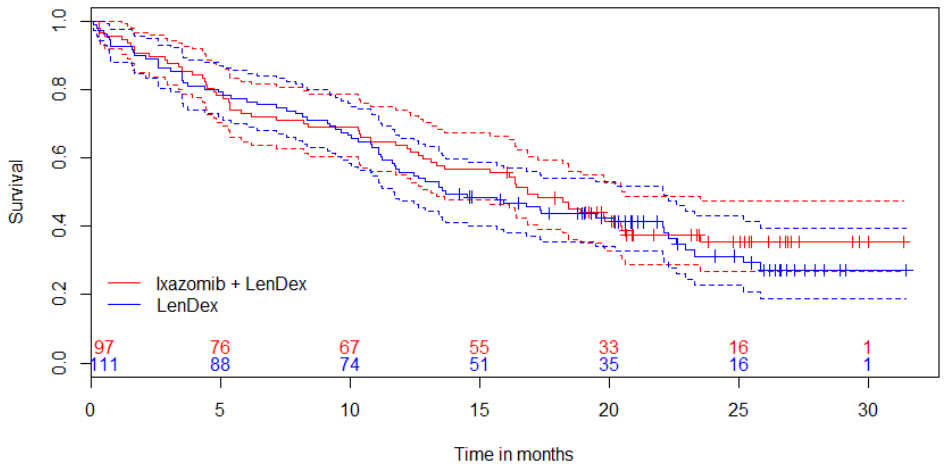

Key: DEX, dexamethasone; IXA, ixazomib; IXALENDX, ixazomib, lenalidomide and dexamethasone; LEN, lenalidomide; LENDX, lenalidomide and dexamethasone; OS, overall survival

Time on treatment (ToT)

The Kaplan-Meier curves, the LCHPs, the Schoenfeld residual plots, the Q-Q plots and the AIC and BIC estimates for the covariate adjusted ToT associated with LEN+DEX are presented in Figure 28 to Figure 31 for the 2-prior lines population. These methods suggest that the exponential provides the most appropriate choice of model; the data satisfy the proportional hazards assumption required when fitting an exponential curve and this curve has relatively low AIC/BIC (

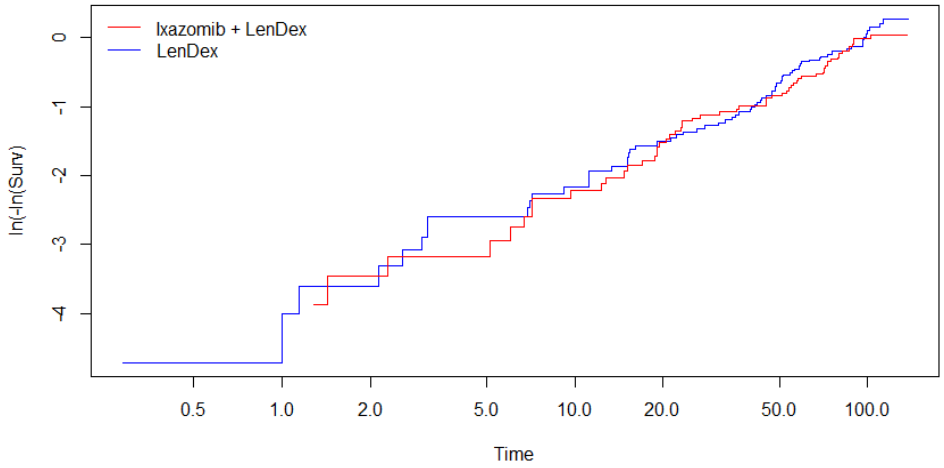
Table 22).

**Figure 28: Kaplan-Meier plot for ToT, 2-prior lines population**



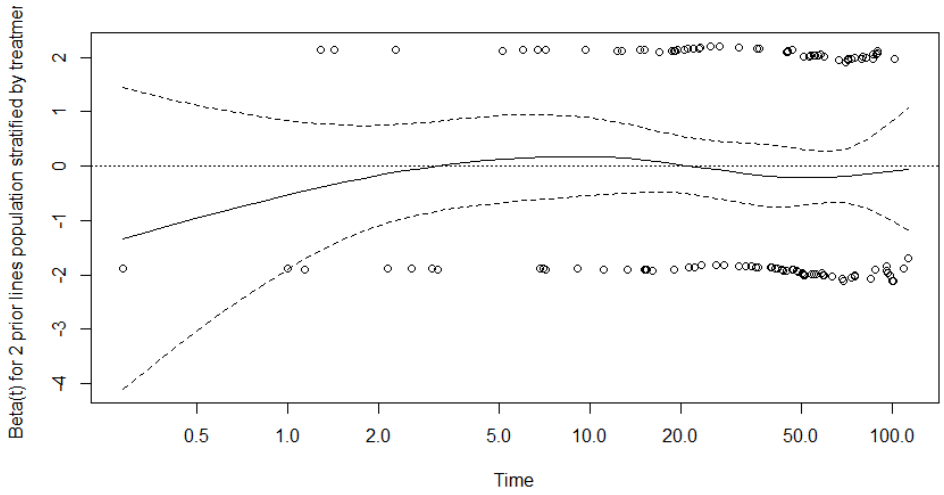

Key: LenDex, lenalidomide and dexamethasone; ToT, time on treatment

**Figure 29: LCHP plot for ToT, 2-prior lines population**



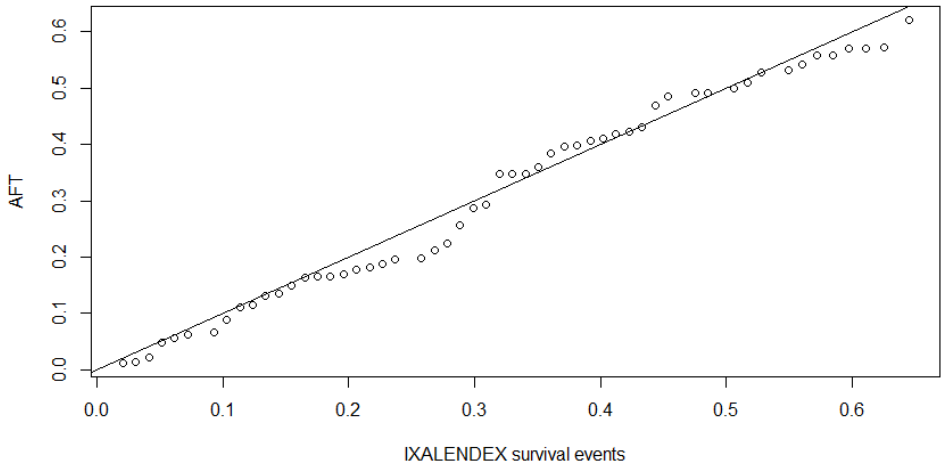

Key: LCHP, log cumulative hazard plot; LenDex, lenalidomide and dexamethasone; ToT, time on treatment

**Figure 30: Schoenfeld residuals plot for ToT, 2-prior lines population**




Key: ToT, time on treatment

**Figure 31: Q-Q curve for ToT, 2-prior lines population**




Key: IXALENDEX, ixazomib, lenalidomide and dexamethasone; ToT, time on treatment

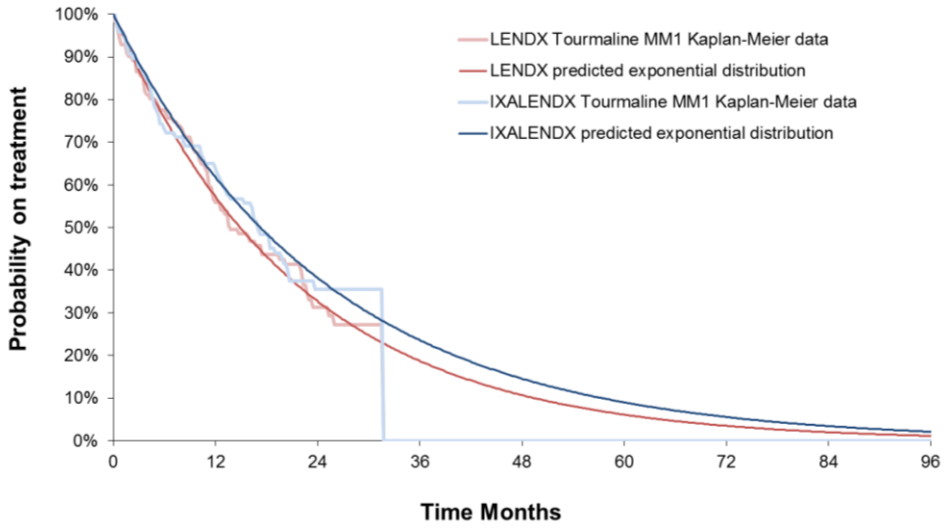
**Table 22: AIC and BIC estimates for covariate adjusted curves for ToT, 2-prior lines population**

| | Model | N | ll(null) | ll(model) | df | AIC | BIC |
|---|---|---|---|---|---|---|---|
| 1 | Exponential | 208 | -739.7423903 | -734.8581395 | 2 | 1477.716279 | 1480.391355 |
| 2 | Weibull | 208 | -739.5827813 | -734.7811943 | 3 | 1479.562389 | 1485.575003 |
| 3 | Gompertz | 208 | -739.7216692 | -734.8581351 | 3 | 1479.71627 | 1485.728884 |
| 4 | Lognormal | 208 | -745.6752931 | -740.1306353 | 3 | 1490.261271 | 1496.273885 |
| 5 | Log logistic | 208 | -741.8952109 | -737.2479134 | 3 | 1484.495827 | 1490.508441 |
| 6 | Gamma | 208 | -739.4522751 | -734.7153492 | 4 | 1481.430698 | 1490.780851 |
| Key: AIC, Akaike information criteria; BIC, Bayesian information criteria; df, degrees of freedom; N, number; ToT, time on treatment | | | | | | | |

The applicability of using unstratified models for the comparison of IXA+LEN+DEX with LEN+DEX for ToT was determined using the LCHP plots, the Q-Q plots and visual inspection. The LCHP and the Q-Q curves support the assumption of proportional hazards and AFT functionality, respectively, and as such a treatment effect was estimated for IXA+LEN+DEX compared with LEN+DEX [treatment effect: 0.86 related to LEN+DEX, 95% CI: 0.61-1.22] and applied to the LEN+DEX fitted exponential covariate-adjusted ToT curve.

Figure 32 compares the modelled IXA+LEN+DEX curves with the original IXA+LEN+DEX data, this indicates a reasonably good visual fit.

**Figure 32: Comparison of fitted covariate adjusted ToT curves (exponential) with unadjusted Kaplan-Meier curves for IXA+LEN+DEX in the 2-prior lines subgroup**




Key: DEX, dexamethasone; IXA, ixazomib; IXALENDX, ixazomib, lenalidomide and dexamethasone; LEN, lenalidomide; LENDX, lenalidomide and dexamethasone; ToT, time on treatment

# 3. Updated results

This Section presents the results associated with the updated model. The updated model has been sent as a separate document: “2017 05 19Ixazomib CEA Model – UK adaptation_Updatev2.”

### 3.1.1 Updated base case results

The base case results for IXA+LEN+DEX compared with LEN+DEX are shown in Table 23 for the patient population that have had at least two prior therapies, used to represent a 3rd line treatment positioning for ixazomib. The list price of ixazomib has been discounted using the PASLU agreed PAS of [redacted]

**Table 23: Base case results of updated model with PAS**

| Treatment | Total Costs £ | Total QALYs | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|---|---|
| IXA+LEN+DEX | **£255,289** | **3.71** | | | |
| LEN+DEX | **£132,369** | **2.73** | **£122,920** | **0.98** | **£125,277** |
| Key: DEX, dexamethasone; ICER, incremental cost effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; QALY, quality-adjusted life year | | | | | |

#### *3.1.1.1* Updated clinical outcomes results

Table 24 displays the clinical outcomes and the model outcomes for the three main measures: OS, PFS and ToT. Model outcomes are presented as a mean across the trial period. Clinical outcomes are presented for all comparisons assuming the base case parametric curve fits and adjusting covariates using the mean of covariates method.

The mean OS, PFS and ToT are comparable and consistent with the respective observed clinical outcomes reported in the TOURMALINE-MM1 clinical trial.

**Table 24: Comparison of clinical outcomes with model outcomes for the 2+ prior lines population**

| Outcome | Clinical trial result | Model result | Clinical trial result | Model result |
|---|---|---|---|---|
| **Median survival (months) 2+ prior lines population (n=297)** | | | | |
| | **IXA+LEN+DEX** | | **LEN+DEX** | |
| Overall Survival | NE | 27.07 | NE | 24.93 |
| Progression-free survival | 22.00 | 19.74 | 13.00 | 16.07 |
| Time on treatment | 17.82 | 18.34 | 12.53 | 15.42 |
| Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; n, number | | | | |

### *3.1.1.2* Updated disaggregated results

Life years

The total life years gained by patients in each health state for IXA+LEN+DEX versus LEN+DEX are detailed in Table 25. Life years are not discounted in line with the NICE reference case.

**Table 25: Summary of life years by health state for the 2+ prior lines population**

| Health state | IXA+LEN+DEX | LEN+DEX | Increment | % increment |
|---|---|---|---|---|
| Pre-progression: Life Years | **3.00** | **2.10** | 0.90 | 70.61% |
| Post-progression: Life Years | **1.85** | **1.48** | 0.37 | 29.39% |
| Life Years: On treatment | **4.85** | **3.58** | 1.27 | 100.00% |
| Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide | | | | |

QALYs

Table 26 details the incremental QALYs gained by health state for IXA+LEN+DEX compared with LEN+DEX. QALYs are calculated using the utilities estimates from the updated regression equation. QALYs are discounted using the 3.5% annual rate.

**Table 26: Summary of QALYs by health state for the 2+ prior lines population**

| Health state | IXA+LEN+DEX | LEN+DEX | Increment | % Increment |
|---|---|---|---|---|
| Pre-progression QALYs | **2.35** | **1.65** | 0.70 | 71.75% |
| Post-progression QALYs | **1.38** | **1.11** | 0.28 | 28.16% |
| Total | **3.71** | **2.73** | 0.98 | 100.00% |

| Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; QALY, quality-adjusted life year |
|---|

Costs

The discounted total costs associated with each health state for IXA+LEN+DEX and LEN+DEX are shown in Table 27. Table 28 shows the summary of predicted resource use by category of cost in the updated base case analysis.

**Table 27: Summary of costs by health state for the 2+ prior lines population**

| Health state | IXA+LEN+DEX | LEN+DEX | Increment | % Increment |
|---|---|---|---|---|
| Pre-progression costs | **£202,514** | **£78,428** | £124,086 | 100.95% |
| Post-progression costs | **£52,775** | **£53,941** | -£1,166 | -0.95% |
| Total costs | **£255,289** | **£132,369** | £122,920 | 100.00% |
| Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide | | | | |

**Table 28: Summary of predicted resource use by category of cost for the 2+ prior lines population**

| Health state | IXA+LEN+DEX | LEN+DEX | Increment | % absolute increment |
|---|---|---|---|---|
| Drug costs and therapy specific resource use | **£193,619** | **£71,452** | £122,166 | 99.39% |
| Concomitant medication | **£9,093** | **£6,717** | £2,376 | 1.93% |
| Adverse events | **£1,645** | **£1,653** | -£7 | -0.01% |
| Disease management | **£49,189** | **£50,653** | -£1,464 | -1.19% |
| Terminal care costs | **£1,743** | **£1,894** | -£151 | -0.12% |
| Total costs | **£255,289** | **£132,369** | £122,920 | 100.00% |
| Key: DEX, dexamethasone; LEN, lenalidomide; QALY, quality-adjusted life year | | | | |

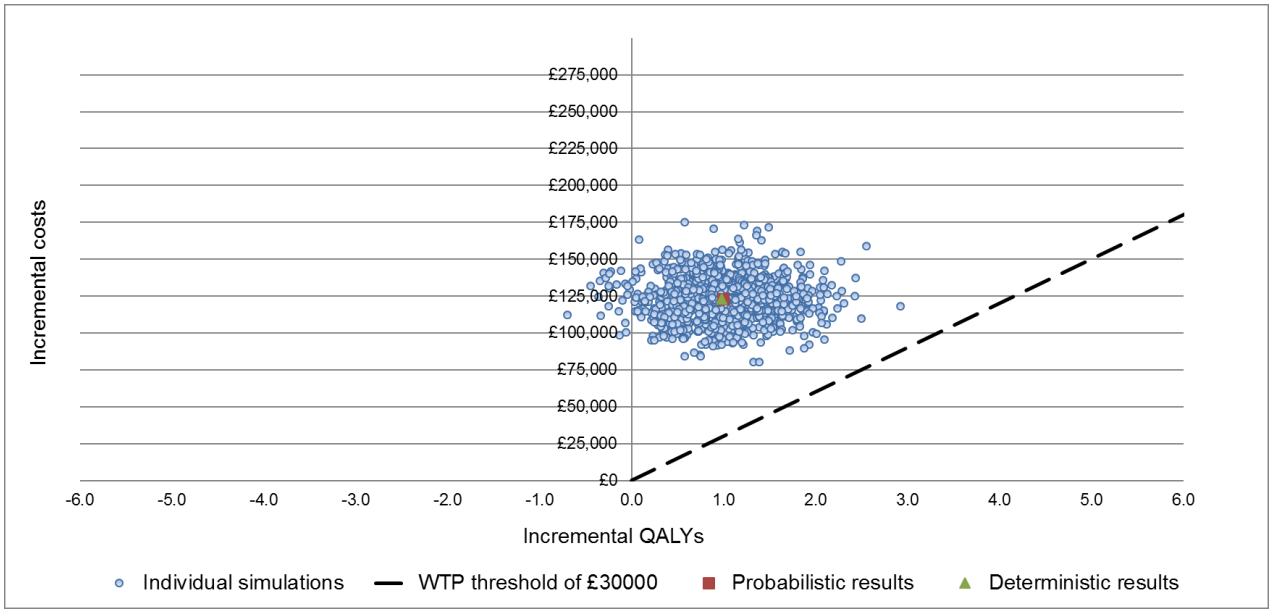
### 3.1.2 Updated sensitivity analysis

#### *3.1.2.1* Updated probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted using the updated model with the PAS discount applied to ixazomib.

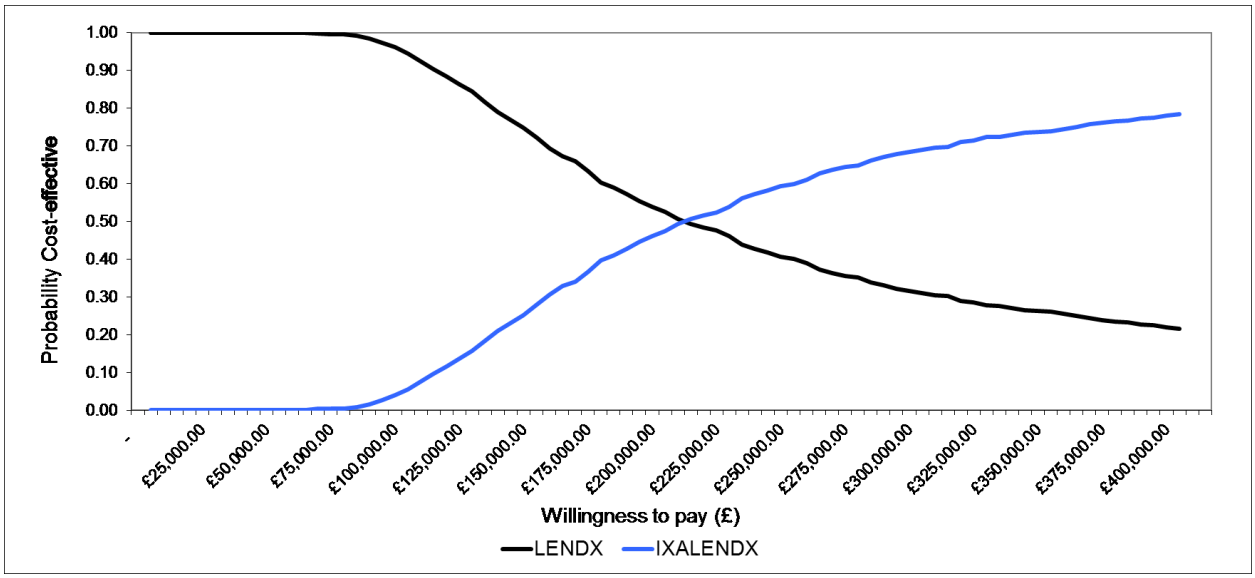
Figure 33 presents the cost-effectiveness plane (CEP) for IXA+LEN+DEX compared with LEN+DEX for the 2+ prior lines population. The 1,000 PSA iterations are presented in Figure 33 and Figure 34 as a CEP and a CEAC. Mean incremental QALYs gained from IXA+LEN+DEX compared to LEN+DEX for the 2+ prior lines population were 0.99. Mean incremental costs were £123,213. The resulting probabilistic ICER is £123,937 which is comparable to the deterministic ICER of £125,777 indicated that the deterministic results is a good approximation of the mean probabilistic value.

**Figure 33 Cost-effectiveness plane from 1,000 PSA iterations for IXA+LEN+DEX compared with LEN+DEX - 2+ prior lines**




Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years; WTP, willingness to pay

**Figure 34: CEAC for IXA+LEN+DEX compared with LEN+DEX – 2+ prior lines**




Key: CEAC, cost-effectiveness acceptability curve; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide

### *3.1.2.2* Updated deterministic sensitivity analysis

One way sensitivity analysis (OWSA) was conducted using the updated model with the PAS discount applied to ixazomib.

Table 299 presents the ten most influential parameters, shown in descending order of ICER sensitivity.

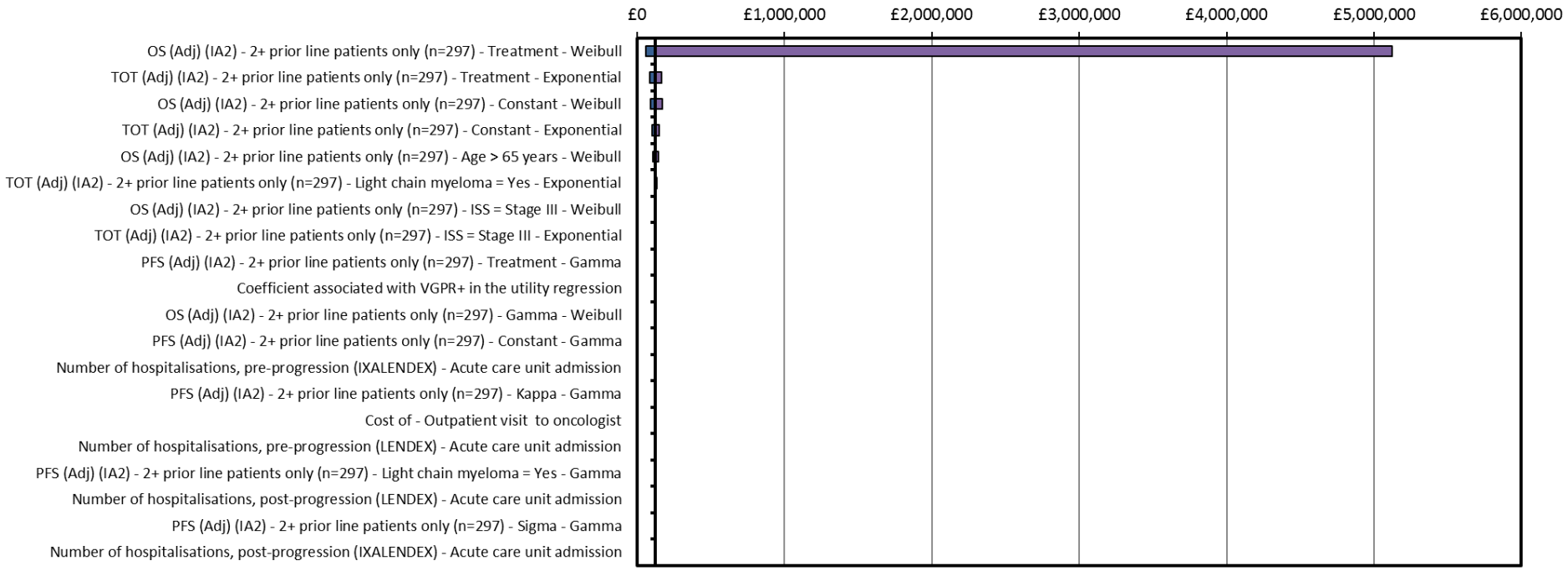
**Table 29: OWSA: ten most influential parameters for IXA+LEN+DEX compared with LEN+DEX – 2+ prior therapies**

| Variable | Lower Bound | Upper Bound | Difference |
|---|---|---|---|
| OS (Adj) (2nd IA) - 2+ prior line patients only (n=297) - Treatment - Weibull | £5,123,923.42 | £59,631.07 | £5,064,292.35 |
| TOT (Adj) (2nd IA) - 2+ prior line patients only (n=297) - Treatment - Exponential | £168,416.53 | £88,618.96 | £79,797.57 |
| OS (Adj) (2nd IA) - 2+ prior line patients only (n=297) - Constant - Weibull | £172,258.23 | £93,639.87 | £78,618.36 |
| TOT (Adj) (2nd IA) - 2+ prior line patients only (n=297) - Constant - Exponential | £149,340.77 | £105,074.87 | £44,265.90 |
| OS (Adj) (2nd IA) - 2+ prior line patients only (n=297) - Age > 65 years - Weibull | £146,098.39 | £108,124.68 | £37,973.71 |
| TOT (Adj) (2nd IA) - 2+ prior line patients only (n=297) - Light chain myeloma = Yes - Exponential | £132,684.40 | £118,282.50 | £14,401.90 |
| OS (Adj) (2nd IA) - 2+ prior line patients only (n=297) - ISS = Stage III - Weibull | £130,857.49 | £120,028.83 | £10,828.66 |
| TOT (Adj) (2nd IA) - 2+ prior line patients only (n=297) - ISS = Stage III - Exponential | £130,433.54 | £120,323.85 | £10,109.69 |
| PFS (Adj) (2nd IA) - 2+ prior line patients only (n=297) - Treatment - Gamma | £128,370.18 | £122,057.13 | £6,313.05 |
| Coefficient associated with VGPR+ in the utility regression | £126,672.84 | £123,911.21 | £2,761.63 |
| Key: Adj, adjusted; IA, interim analysis; ISS, International Staging System; n, number; OS, overall survival; PFS, progression free survival; ToT, time on treatment | | | |

Figure 35 depicts a tornado diagram presenting these results visually. It is clear in the tornado diagram that the parameter with the greatest impact on model outcomes is the coefficient associated with treatment in the OS parametric curve. This is in line with the results of the original submission.

The uncertainty associated with the treatment effect used for OS extrapolation far outweighs the impact of any other uncertainty within the model, which shows the model to be reasonably robust. These results are in line with the wide 95% CI estimated for the hazard ratio of IXA+LEN+DEX relative to LEN+DEX varying from 0.48 to 1.00. The OS data from the 2ND IA data cut of the TOURMALINE-MM1 clinical trial is still extremely immature (with events recorded for less than 22.30% and 30.20% of patients for the IXA+LEN+DEX and LEN+DEX arms, respectively). As such, there is a large amount of uncertainty associated with the extrapolation of these data. More mature data from the later data cuts (i.e. IA3 due Q3 2017) will reduce the uncertainty in the model and improve the robustness of results.

**Figure 35: Results of one-way sensitivity analysis – 2+ prior therapies – IXA+LEN+DEX vs LEN+DEX**




Key: Adj, adjusted; IA, interim analysis; ISS, International Staging System; IXALENDEX, ixazomib + lenalidomide + dexamethasone; LENDEX, lenalidomide + dexamethasone; n, number; OS, overall survival; PFS, progression free survival; ToT, time on treatment

### 3.1.3 Updated scenario analyses

#### *3.1.3.1* Updated scenarios included in the original submission

The main scenario analyses explored within the original submission are presented in Table 30 using the updated model. Scenario analyses were conducted using the updated model with the PAS discount applied to ixazomib.

**Table 30: Scenario analysis updated results for 2+ prior therapies**

| Scenario | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|
| Time horizon 15 years | £122,983 | 0.992 | £123,964 |
| Time horizon 20 years | £123,238 | 1.042 | £118,302 |
| Non-covariate adjusted clinical endpoints | £119,751 | 0.870 | £137,686 |
| Cap ToT by PFS | £122,953 | 0.981 | £125,310 |
| PFS parametric curve: Exponential | £120,783 | 0.979 | £123,313 |
| PFS parametric curve: Weibull | £120,893 | 0.975 | £124,016 |
| PFS parametric curve: Gompertz | £120,968 | 0.972 | £124,414 |
| PFS parametric curve: Log-normal | £122,667 | 0.980 | £125,109 |
| PFS parametric curve: Log-logistic | £122,760 | 0.980 | £125,232 |
| PFS parametric curve: Gamma | £122,920 | 0.981 | £125,277 |
| OS parametric curve: Exponential | £123,081 | 1.391 | £88,453 |
| OS parametric curve: Weibull | £122,920 | 0.981 | £125,277 |
| OS parametric curve: Gompertz | £121,547 | 0.674 | £180,446 |
| OS parametric curve: Log-normal | £124,166 | 1.203 | £103,233 |
| OS parametric curve: Log-logistic | £123,844 | 1.094 | £113,179 |
| OS parametric curve: Gamma | £123,311 | 1.205 | £102,307 |
| ToT parametric curve: Exponential | £122,920 | 0.981 | £125,277 |
| ToT parametric curve: Weibull | £122,220 | 0.981 | £124,562 |
| ToT parametric curve: Gompertz | £123,150 | 0.981 | £125,512 |
| ToT parametric curve: Log-normal | £163,221 | 0.981 | £166,396 |
| ToT parametric curve: Log-logistic | £156,372 | 0.981 | £159,394 |
| ToT parametric curve: Gamma | £126,583 | 0.981 | £129,015 |
| 25% reduction in ToT on IXA+LEN+DEX | £76,499 | 0.982 | £77,870 |
| Utility source: TOURMALINE-MM1 clinical trial | £122,920 | 0.981 | £125,277 |
| Utility source: TA171 | £122,920 | 0.934 | £131,541 |
| Utility source: TA338 | £122,920 | 0.888 | £138,431 |
| 2 prior lines population only: Only additional LEN+DEX costed in the IXA+LEN+DEX arm (over and above the LEN+DEX arm) | £122,920 | 0.981 | £125,277 |
| 2 prior lines population only: Additional LEN+DEX in the IXA+LEN+DEX arm (over and | £122,920 | 0.981 | £125,277 |

| | | | |
|---|---|---|---|
| above the LEN+DEX arm) is not costed | | | |
| Setting the cost of IXA to £0 | £11,763 | 0.981 | £11,988 |
| Discount rate costs and QALYs: 0% | £132,424 | 1.206 | £109,818 |
| Discount rate costs and QALYs: 6% | £117,312 | 0.857 | £136,838 |
| Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; ITT, intention to treat; IXA, ixazomib; LEN, lenalidomide; NMA, network meta-analysis; ORR, overall response rate; OS, overall survival; PFS, progression free survival; QALYs, quality adjusted life years; RCTs, randomised controlled trials; RWE, real world evidence; ToT, time on treatment | | | |

### *3.1.3.2* Scenario considering 2-prior only data

Section 2.1.5 details a new scenario analysis considered in response to NICE Committee and ERG feedback. This scenario considers the results of the 2-prior only data and examines the impact of this on the cost-effectiveness of IXA+LEN+DEX in this subgroup.

The base case results when using 2-prior only data, covariate adjusted, are shown in Table 31. The list price of ixazomib has been discounted using the PASLU agreed PAS of [redacted]

**Table 31: Results of updated model for 2-prior only population with PAS**

| Treatment | Total Costs £ | Total QALYs | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|---|---|
| IXA+LEN+DEX | £313,937 | 5.1466 | | | |
| LEN+DEX | £141,402 | 3.6010 | £172,535 | 1.5455 | £111,635 |
| Key: DEX, dexamethasone; ICER, incremental cost effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; QALY, quality-adjusted life year | | | | | |

### *3.1.3.3* Updated clinical outcomes results

Table 32 displays the clinical outcomes and the model outcomes for the three main measures: OS, PFS and ToT for the 2-prior population. Model outcomes are presented as a mean across the trial period. Clinical outcomes are presented for all comparisons assuming the base case parametric curve fits and adjusting covariates using the mean of covariates method.

The mean OS, PFS and ToT are comparable and consistent with the respective observed clinical outcomes reported in the TOURMALINE-MM1 clinical trial.

**Table 32: Comparison of clinical outcomes with model outcomes for the 2-prior lines population**

| Outcome | Clinical trial result | Model result | Clinical trial result | Model result |
|---|---|---|---|---|
| **Median survival (months) 2+ prior lines population (n=297)** | | | | |
| | **IXA+LEN+DEX** | | **LEN+DEX** | |
| Overall Survival | NE | 21.10 | NE | 19.82 |
| Progression-free survival | 19.2 | 16.06 | 15.5 | 14.75 |
| Time on treatment | 16.9 | 15.20 | 13.7 | 14.27 |
| Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; n, number; NE, not evaluable | | | | |

### *3.1.3.4* Updated disaggregated results

Life years

The total life years gained by patients in each health state for IXA+LEN+DEX versus LEN+DEX are detailed in Table 33. Life years are not discounted in line with the NICE reference case.

**Table 33: Summary of life years by health state for the 2-prior lines population**

| Health state | IXA+LEN+DEX | LEN+DEX | Increment | % increment |
|---|---|---|---|---|
| Pre-progression: Life Years | 2.26 | 1.84 | 0.42 | 20.39% |
| Post-progression: Life Years | 4.57 | 2.93 | 1.64 | 79.61% |
| Life Years: On treatment | 6.83 | 4.77 | 2.06 | 100.00% |
| Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide | | | | |

QALYs

Table 34 details the incremental QALYs gained by health state for IXA+LEN+DEX compared with LEN+DEX. QALYs are calculated using the utilities estimates from the updated regression equation. QALYs are discounted using the 3.5% annual rate.

**Table 34: Summary of QALYs by health state for the 2-prior lines population**

| Health state | IXA+LEN+DEX | LEN+DEX | Increment | % Increment |
|---|---|---|---|---|
| Pre-progression QALYs | 1.775 | 1.444 | 0.33 | 21.43% |
| Post-progression QALYs | 3.395 | 2.183 | 1.21 | 78.42% |
| Total | 5.147 | 3.601 | 1.55 | 100.00% |

| Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; QALY, quality-adjusted life year |
|---|

Costs

The discounted total costs associated with each health state for IXA+LEN+DEX and LEN+DEX are shown in Table 35. Table 36 shows the summary of predicted resource use by category of cost in the updated base case analysis.

**Table 35: Summary of costs by health state for the 2-prior lines population**

| Health state | IXA+LEN+DEX | LEN+DEX | Increment | % Increment |
|---|---|---|---|---|
| Pre-progression costs | £254,070 | £82,246 | £171,824 | 99.59% |
| Post-progression costs | £59,867 | £59,155 | £711 | 0.41% |
| Total costs | £313,937 | £141,402 | £172,535 | 100.00% |
| Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide | | | | |

**Table 36: Summary of predicted resource use by category of cost for the 2-prior lines population**

| Health state | IXA+LEN+DEX | LEN+DEX | Increment | % absolute increment |
|---|---|---|---|---|
| Drug costs and therapy specific resource use | £246,864 | £75,639 | £171,225 | 99.24% |
| Concomitant medication | £13,331 | £9,318 | £4,014 | 2.33% |
| Adverse events | £1,551 | £1,799 | -£248 | -0.14% |
| Disease management | £50,579 | £52,838 | -£2,258 | -1.31% |
| Terminal care costs | £1,611 | £1,809 | -£198 | -0.11% |
| Total costs | £313,937 | £141,402 | £172,535 | 100.00% |
| Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide | | | | |

# 4. Conclusion

The company is seeking a recommendation for the use of ixazomib after 2 or 3 prior therapies (which is a change from the original positioning sought of after 2 prior therapies alone, but is now in line with the expected use in clinical practice as specified by the Appraisal committee in the ACD). The economic model has been updated to address concerns and issues raised in the ACD for ixazomib. The modifications have been presented above, but it can be seen that the main impact of the model modifications is a base case ICER estimate of £125,277 per QALY gained with PAS for IXA + LEN + DEX vs. LEN +DEX in patients receiving 2/3 prior therapies, which is the clinically relevant positioning in the RRMM treatment pathway for ixazomib. The scenario analysis in patients with 2 prior therapies only demonstrates an ICER that is lower than the base case (£111,635 per QALY gained) giving re-assurance that cost-effectiveness is reasonably stable across the sub-groups (2 prior vs 2/3 prior therapies, with the latter representing the more robust dataset for the economic analysis). Other scenario/sensitivity analysis indicated the importance of OS uncertainty in its impact on the ICER.

The base case ICER is an improvement on the ICERs based on the ERG analysis using the old model presented in section 3.25 of the ACD (a range of analyses showing ICERs of £138,000 to £176,000 per QALY gained). The improved ICERs are associated with the use of more mature 2nd IA data for PFS, OS and ToT estimation, combined with an updated utility analysis of the EQ 5D data based also on the 2nd IA data. The QALY gain is estimated to be 0.98 based on the updated analyses. We have also based treatment costs on the time to treatment estimates rather than PFS extrapolation as performed by the ERG as we have argued in the main response to the ACD that using PFS as the measure of treatment duration and cost is not appropriate. The inclusion of regular post progression treatment costs increases the ICER, but the impact of this is more than offset by the positive impact of the use of more mature TOURMALINE-MM1 clinical trial data. In addition, in using the 2nd IA data cut we have improved transparency to attempt assuage ERG concerns (as alluded to in section 3.15 of the ACD) over its use in the economic modelling.

With the new analysis, the utility estimates are now showing a clinically plausible difference between stable disease and progressed disease (the original utility values were criticised as not plausible in section 3.19 of the ACD). We have also performed additional analysis on the EQ 5D data, using a time to death utility analysis approach. This analysis supports the notion of a fairly stable HRQL over time for patients as patients continue to receive treatments and symptoms are managed, until the last few months of life when HRQL is expected to decline. This pattern was verified by an advisory board of multiple myeloma clinical experts, and provides support for the utility values used in the updated economic model which are representative of this pattern.

Overall, the new ICERs are still too high for ixazomib to be considered a cost-effective use of resources. However, Appendix 2 presents the ICERs with the CAA applied, which reduces the base case ICER with updated model to £48,419/QALY gained, an ICER which demonstrates the potential for IXA in patients with 2/3 prior therapies to be considered cost-effective for inclusion in the CDF. As argued in the main response to the ACD, ixazomib may

be eligible for application of new EoL criteria and hence a threshold of £50,000/QALY would then apply (see Section 3.2.11 of the main response document).

# References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## Myeloma UK response to NICE Appraisal Consultation Document (ACD) on ixazomib (Ninlaro®)

### Introduction

Myeloma UK welcomes the opportunity to comment on the NICE ACD on ixazomib in combination with lenalidomide (Revlimid®) and dexamethasone. We continue to value the important role NICE plays in enabling access for patients to the most effective new treatments, while ensuring value for money to the NHS. However, we are obviously very disappointed by the decision reached by the Appraisal Committee in relation to ixazomib, lenalidomide and dexamethasone as a treatment for relapsed myeloma.

There are a number of systemic issues at play within the context of this appraisal – in particular, the difficulties faced by NICE in considering the value proposition of combination treatments where the "backbone" treatments (in this case lenalidomide and dexamethasone) are already challenging to cost-effectiveness thresholds. This is particularly true when treatments are prescribed until progression.

Whilst we accept the difficulties that NICE has in this regard, treatment combinations are increasingly seen as the international standard in myeloma and other cancers, which UK healthcare systems should be aspiring to meet. We know that NICE is alert to this issue and hope it continues to work in partnership to find a solution, not just for myeloma but for all conditions that this issue affects.

Myeloma is a highly individual and complex cancer which evolves over time and eventually becomes resistant to treatment. It is crucial to have a range of novel agents available to ensure that doctors have the prescribing options they need to deliver optimum care to patients.

The patient benefits of ixazomib are clearly outlined and accepted by NICE in the ACD. We therefore hope that NICE, working with Takeda, will reach a pragmatic solution to providing access to ixazomib, a life-prolonging treatment, for relapsed patients on the NHS. To assist the decision-making of NICE, we would like to restate the following comments on the importance of ixazomib for myeloma patients. This is supported by Annex A, where we set out the views of three patients who have been treated with ixazomib.

**Ixazomib is a safe and highly effective treatment in relapsed myeloma.**

There is UK and global consensus amongst clinicians and patient groups that ixazomib is a highly effective treatment for myeloma patients. The ACD acknowledges this, particularly as it would provide patients access to a new oral proteasome inhibitor, given in a treble combination with lenalidomide and dexamethasone – a gold standard in the treatment of myeloma.

The data from the TOURMALINE–MM1 trial clearly demonstrates its clinical effectiveness in the relapsed and refractory setting. Median overall survival was not a primary endpoint in the trial and has not yet been reached. However, the trial demonstrated significant progression free survival (PFS) benefit - an endpoint that patients value highly[1] and one that is a proxy measure of overall survival.[2]

[1] A Multi Criteria Decision Analysis methodological survey funded by Myeloma UK and conducted in collaboration with the European Medicines Agency and the University of Groningen, Netherlands (PCN208, ISPOR, 2016). Postmus, D, Richard, S, Bere, N et al Eliciting Individual Patient

Evidence from patients, family members and clinicians involved in the Named Patient Programme (NPP) confirms that ixazomib is an effective treatment option which performs well in the UK real-world setting, confirming the findings of the TOURMALINE-MM1 trial.

**Ixazomib is a new oral proteasome inhibitor which is valued by patients and their carers.**

Ixazomib is the first oral proteasome inhibitor, a significant breakthrough which will deliver major benefit to patients who find it difficult to attend regular hospital appointments; whether they are frail and elderly, or have work or family commitments. This is important for the carers of myeloma patients too, as oral treatment options can reduce the burden on carers of attending hospital visits. The addition of a novel triplet oral regime also adds no additional practical burden to the NHS.

We note the Committee's comments that the comparator of lenalidomide and dexamethasone is also an oral regimen. However, we do not accept that this undermines the case for the approval of ixazomib – rather, it provides patients access to an effective three-drug combination that they can receive outside of a hospital setting.

**Triple therapy combinations are a "gold standard of care" in myeloma.**

Triple therapy regimens including a proteasome inhibitor and an immunomodulatory agent are increasingly seen as the international standard in the treatment of myeloma. Patients in the UK need and deserve access to such treatment combinations. As yet, despite several EMA approvals of triplet regimens with lenalidomide and dexamethasone as the backbone, none are available routinely in the UK. We strongly consider that ixazomib, lenalidomide and dexamethasone is a strong candidate for approval, particularly given the innovation of its oral regimen.

**Duration on treatment and progression free survival are not the same thing.**

We note the Committee's comments on the difference between time on treatment and progression free survival in the company's health economic modelling. The detail of the modelling is not for us to comment on. However, we would strongly support evidence submitted to the Committee that there are clear reasons why patients would stop treatment prior to disease progression.

This could be because the patient agrees a break from treatment with their consultant or, although oral treatments such as ixazomib, lenalidomide and dexamethasone are generally well tolerated, due to side-effects.

It is also both plausible and logical that patients could have longer periods without treatment prior to progression on ixazomib, lenalidomide and dexamethasone than on lenalidomide and dexamethasone alone. This would be consistent with the ixazomib combination delivering a deeper response which produces a longer remission.

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Preferences on the Benefits and Risks of Cancer Treatments: Results from a Survey Conducted in Myeloma Patients, Value In Health, November 2016, Volume 9, Issue 7

[2] Jorge, F, Aragao, F, Almeida, J et al Time-dependent endpoints as predictors of overall survival in multiple myeloma BMC Cancer 2013 13:122

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**Ixazomib is best placed to fit into the myeloma pathway at second relapse (third line) or beyond.**

In line with the trial data and following the discussions we had during the Committee meeting, it is clear that ixazomib will fit into the myeloma pathway at second relapse and beyond (third line). The central comparator is therefore lenalidomide and dexamethasone.

**Takeda has been cooperative and demonstrated a willingness to do the best thing for patients at every stage.**

As we put on record during the Appraisal Committee meeting, throughout the process of bringing ixazomib to market, Takeda has shown a real commitment to working with patient groups and NICE so that ixazomib is made available for patients. Key examples of this are working with Myeloma UK to bring their ixazomib clinical development programme to NICE scientific advice and establishing the NPP which provides ixazomib free of charge to myeloma patients in the UK. We understand the challenges in the appraisal and that NICE cannot approve a new medicine solely on the actions of a company. However, we hope that this cooperation is taken into account by the Committee alongside the clinical and patient evidence supporting the case for ixazomib.

**Ixazomib is an increasingly good candidate for the Cancer Drugs Fund**

We note the Committee's conclusion that ixazomib does not currently meet the criteria to be included in the Cancer Drugs Fund (CDF). However, as the ACD recognises, the TOURMALINE trial is ongoing and can deliver robust new data, including on overall survival. There is significant potential to collect important new data which could impact positively on the value proposition of ixazomib. This, combined with Takeda's track record of collaboration and flexibility in bringing this treatment to market, means that we believe that there is merit in NHS England, NICE and the company continuing to explore the benefits of making ixazomib available via the CDF.

**Conclusion**

Patients in the UK need and deserve access to the most effective treatments which meet internationally recognised best practice in the treatment of myeloma. This means access to effective triple combination treatments, including a proteasome inhibitor and an immunomodulatory agent. Ixazomib provides this access, with the added benefit of the patient choice and convenience provided by its oral formulation.

We urge NICE and Takeda to work together in order to find a solution that benefits everyone by providing vital access to a new and innovative treatment for myeloma patients on the NHS.

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**Annex A**

Below are extracts from interviews with myeloma patients who have been treated with ixazomib, lenalidomide and dexamethasone.

**Carol**

***"There is no cure for myeloma. You can't operate on myeloma and take it away. We rely on drugs to keep us well."***

Carol was diagnosed with myeloma in 2004. She has had two previous lines of treatment and an autologous stem cell transplant. She began treatment with ixazomib, lenalidomide and dexamethasone in December 2016 and so far has received 5 cycles.

"I have found ixazomib to be very effective. In the first few weeks my paraprotein numbers went down quite dramatically.

"I feel very pleased and lucky to be able to have this treatment. The alternative would have meant intravenous or subcutaneous delivery and with ixazomib there is less risk of peripheral neuropathy which is very important to me since I suffer from peripheral neuropathy due to earlier thalidomide treatment.

"I have a good quality of life on ixazomib. I am married and have two grown-up children living at home. I'm able to run the house, go on holidays'; I recently joined the University of the Third Age and I look forward to doing more with that in the future. Basically, I can do all the things I would normally do and that I enjoy in life.

"Ixazomib scores very highly in terms of what I want from a treatment. It is very beneficial that it is an oral treatment. It saves me time and it saves the hospital and doctors' time – it also saves the NHS money because you don't have to go into hospital. The regimen is very easy to take at home. I really think the fact that it is an oral treatment is so important.

"I think ixazomib should be available on the NHS. It is another really effective treatment option. That is so important for myeloma. There is no cure for myeloma. You can't operate on myeloma and take it away. We rely on drugs to keep us well. When one stops working there has to be another one there. The fact that ixazomib is taken orally is also a huge benefit."

**John**

***"Ixazomib gives you the gift of time."***

John was diagnosed in February 2011. He has had two vertebroplasties, two previous lines of treatment, an autologous stem cell transplant and subsequently a donor stem cell transplant. He received ixazomib, lenalidomide and dexamethasone between February and October 2016 which produced the remission that enabled him to have his second transplant.

"It was brilliant that ixazomib was an oral treatment. I was able to go on holiday and just do all the normal things that you enjoy in life.

"I also didn't experience any side-effects that I would put down to the ixazomib. While on ixazomib my quality of life wasn't 10/10 but it was pretty good – I'd say an 8.

“Ixazomib gives you the gift of time. It gives you the gift of time in two ways. It gives you time back. It gives back the time you might otherwise have spent in the day unit in hospital. It also gives you time, respite, before you have to move onto the next line of treatment.

“It is important for people to understand what it’s like to have myeloma – that it is not curable but it is controllable. In the absence of a curative drug it is so important to have drugs that give you greater control. You need to have options.”

**Kevin and Nicki**

***“It is so important not to become a victim of your treatment. Your treatment should be there to help you, not restrict you. With ixazomib I feel I am in control.”***

Kevin was diagnosed in 2013. He has received two previous lines of treatment for myeloma and has undergone an autologous stem cell transplant. In 2007 he was diagnosed with Stage 3 renal cell carcinoma cancer in his right kidney and Stage 1 RCC in his left kidney which was treated successfully by surgery.

Two years ago Kevin suffered a minor stroke which affected his sight. He he can no longer drive and finds travelling alone on public transport difficult. Since his initial diagnosis Kevin’s wife, Nicki, has played an active part in supporting implementation of Kevin’s treatment.

**Kevin**
“It is so important not to become a victim of your treatment. Your treatment should be there to help you, not restrict you. With ixazomib I feel I am in control. It is difficult living with an incurable cancer. Most of the time I don’t want to think about it. A treatment like ixazomb means that most of the day I don’t even consider it.”

“At times with previous treatments I have been breathless and my legs have felt like lead. I was having to go upstairs on all fours. I would say I have had no side-effects at all from ixazomib. The fact that I can take Ixazomib at home makes life so much easier. I am in a senior position in my company and continue to perform highly bringing in significant amounts of business and revenue.

**Nicki**
“Ixazomib has been the most effective of Kevin’s treatments to date and has helped us to have a normal life more than any other treatment. Taking Ixazomib means that Kevin can largely forget that he has incurable cancer.

“Previously I had to accompany Kevin to the hospital for infusions. Our public transport costs were £50 each time we travelled and took up a whole day. The impact of all of that was very significant. I had to give up my career. We have a holiday home which we couldn’t ever visit because Kevin needed to attend hospital.

“I think it is significant that we have had the experience of Kevin being diagnosed and treated with a solid tumour. If you are able to have a curative treatment as Kevin has, the fact is you can then forget about it and just get on with a normal life.

“Myeloma is much tougher. You will live with it till the day you die, it cannot be cured. The way that you cope is by keeping normality in your life. An oral regime is hugely important in enabling us to do that.”

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**UKMF Feedback for NICE Ixazomib ACD**

We have read the Appraisal consultation document – Ixazomib with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma by National Institute for Health and Care Excellence.

**Clinical effectiveness of Ixazomib in combination with Lenalidomide and Dexamethasone:** We would like to clarify to the committee that trials recruiting MM patients who have had between 1- 3 prior therapies often do not show any difference in overall survival, until data matures. This remains the case where clear progression free survival difference has been established in published trials (POLLUX NEJM 2016, ELOQUENT-2 NEJM 2016, PANORAMA-1 Lancet Oncology 2014, ASPIRE NEJM 2014). Although the PFS difference in the ITT population appears less in Interim Analysis 2, this change is driven by the improved outcomes in the control arm in patients who had only received one prior line. For patients who had received 2 or 3 prior lines, the PFS difference remained significant. This was a pre-specified subgroup analysis. Overall we believe the PFS differences observed in the trial are clinically meaningful. This is supported by the high uptake of the named patient programme for Ixazomib in the UK. UK clinicians have personal experience of using Ixazomib in combination with Lenalidomide and dexamethasone for relapsed myeloma patients. The drug is well tolerated in patients who on this therapy, and we have been struck by the rapidity and depth of response in some patients, who would otherwise have continued to suffer organ damage as a result of active myeloma. Although it is too early to comment on overall survival, the early clinical experiences are very promising. In support of this, real world data are available in the form of an abstract submitted to the European Haematology Association. This abstract (Ziff et al, 2017, EHA-2162) reports a series of 30 patients treated with Ixazomib, Lenalidomide and Dexamethasone for relapsed myeloma, all of whom had received 2 or more prior lines, in accordance with the use of Lenalidomide in the UK. Only 20.8% of patients experienced more than Grade 3 neutropenia and thrombocytopenia. Overall response rate was 70.8%, and progression free survival in this small cohort was 19.2 months. This UK real world experience of Ixazomib is remarkably

similar to the phase 3 trial results, and support the benefit of this regimen in our patients with relapsed myeloma.

**Why do we need Ixazomib combination therapy for our patients:** We note that appraisal committee has considered the change in standard of care from doublet to triplet therapies for relapsed myeloma. This is supported by improved outcomes observed in trials with Proteasome inhibitor (eg Ixazomib) and IMiD (Lenalidomide) based combination therapies. Additionally, the scientific rationale of synergy between these agents, and the ability of the combination to tackle the enrichment of genetic lesions in relapsed myeloma underpins the clinical activity. This is the first oral proteasome inhibitor licensed in myeloma. Clinical trial, and our own local experience indicate that Ixazomib is a well-tolerated proteasome inhibitor with no cardiac or renal problems and limited neuropathic effects, which limit use of other available proteasome inhibitors. The widely used proteasome inhibitor Bortezomib is delivered parenterally as a subcutaneous injection. Patients often attend once or twice a week for these injections. At Oxford a time in motion study was conducted in Myeloma patients receiving Bortezomib. The study reported at European Haematology Association 2017 by Tatarczuch et al (EHA-3856) of the 'real-world cost' of delivering Bortezomib therapy is 37% higher (median cost of £4640 per patient) than the drug-costs alone. In addition the impact on patients is substantial: over a two year period 127 patients required 2134 visits (median of 16 visits per patient) with a median time spent in day unit of 63 minutes and a median travel time for therapy of 90 minutes per visit.

**Positioning of Ixazomib Lenalidomide and dexamethasone in patient treatment pathway:**

We read the appraisal document and note that Ixazomib in combination with Lenalidomide and dexamethasone has been considered in its marketing authorization. The committee also noted our comments that Ixazomib will be used in position where there is current use of Lenalidomide and dexamethasone. This will be in the second relapse, or third relapse. There will be a proportion of patients who enter clinical trials who receive Lenalidomide combination at a later time point in their treatment pathway. The committee should allow for this to

ensure that patients are not penalized for entering trials on the NIHR approved cancer portfolio. We want to register with the committee again that clinicians preferentially use Lenalidomide based therapy prior to Bortezomib Dexamethasone and panobinostat (PVD) combination based on clinical activity and tolerability. This will be borne out on SACT data analysis from NHS England. Therefore we do not see PVD be a comparator to Ixazomib combination therapy.

**Health related quality of life:** – In the Tourmaline MM1 trial patients completed EORTC QLQ –C30 QoL score every 2 cycles. This data is instructive for a number of reasons. This is the first Phase III relapsed refractory study, which is double blind placebo controlled and hence patient bias, has been removed from QoL recording. Also the duration of QoL analysis within this trial is the longest reported to date in relapsed/refractory Phase III clinical trials. EORTC QLC Q30 scores show maintained quality of life during therapy. It is significant that QoL was maintained despite the addition of Ixazomib to the standard Lenalidomide and dexamethasone confirming that treatment efficacy did not come with an associated cost in terms of reduced QoL. This is reflected in maintained health utility noted in patients despite evidence of disease progression. This data also shows the ability of patients to be commenced on another therapy i.e trial or non-trial early. In some circumstances, patients may have stopped therapy 1or 2 months prior to coming off the trial for disease progression. This can happen due to presence of other comorbidities, and patients can remain in remission for a considerable period of time before disease starts progressing. This would be particularly true, for example, with patients who have a deeper response, as seen in the study where more patients achieved deep responses (VGPR or CR) in the Ixazomib arm. This is increasingly an observation noted in relapsed trials with combination of antimyeloma drugs where progression (as defined by set criteria by International myeloma working group) does not occur immediately after a drug is stopped.

# Comments on the ACD Received from the Public through the NICE Website

| | |
|---|---|
| **Name** | [redacted] |
| **Role** | NHS Professional |
| **Other role** | [redacted] |
| **Organisation** | |
| **Location** | England |
| **Conflict** | [redacted] |
| **Notes** | |
| **Comments on individual sections of the ACD:** | |
| **General comment** | In this document it is accepted that triplet therapy is better than doublet therapy. Here we have a randomized placebo controlled trial that shows a clear benefit to novel triplet therapy. However the additional costs that accrue are not only related to the new technology ixazomib but also the older technology revlimid and dexamethasone and it becomes virtually impossible for any new technology to be cost effective in this situation. This has already led to two very effective triplets elotuzumab/rev/dex and carfilizomib/rev/dex not being brought before nice. The U.K. Will rapidly fall behind the USA and Europe if state of the art triplet therapies are not considered or even put before NICE because of this prohibitive way of assessing cost effectiveness.<br><br>I am stunned that NICE would produce a statistically grossly invalid comparison as fact. Stating that Ixazomib/rev/dex is less effective than velcade and dexamethasone by doing cross comparisons across studies and using trials separated by a number of years is highly statistically invalid and should be dropped.<br><br>Ixazomib with revlimid and dexamethasone is an active all oral regime which benefits the whole myeloma patient population whilst reducing the massive burden of additional hospital visits. The huge success of the company access scheme is a testament to the value top myeloma clinicians place on this technology. I cannot think of a patient of mine where I would not recommend IRD over Rd if available and I have not met a myeloma physician who disagrees. It is highly effective well-tolerated, easy to deliver and places no additional burden on busy Chemo day units.<br><br>As a trialist and someone brought up on evidence based medicine and the danger of non-specified splitting of the data, requesting analyses that are not pre-specified and looking at sub groups which are inappropriate or statistically invalid is not something that is appropriate or valid. |

| | |
|---|---|
| **Name** | [redacted] |
| **Role** | NHS Professional |

| | |
|---|---|
| **Other role** | [redacted] |
| **Organisation** | [redacted] |
| **Location** | England |
| **Conflict** | [redacted] |
| **Notes** | |
| **Comments on individual sections of the ACD:** | |
| **Section 1** (Appraisal Committee's preliminary recommendations) | Section 1.1 – 1.2: page 3-4<br>The statement that the benefit appears to reduce after longer follow-up is not statistically valid as includes non-primary endpoint data and should be interpreted with caution.<br><br>The statement that for one prior therapy ixazomib (with lenalidomide and dexamethasone) was less effective than bortezomib and dexamethasone is clinically implausible and raises a question about the validity of the analysis. |
| **Section 2** (The technology) | |
| **Section 3** (The manufacturer's submission) | <u>Section 3.2: page 5</u><br>Triple therapy is standard of care at all stages of myeloma therapy, not just later in the treatment pathway. Suggest refer to SACT data. The remains a need for highly effective and well tolerated treatments.<br><br><u>Section 3.5: pages 6-7</u><br>I concur that lenalidomide-based therapy is generally used after 2 or 3 prior therapies and panobinostat after 3 or 4 prior therapies, generally following after lenalidomide-based therapies. A more appropriate comparator for panobinostat is pomalidomide (having already been treated with lenalidomide). It is not appropriate to compare ixazomib with panobinostat.<br><br><u>Section 3.7: pages 8</u><br>Ixazomib (with lenalidomide and dexamethasone) will be used as an alternative to lenalidomide and dexamethasone. It is currently being used in this situation in this Trust through the expanded access scheme.<br><br><u>Section 3.8: page 8</u><br>Bortezomib remains on the NICE pathway for people who have had one prior therapy and the NICE Guidance does not stipulate what treatment has previously been given. Bortezomib plus dexamethasone is a suitable comparator for all patients at first relapse.<br><br><u>Section 3.9: page 9</u><br>It is clinically appropriate to consider ixazomib after two or three prior therapies. The precise choice of therapy depends on prior availability of treatment, response and toxicity and therefore requires clinical judgement.<br><br><u>Section 3.12 – 3.13: page 10 -11</u><br>The conclusion that ixazomib may be more effective after 3 rather than 2 prior therapies is a flawed analysis as it is not a pre-stratified analysis and is statistically unsound. It is also clinically unsound as there is no firm biological evidence that |

| | |
|---|---|
| | the combination will be more effective after 3 rather than 2 prior therapies. To undertake such an analysis would require balancing for all key prognostic factors such as cytogenetic risk, age, renal function and ISS. To separate the two groups is highly dubious.<br><br><u>Section 3.16: page 13</u><br>It is inappropriate to undertake subgroup analysis on such small patient populations when the study has not been powered in this way. There can be limited validity to any conclusions drawn from this analysis.<br><br><u>Section 3.19: pages 14-15</u><br>HRQL after progression depends on what happens to a patient after progression. If the patient progresses and receives another treatment their QOL will improve. What is most relevant is how advanced or end stage the patinet is. If a patient is approachin end of life their QOL will inevitably deteriorate whereas if there is an effective next treatment it will improve. This analysis will be biased by geography. Because there are better approved treatments in the US it would be expected that UK QOL would be worse after progression than in the UK which may inform the analysis.<br><br><u>Section 3.21: pages 15-22</u><br>Any treatment that results is deeper responses will in general result in longer PFS. This is the case for most drugs of fixed duration, the PFS will be longer than the time on treatment. Assuming the toxicity of both arms were the same, any treatment resulting in a deeper response would be expected to result in a longer duration of response (and longer PFS) than an inferior treatment. It is therefore completely expected that the ratio of time on treatment to PFS be lower with ixazomib because the data demonstrates that it is a more effective treatment. The subsequent conclusions do not appear valid.<br><br><u>Section 3.24: page 17</u><br>I have concerns over the conclusion as this is not clinically plausible. |
| **General** | Ixazomib plus lenalidomide and dexamethasone has already been used extensively in my Trust and across the UK as there is clinical demand for an effective oral triplet therapy in relapsed myeloma. The large real world usage of the combination already in the UK supports the clinical trial data that this is both an effective and well tolerated treatment that adds to the limited options available in relapsed myeloma. |

| | |
|---|---|
| **Name** | [redacted] |
| **Role** | |

| | |
|---|---|
| **Other role** | |
| **Organisation** | |
| **Location** | |
| **Conflict** | |
| **Notes** | |
| **Comments on individual sections of the ACD:** | |
| **General comment** | I am disappointed to learn that the use of the above drug to treat Myeloma with Velcade or with Revlmid has been turned down on grounds of cost.<br><br>My consultant had intended to use Ninlaro on a "Named Patient" basis, but clearly her concern for my life is somewhat more than that of panel members of NICE. Do be aware that this decision has not been made by "NICE" as some faceless body, but it has been made by individual people to whom care of the patient is seemingly secondary to administrative concerns.<br><br>What a disgrace! |

**Single technology appraisal**
**Ixazomib citrate for treating relapsed or refractory multiple myeloma [ID807]:**
**-**
**ERG clarification questions following the additional evidence submitted by the company**

6th June 2017

## Section A: Clarification on clinical effectiveness data

A1.**PRIORITY QUESTION**: Please present the numbers of patients with best overall responses (BoR) of PD, SD, PR and VGPR+ by arm and subgroup for the 2IA data cut.

| | 2 Prior | | 2+ Prior | |
|---|---|---|---|---|
| | IXAL | LEND | IXAL | LEND |
| VGPR+ | N=??? | N=??? | N=??? | N=??? |
| PR | N=??? | N=??? | N=??? | N=??? |
| SD | N=??? | N=??? | N=??? | N=??? |
| PD | N=??? | N=??? | N=??? | N=??? |

A2.Please clarify whether the forest plots of the 2IA data division of prior treatment use into 1 prior, 2 prior and 3 prior was pre-specified, and if it was pre-specified why this was chosen rather than 1 prior and 2+ prior split given trial stratification. If any of the results of the 2IA forest plots are adjusted for baseline characteristics please provide a summary of this.

A3.Please provide the patient characteristic patient numbers across all patients and by prior treatment subgroups defined by the number of previous treatments used during stratified randomisation, including the 2 prior subgroup if this data is available at randomisation.

| | All patient | | 2+ prior | | 2 prior | |
|---|---|---|---|---|---|---|
| | IXAL | LEND | IXAL | LEND | IXAL | LEND |
| Patients (total) | n=??? | n=??? | n=??? | n=??? | n=??? | n=??? |
| Prior Lines = 2 or 3 | n=??? | n=??? | n=??? | n=??? | n=??? | n=??? |
| Cytogenetics = High Risk | n=??? | n=??? | n=??? | n=??? | n=??? | n=??? |
| ISS = Stage III | n=??? | n=??? | n=??? | n=??? | n=??? | n=??? |
| Age > 65 years | n=??? | n=??? | n=??? | n=??? | n=??? | n=??? |
| Light chain myeloma = Yes | n=??? | n=??? | n=??? | n=??? | n=??? | n=??? |
| Relapsed and refractory = Yes | n=??? | n=??? | n=??? | n=??? | n=??? | n=??? |
| Primary refractory = Yes | n=??? | n=??? | n=??? | n=??? | n=??? | n=??? |
| Proteasome inhibitor = Yes | n=??? | n=??? | n=??? | n=??? | n=??? | n=??? |
| Immunomodulation agent = Yes | n=??? | n=??? | n=??? | n=??? | n=??? | n=??? |
| ECOG performance score = 2 | n=??? | n=??? | n=??? | n=??? | n=??? | n=??? |
| ASCT undertaken = Yes | n=??? | n=??? | n=??? | n=??? | n=??? | n=??? |
| History of bone lesions = Yes | n=??? | n=??? | n=??? | n=??? | n=??? | n=??? |
| Renal dysfunction = Yes | n=??? | n=??? | n=??? | n=??? | n=??? | n=??? |
| Asian = Yes | n=??? | n=??? | n=??? | n=??? | n=??? | n=??? |
| Gender = male | n=??? | n=??? | n=??? | n=??? | n=??? | n=??? |
| Race = white | n=??? | n=??? | n=??? | n=??? | n=??? | n=??? |

Please provide the patient characteristic patient numbers across all patients and by prior treatment subgroups defined by the independent review committee (IRC), including the 2 prior subgroup if this data is available.

A4.Please indicate which set of patient characteristics, randomisation stratification or IRC, were used in the adjusted analyses of the economics and why.

A5.**PRIORITY QUESTION:** for the 2+ prior population please supply the following data:

| OS | | | | | | |
|---|---|---|---|---|---|---|
| PATIENT | IXAL(Y) /LEND (N) | TIME (months) | Event (Y) /cens (N) | Stage3+ (Y/N) | Age >65 (Y/N) | |
| 1 | Y/N | t=??? | Y/N | Y/N | Y/N | |
| 2 | Y/N | t=??? | Y/N | Y/N | Y/N | |
| 3 | Y/N | t=??? | Y/N | Y/N | Y/N | |
| 4 | Y/N | t=??? | Y/N | Y/N | Y/N | |
| ETC | ETC | ETC | ETC | ETC | ETC | |
| | | | | | | |
| PFS | | | | | | |
| PATIENT | IXAL (Y) /LEND (N) | TIME (months) | Event (Y) /cens (N) | light chain myeloma+ (Y/N) | | |
| 1 | Y/N | t=??? | Y/N | Y/N | | |
| 2 | Y/N | t=??? | Y/N | Y/N | | |
| 3 | Y/N | t=??? | Y/N | Y/N | | |
| 4 | Y/N | t=??? | Y/N | Y/N | | |
| ETC | ETC | ETC | ETC | ETC | | |
| | | | | | | |
| ToT | | | | | | |
| PATIENT | IXAL (Y) /LEND (N) | TIME (months) | Event (Y) /cens (N) | Stage3+ (Y/N) | light chain myeloma+ | |
| 1 | Y/N | t=??? | Y/N | Y/N | Y/N | |
| 2 | Y/N | t=??? | Y/N | Y/N | Y/N | |
| 3 | Y/N | t=??? | Y/N | Y/N | Y/N | |
| 4 | Y/N | t=??? | Y/N | Y/N | Y/N | |
| ETC | ETC | ETC | ETC | ETC | ETC | |
| | | | | | | |

**Please repeat, with appropriate covariates, for the 2 prior population**

A6. What are the KM hazard ratios (95% CIs) and CIs for OS, PFS and ToT of the 2IA data cut for the 2 prior and the 2+ prior. What are the KM hazard ratios (95% CIs) for OS, PFS and ToT of the 2IA data cut for the 2 prior and the 2+ prior when adjusted for the baseline characteristics that are used to adjust the parameterised curves in the adjusted curves analyses of the economics using e.g. Peto-Prentice weighted Wilcoxon's, Cox regression, please specify methods used.

A7. Please supply the results of formal statistical tests of proportional hazards.

**A8. PRIORITY QUESTION:** For OS, PFS, and ToT (Appendix 1 section 2.1.2.1) please tabulate the "mean of covariate" values used in in the adjusted parametric models for both the 2+ prior subgroup and the 2 prior subgroup. Please define the procedure described as "mean of covariates method" and describe why it was chosen over the alternatives.

A9. Please present the statistical analyses that lead to only a subset of the patient characteristics being presented in Table 2 and Table 3 of section 3.2.5.of the main submission. Please outline why the set of characteristics in Table 2 and Table 3 of section 3.2.5.of the main submission differ from those of section 2.1.2.1 of Appendix 1 for the 2+ prior subgroup and from those of the economic model for the 2 prior subgroup. Please present the statistical analyses including the log rank tests used to "detect significant differences in clinical end points between treatments" and the results of the various backward iterations that lead to only a subset of the patient characteristics being considered for the 2IA 2+ prior subgroup. In the light of the final covariates differing for the 2IA 2 prior subgroup please present the corresponding statistical analyses for the 2IA 2 prior subgroup. Please also present the central estimates and p-values for the treatment effect covariate and each of the patient characteristics covariates for each of the adjusted parameterised curves for the 2IA OS, PFS and TOT curves, separately for the 2+ prior and the 2 prior.

**Section B: Clarification on cost-effectiveness data**

B1. Please tabulate the mean durations of the OS, PFS and ToT parameterised curves for the 1IA for the 1 prior and the 2+ prior and for the 2IA for the 1 prior (if available), the 2 prior and the 2+ prior along the following lines. Please also provide the medians of the unadjusted KM curves alongside these (5 tables).

| | OS | | PFS | | ToT | |
|---|---|---|---|---|---|---|
| | Unadjusted | Adjusted | Unadjusted | Adjusted | Unadjusted | Adjusted |
| Exponential | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? |
| Weibull | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? |
| Log Normal | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? |
| Log Log | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? |
| Gompertz | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? |
| Weibull | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? | $\mu_t$=??? |
| KM Median | $\tilde{x}$=??? | $\tilde{x}$=??? | $\tilde{x}$=??? | $\tilde{x}$=??? | $\tilde{x}$=??? | $\tilde{x}$=??? |

B2. Please present the AIC and BIC for the unadjusted OS, PFS and TOT curves of the 2IA analysis separately for the 2 prior subgroup and the 2+ prior subgroup.

B3. Within the economic model please clarify if E21 (CovariateAdj_mainsettings) in Main Settings worksheet only directly determines E46 (Adjusted) in Parameters worksheet with the Adjusted variable then directly determining everything else thereafter, or does it directly determine values in addition to E46 (Adjusted) in the Parameters worksheet?

B4. The Main Settings worksheet E55 is described as "Total number of week payer is responsible for treatment costs. Please find input on the results sheet". The ERG cannot identify this element in the Results worksheet and would welcome clarification on this.

B5. Please outline the role of the TxEffectSubgrps variable within the model and its direct effects upon other variables in the model. How does this differ from applying the adjusted curves?

B6. The values of Appendix 1 Table 9 P24 are not aligned with those of cells D156:G175 of the TRAEs worksheet of the economic model. Please clarify which is correct. Please provide the equivalent data to the TRAEs worksheet cells D130:E149 for the 2IA data cut for the TMM-1 trial as a whole. The average duration of AEs appears to be draw from the previous model and is not arm specific. Please outline the reasons for this.

B7. **PRIORITY QUESTION:** For the discontinuation data of Appendix 1 Table 16 P39 the distributions of the total patient numbers for each category in terms of progression status appear to fall into one of three categories:

1. Progression measured before end of data cut
2. Progression free measured at end of data cut
3. Progression status not available at end of data cut

Please confirm if the ERG interpretation of this for the progression column is correct. Please fill in the patient numbers for the other columns for the 2IA data cut. Please confirm if patients in the third category of progression status not available at end of data cut were treated as censored in the construction of the PFS Kaplan Meier curves. Please also outline which if any of the patient numbers involve LOCF and to what degree and why LOCF is necessary for these patients. This may be submitted after the main clarification response.

| | Prog. | AE | Withdr. | S. Term. | Pr. Viol. | Other | Censor |
|---|---|---|---|---|---|---|---|
| 2IA LEN+DEX (Total) | N = 57 | N = 30 | N = 13 | N = 1 | N = 1 | N = 1 | N = 46 |
| 1. Prog measured before 2IA | N=57 | N=??? | N=??? | N=??? | N=??? | N=??? | N=??? |
| 2. Measured prog free at 2IA | N=0 | N=??? | N=??? | N=??? | N=??? | N=??? | N=??? |
| 3. Prog status at 2IA n.a. | N=0 | N=??? | N=??? | N=??? | N=??? | N=??? | N=??? |
| 2IA IXA+LEN+DEX (Total) | N = 46 | N = 24 | N = 14 | N = 1 | N = 0 | N = 3 | N = 60 |
| 1. Prog measured before 2IA | N=46 | N=??? | N=??? | N=??? | .. | N=??? | N=??? |
| 2. Measured prog free at 2IA | N=0 | N=??? | N=??? | N=??? | .. | N=??? | N=??? |
| 3. Prog status at 2IA n.a. | N=0 | N=??? | N=??? | N=??? | .. | N=??? | N=??? |

B8. **PRIORITY QUESTION:** Please outline which events in Appendix 1 Table 16 P39 are treated as discontinuation events and which as censoring events within the DOT curves of the model.

B9. **PRIORITY QUESTION:** Please present the correlation data alluded to in Appendix 1 Section 2.1.3.1, including that for variables that were considered as candidates but not included in the final model. The text suggests that the list of covariates that were included, as listed in table 11, was decided a priori rather than through statistical tests. Why? It seems surprising to the ERG that line of therapy was not included or explored. What reasons did the clinicians give for not including this? Please present the results of each of the forwards and backwards stepwise selection approach and the statistical tests which resulted in the final model. What was the time window for hospitalisations and is the definition of hospitalisations the same as that for the hospitalisation patient count data of the Hospitalisation worksheet of the model? What is the reference age for the age coefficient? What was the number of EQ-5D responses in the 2IA analysis:

- With PD
- With both PD and within 3 months of death
- With hospitalisation
- With both hospitalisation and within 3 months of death

B10. It is difficult to read across between the original and the revised EQ-5D analyses. Please present the equivalent of Appendix 1 Table 12 P30 for the 1IA data cut. This may be submitted after the main clarification response.

B11. **PRIORITY QUESTION** Is the revised EQ-5D analysis based on IA2 all patient data or IA2 2+prior patient data? If it is based upon all patient data what effect does including the number of previous treatments as a covariate (1 prior and 2+ prior with 1 prior as the reference) have upon the estimates of Appendix 1 Table 12 P30 and what is the p-value for this covariate? What effect upon the estimates does removing:

- age as a covariate have?
- death within 3 months as a covariate have?
- sex and race as covariates have?

B12. **PRIORITY QUESTION:** What was the mean baseline EQ-5D value in the TMM-1 trial among all patients, among the 1 prior, among the 2+ prior and among the 2 prior?

B13. Please present the arithmetic underlying the calculation of VGPR+ 0.689, PR 0.690, SD 0.678 and PD 0.650 quality of life values of Appendix 1 P31, documenting the inputs to this. This may be presented within an excel spreadsheet if this is easier. Please outline how these relate to the values of Appendix 1 Table 12 P30.

B14. The number of hospice admissions of D54 of the Hospitalisations worksheet is not aligned with those of cells D13, D24, D35 and D46 of the Hospitalisations worksheet. Please account for this. The average length of Hospice stay differs somewhat from the previous submission. Please account for this.

B15. **PRIORITY QUESTION:** Please provide the data in cells D8:E22 of the PostProgression worksheet split by arm. Please augment this with the arm and subgroup specific values (4 values) for patient years of follow-up post-progression.

**Section C: Textual clarifications and additional points**

C1. Please clarify whether the values of Appendix 1 Table 8 P23 are restricted to the periods when on IXA+LEN+DEX or LEN+DEX treatment or include AEs after discontinuation of IXA+LEN+DEX or LEN+DEX treatment.

C2. Please provide for completeness as an appendix a copy of the CSR for the 2IA data cut; i.e. the equivalent of reference 42 of the original submission for the 2nd interim analysis.

C3. If there is a report underlying the summary of the EQ-5D analysis of Appendix 1 section 2.1.3.1 please provide it as an appendix.

# Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma [ID807] Response to clarification questions

**Submitted by Takeda UK Ltd.**

**Single Technology Appraisal (STA)**
**National Institute of Health and Care Excellence**

Submitted 14th June 2017

# Table of Contents

# List of Tables

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# List of Abbreviations

| | |
|---|---|
| AE | adverse event |
| BoR | best-of response |
| BORT | bortezomib |
| DEX | dexamethasone |
| HR | hazard ratio |
| IXA | ixazomib |
| KM | Kaplan-Meier |
| LEN | lenalidomide |
| MP | melphalan-prednisone |
| NMA | network meta-analysis |
| ORR | overall-response rate |
| OS | overall survival |
| PD | progressive disease |
| PFS | progression-free survival |
| PR | partial response |
| RRMM | relapsed refractory multiple myeloma |
| SD | stable disease |
| THAL | thalidomide |
| ToT | time on treatment |
| TTP | time-to-progression |
| VGPR | very good partial response |

# 1. Overview

This document contains the response to the clarification questions from the evidence review group (ERG) sent to Takeda on Wednesday 7th June. We have attempted to address all questions as fully as possible within the timeframe permitted (deadline of 14th June 2017). Please note two caveats:

a) A few of the questions relate to requests for additional one prior therapy analyses (in particular, QB1, and QB12). However, in our response to the ACD we have stated that we no longer wish to consider a positioning for ixazomib at the current time in patients who have received only one prior therapy. Hence, our ACD response and new evidence/analyses submitted to NICE on 19th May 2017 stated this (see section 2.2 of the ACD response document) and focussed only on patients who had 2 or 3 prior therapies. We kindly request all attention should be given to this patient population. Therefore, we have not provided below any additional analyses requested by the ERG for the one prior therapy patient population.

b) A few of the questions also ask for analyses using the first interim analysis (IA1) dataset (in particular, QB1, and B10). However, in the ACD the NICE Appraisal Committee concluded that it would prefer to see an economic model informed by the most recent clinical data for ixazomib (i.e. the second interim analysis dataset - IA2) (see section 3.15 of the ACD). All our new evidence/analyses submitted post ACD relates to use of the more mature dataset and this has replaced the analyses using the less mature datacut. Given this we are not clear of the rationale for the requests in QB1 and QB10 for the IA1 datacut. We believe the analyses based on the IA2 should be considered as completely separate to the earlier analyses based on IA1, and so reference to analysis based on IA1 is of low relevance for consideration of the new evidence. If the ERG feel strongly that they require IA1 based analyses then these can be provided, but as it would take some time to address these then that would be after the deadline for response to the clarification questions (the ERG have stated that this would be acceptable at least in relation to QB10).

# 2. Response to clarification questions

Please find below responses by Takeda to each of the questions raised by The Evidence Review Group, Warwick Evidence, and the technical team at NICE.

## Section A: Clarification on clinical effectiveness data

A1. **PRIORITY QUESTION**: Please present the numbers of patients with best overall responses (BoR) of PD, SD, PR and VGPR+ by arm and subgroup for the second interim analysis (IA2) data cut.

**Response:** The number of patients with BoR of PD, SD, PR and VGPR+ by arm and subgroup for the IA2 data cut are presented in Table 1. These data are also within the model sent to NICE in response to the Appraisal Consultation Document (ACD) and can be found on sheet "BoR."

**Table 1: BoR by arm and subgroup using IA2 data**

| | 2 prior | | 2+ prior | |
|---|---|---|---|---|
| | **IXA+LEN+DEX** | **LEN+DEX** | **IXA+LEN+DEX** | **LEN+DEX** |
| VGPR+ | 50 | 46 | 80 | 54 |
| PR | 26 | 31 | 39 | 45 |
| SD | 7 | 17 | 11 | 26 |
| PD | 5 | 7 | 7 | 8 |
| Missing | 9 | 10 | 11 | 16 |

**Key:** BoR, best overall response; DEX, dexamethasone; IA, interim analysis; IXA, ixazomib; LEN, lenalidomide; PD, progressed disease; PR, partial response; SD, stable disease; VGPR, very good partial response

A2. Please clarify whether the forest plots of the IA2 data split into 1 prior, 2 prior and 3 prior treatments was pre-specified. If it was pre-specified, why was this split chosen instead of the trial stratification of 1 prior and 2+ prior? If any of the results of the IA2 forest plots are adjusted for baseline characteristics please provide a summary of this.

**Response:** The number of prior therapies (both investigator-stratified by 1 vs 2/3 prior lines as well as sponsor-assessed 1 vs 2 vs 3 prior lines) were pre-specified subgroups. The investigator-determined number of prior therapies was used to stratify patients as 1 vs 2/3 prior lines before randomisation. The subgroup of 2/3 prior therapies as a stratification factor was proposed because of its prognostic value in MM and the potential for a differential treatment effect. In addition, following study entry, the sponsor assessed the number of prior lines received and assigned patients into 1 vs 2 vs 3 prior therapies and, as discussed in previous correspondence, some differences were identified between the number of prior therapies as determined by the investigator and the number following sponsor medical

review. The advantage of the 1 vs 2/3 prior lines investigator-derived subgroup is that this benefits from stratified randomisation and is indicative of real-world practice (clinicians assessing the medical history of their patients). The IA2 forest plots are not adjusted for baseline characteristics.

A3.Baseline characteristics

a. Please provide the patient numbers for baseline characteristics across all patients and for subgroups according to prior treatments (defined by the number of previous treatments used during stratified randomisation), including the 2 prior subgroup if this data is available at randomisation.

**Response**: The baseline characteristics according to prior treatments defined during randomisation are outlined in Table 2. The 2 prior subgroup has not been included as these patients cannot be separated out of the 2 or 3 prior lines variable.

**Table 2: Baseline characteristics according to prior treatments defined during randomisation**

| | **All patient** | | **2+ prior** | |
|---|---|---|---|---|
| | **IXA+LEN+DEX** | **LEN+DEX** | **IXA+LEN+DEX** | **LEN+DEX** |
| Patients (total) | n=360 | n=362 | n=148 | n=149 |
| Prior Lines = 2 or 3* | n=148 | n=149 | n=148 | n=149 |
| Cytogenetics = High Risk | n=75 | n=62 | n=30 | n=28 |
| ISS = Stage III | n=46 | n=44 | n=20 | n=18 |
| Age > 65 years | n=192 | n=186 | n=80 | n=77 |
| Light chain myeloma = Yes | n=67 | n=86 | n=32 | n=31 |
| Relapsed and refractory = Yes | n=43 | n=43 | n=42 | n=41 |
| Primary refractory = Yes | n=24 | n=22 | n=11 | n=10 |
| Proteasome inhibitor = Yes | n=250 | n=253 | n=113 | n=114 |
| Immunomodulation agent = Yes | n=193 | n=204 | n=100 | n=102 |
| ECOG performance score = 2 | n=18 | n=24 | n=10 | n=15 |
| ASCT undertaken = Yes | n=212 | n=199 | n=86 | n=81 |
| History of bone lesions = Yes | n=254 | n=249 | n=111 | n=106 |

| | | | | |
|---|---|---|---|---|
| Renal dysfunction = Yes | n=36 | n=56 | n=18 | n=23 |
| Asian = Yes | n=27 | n=26 | n=12 | n=15 |
| Gender = male | n=207 | n=202 | n=81 | n=86 |
| Race = white | n=311 | n=302 | n=125 | n=120 |
| ** Prior lines defined during randomisation* | | | | |

b. Please provide the baseline characteristic patient numbers across all patients and for subgroups according to prior treatments (defined by the independent review committee (IRC)), including the 2 prior subgroup if this data is available.

**Response:** The baseline characteristics according to prior treatments defined by the IRC are outlined in Table 3.

**Table 3: Baseline characteristics according to prior treatments defined during randomisation**

| | **All patient** | | **2 prior** | | **2+ prior** | |
|---|---|---|---|---|---|---|
| | **IXA+LEN +DEX** | **LEN+ DEX** | **IXA+LEN+ DEX** | **LEN+ DEX** | **IXA+LEN+ DEX** | **LEN+ DEX** |
| Patients (total) | n=360 | n=362 | n=97 | n=111 | n=136 | n=145 |
| Prior Lines = 2 or 3 | n=148 | n=149 | n=91 | n=102 | n=130 | n=135 |
| Cytogenetics = High Risk | n=75 | n=62 | n=20 | n=17 | n=27 | n=26 |
| ISS = Stage III | n=46 | n=44 | n=11 | n=10 | n=17 | n=17 |
| Age > 65 years | n=192 | n=186 | n=53 | n=53 | n=74 | n=73 |
| Light chain myeloma = Yes | n=67 | n=86 | n=16 | n=22 | n=29 | n=27 |
| Relapsed and refractory = Yes | n=43 | n=43 | n=23 | n=25 | n=43 | n=43 |
| Primary refractory = Yes | n=24 | n=22 | n=8 | n=9 | n=12 | n=11 |
| Proteasome inhibitor = Yes | n=250 | n=253 | n=76 | n=86 | n=104 | n=112 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Immunomodulation agent = Yes | n=193 | n=204 | n=63 | n=76 | n=94 | n=99 |
| ECOG performance score = 2 | n=18 | n=24 | n=7 | n=11 | n=10 | n=15 |
| ASCT undertaken = Yes | n=212 | n=199 | n=56 | n=68 | n=79 | n=82 |
| History of bone lesions = Yes | n=254 | n=249 | n=78 | n=80 | n=105 | n=105 |
| Renal dysfunction = Yes | n=36 | n=56 | n=10 | n=12 | n=15 | n=20 |
| Asian = Yes | n=27 | n=26 | n=6 | n=11 | n=8 | n=12 |
| Gender = male | n=207 | n=202 | n=59 | n=63 | n=79 | n=83 |
| Race = white | n=311 | n=302 | n=85 | n=90 | n=118 | n=122 |
| * *Prior lines defined during randomisation* | | | | | | |

**A4.** Please indicate which set of patient characteristics, randomisation stratification or IRC, were used in the adjusted analyses of the economics and why.

**Response:** For the 2+ prior line analysis, patient characteristics based on randomisation stratification were used to preserve the balancing of the two arms that came with study randomisation. For the 2-prior line population however, IRC based patient characteristics were used due to the inability to separate out patients with 2 previous lines of therapy or 3 previous lines of therapy from the 2 or 3 previous lines of therapy classification.

A5. **PRIORITY QUESTION:**

a. for the 2+ prior population please supply the following data:
b. Please repeat, with appropriate covariates, for the 2 prior population

**Response:** Please find attached response to both question A5 a and b saved as the following;

- 2 prior lines data OS,
- 2 prior lines data PFS
- 2 prior lines data TOT
- 2+ prior lines data OS,
- 2+ prior lines data PFS
- 2+ prior lines data TOT

A6. Please provide the KM hazard ratios (and 95% CIs) for OS, PFS and ToT of the IA2 data cut for:

a. the 2 prior and the 2+ prior subgroup
b. the 2 prior and the 2+ prior when adjusted for the baseline characteristics that are used to adjust the parameterised curves in the adjusted curves analyses of the economics using e.g. Peto-Prentice weighted Wilcoxon's, Cox regression, please specify methods used.

**Response:** Table 4 outlines the hazard ratios with 95% CIs as requested. Cox regression was used to adjust the parameterised curves for the covariates within the parametrised curves.

**Table 4: KM hazard ratios (and 95% CIs) for unadjusted and adjusted OS, PFS and ToT of the IA2 data cut for the 2 prior and 2+ prior subgroups**

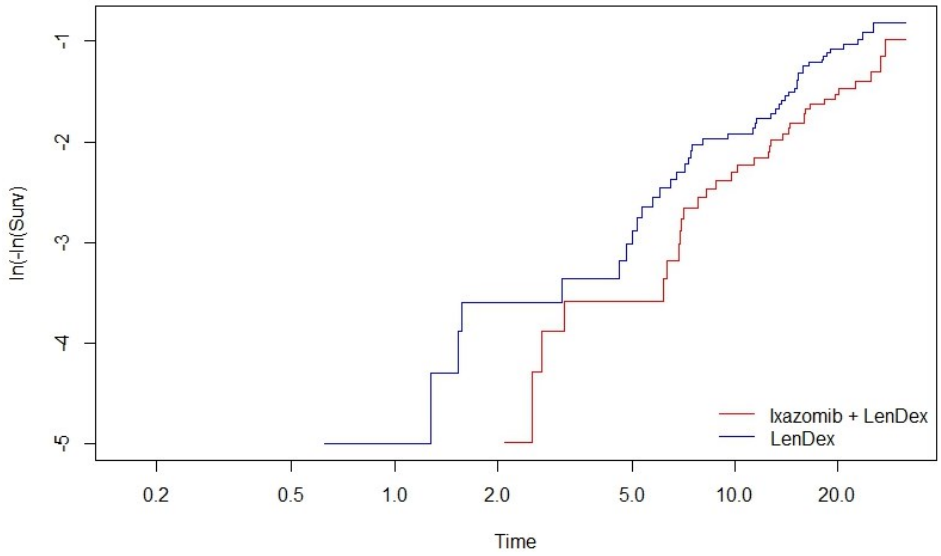
| | | OS | PFS | TOT |
|---|---|---|---|---|
| | **Covariate** | **HR (95% CI)** | **HR (95% CI)** | **HR (95% CI)** |
| **Unadjusted** | | | | |
| 2+ Prior Lines | IXA+LEN+DEX | 0.68 (0.43-1.06) | 0.62 (0.45-0.86) | 0.75 (0.56-1.00) |
| 2 Prior Lines | IXA+LEN+DEX | 0.78 (0.45-1.34) | 0.79 (0.54-1.17) | 0.90 (0.64-1.27) |
| **Adjusted for covariates** | | | | |
| 2+ Prior Lines | IXA+LEN+DEX | 0.64 (0.40-1.00) | 0.61 (0.44-0.85) | 0.72 (0.54-0.96) |
| | ISS III | 1.91 (1.10-3.32) | | 1.75 (1.18-2.59) |
| | Elderly | 1.79 (1.13-2.85) | | |
| | Light Chain Myeloma | | 1.46 (1.01-2.12) | 1.53 (1.10-2.15) |
| 2 Prior Lines | IXA+LEN+DEX | 0.61 (0.95-1.07) | 0.79 (0.54-1.17) | 0.86 (0.61-1.21) |
| | ISS III | 3.07 (1.51-6.23) | | 1.72 (1.04-2.84) |
| | Elderly | 2.34 (1.32-4.14) | | |
| | History of Bone Lesions | 2.17 (1.03-4.59) | | |
| | Light Chain Myeloma | | 1.71 (1.08-2.69) | |
| | Renal Dysfunction | | | 1.78 (1.08-2.94) |

A7.Please supply the results of formal statistical tests of proportional hazards.

**Response:** The log-cumulative hazard plots (LCHPs), Schoenfeld residual and QQ plots for OS, PFS and ToT for the 2+ prior lines and 2 prior lines subgroup using the IA2 data are presented in Section 2.1.2.1 and Section 2.1.6.1 in Appendix 1 submitted in response to the ACD. These plots are also presented below alongside the Schoenfeld residuals statistics.

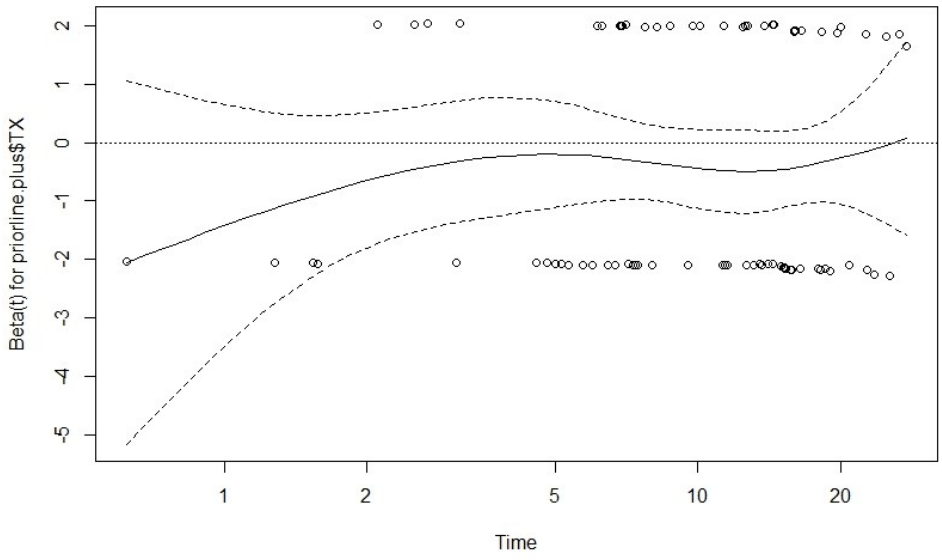
<u>OS - 2+ prior</u>

**Figure 1: LCHP plot for OS, 2+ prior lines population**




**Key:** LCHP, log cumulative hazard plot; LenDex, lenalidomide plus dexamethasone; OS, overall survival

**Figure 2: Schoenfeld residuals plot for OS, 2+ prior lines population**

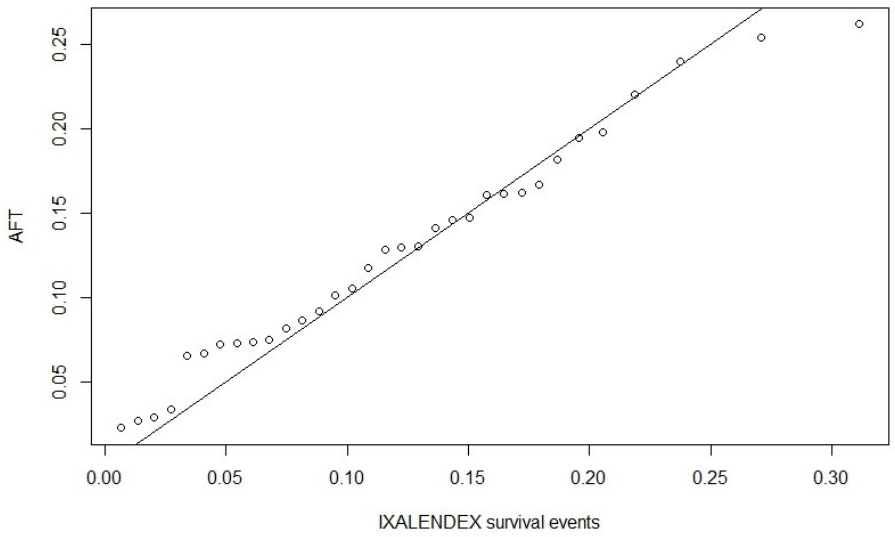



**Key:** OS, overall survival

**Table 5: Schoenfeld residuals OS 2+ prior lines (IA2)**

| Population | Time p-value | Log(Time) p-value | Time^2 p-value |
|---|---|---|---|
| OS 2+ prior lines | 0.613 | 0.515 | 0.57 |
| **Key:** OS, overall survival | | | |

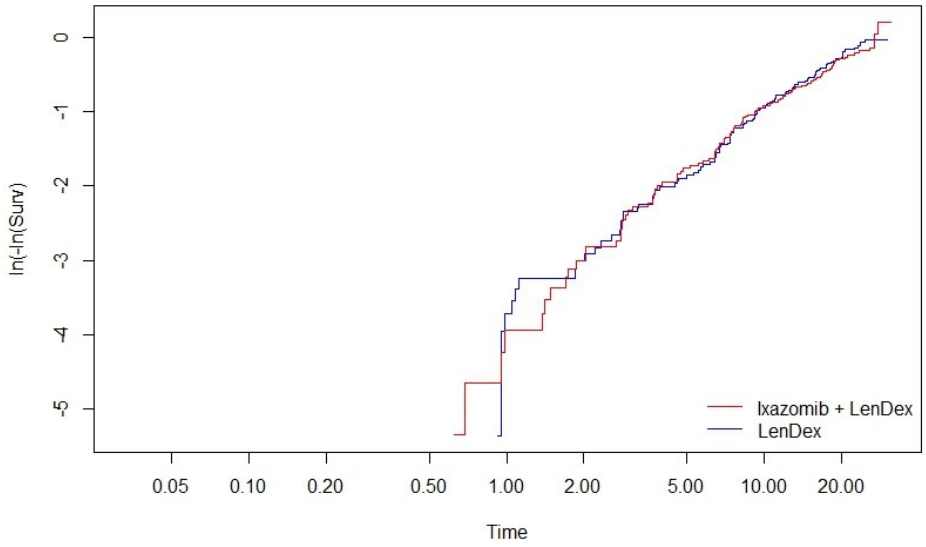
**Figure 3: Q-Q curve for OS, 2+ prior lines population**




**Key:** AFT, accelerated failure time; IXALENDEX, ixazomib, lenalidomide plus dexamethasone; OS, overall survival

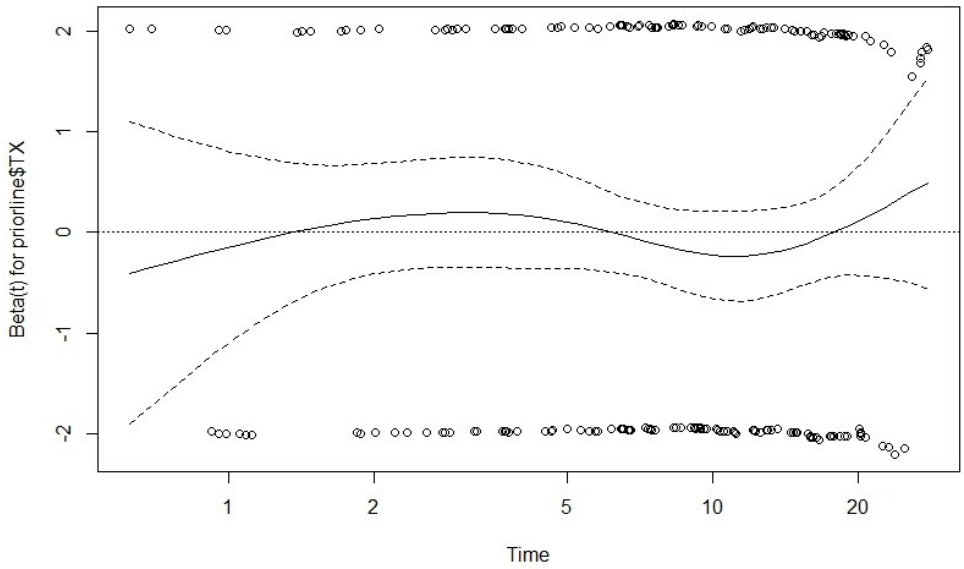
## PFS - 2+ prior

**Figure 4: LCHP plot for PFS, 2+ prior lines population**




**Key:** LCHP, log cumulative hazard plot; LenDex, lenalidomide plus dexamethasone; PFS, progression free survival

**Figure 5: Schoenfeld residuals for PFS, 2+ prior lines population**

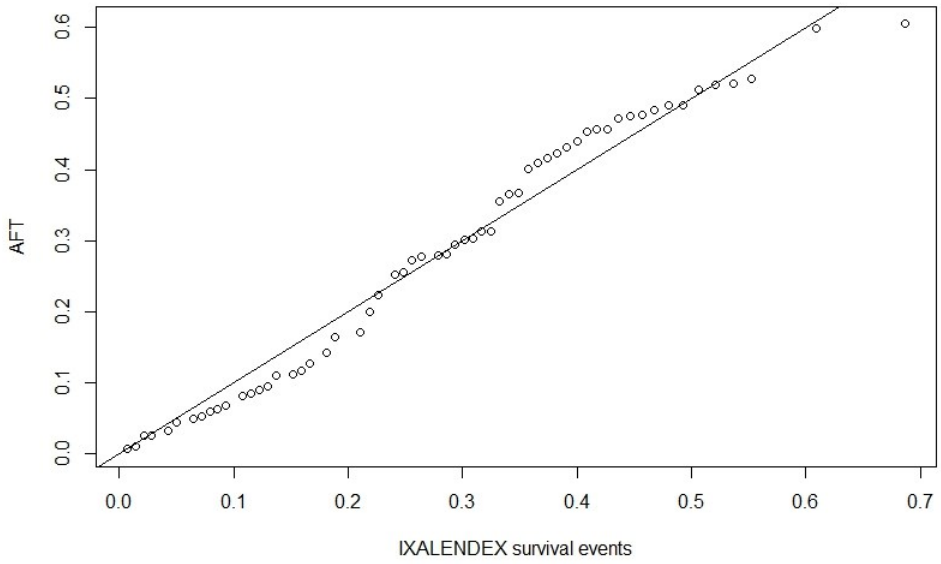



**Key:** PFS, progression free survival

**Table 6: Schoenfeld residuals PFS 2+ prior lines (IA2)**

| Population | Time p-value | Log(Time) p-value | Time^2 p-value |
|---|---|---|---|
| PFS 2+ prior lines | 0.9 | 0.892 | 0.8 |
| **Key:** PFS, progression free survival | | | |

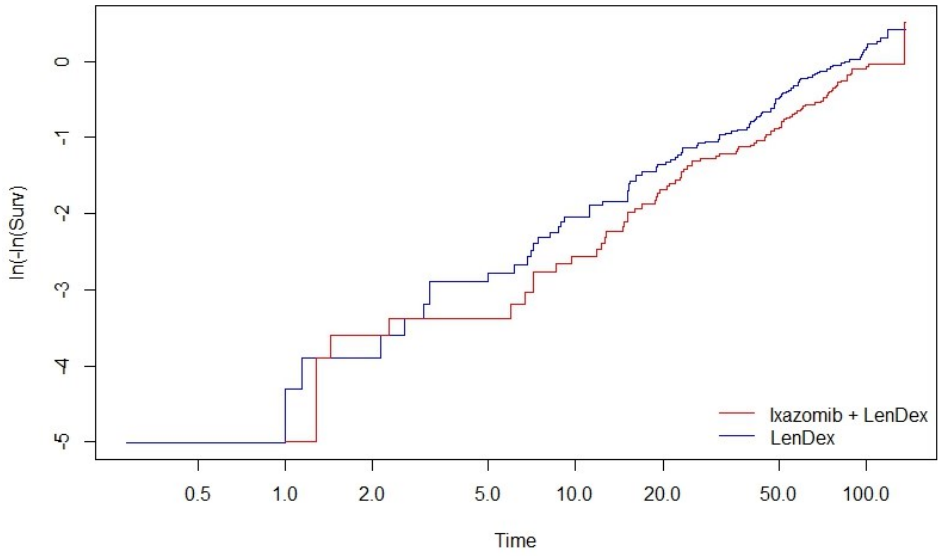
**Figure 6: Q-Q curves for PFS, 2+ prior lines population**




**Key:** AFT, accelerated failure time; IXALENDEX, ixazomib plus lenalidomide plus dexamethasone; PFS, progression free survival

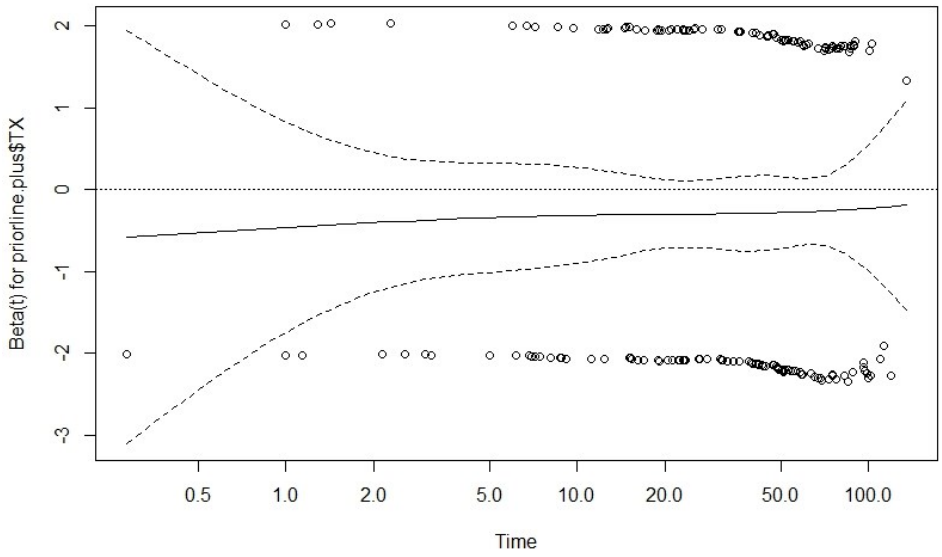
ToT - 2+ prior

**Figure 7: LCHP plot for ToT, 2+ prior lines population**




**Key:** LCHP, log cumulative hazard plot; LenDex, lenalidomide plus dexamethasone; ToT, time on treatment

**Figure 8: Schoenfeld residuals plot for ToT, 2+ prior lines population**

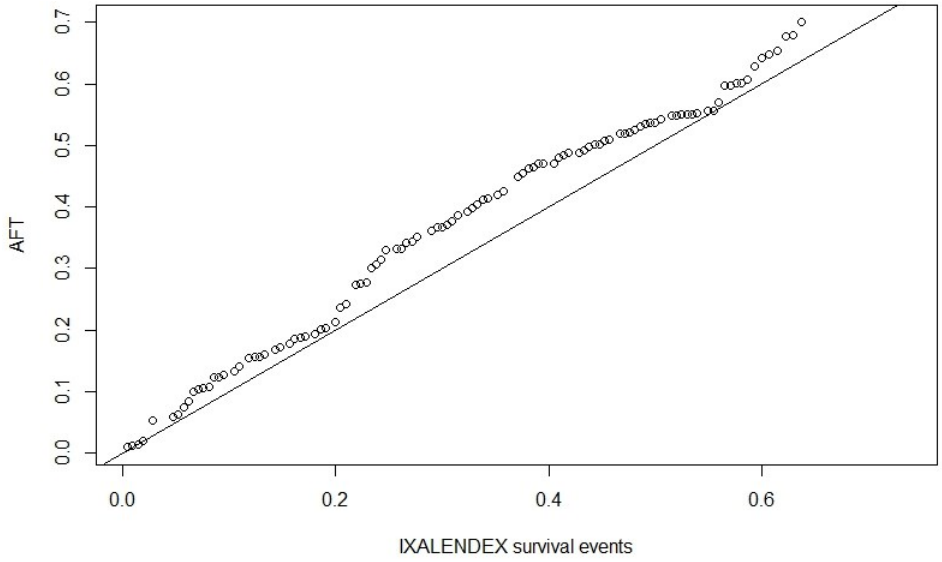



Key: ToT, time on treatment

**Table 7: Schoenfeld residuals ToT 2+ prior lines (IA2)**

| Population | Time p-value | Log(Time) p-value | Time^2 p-value |
|---|---|---|---|
| TOT 2+ prior lines | 0.822 | 0.754 | 0.91 |
| **Key:** ToT, time on treatment | | | |

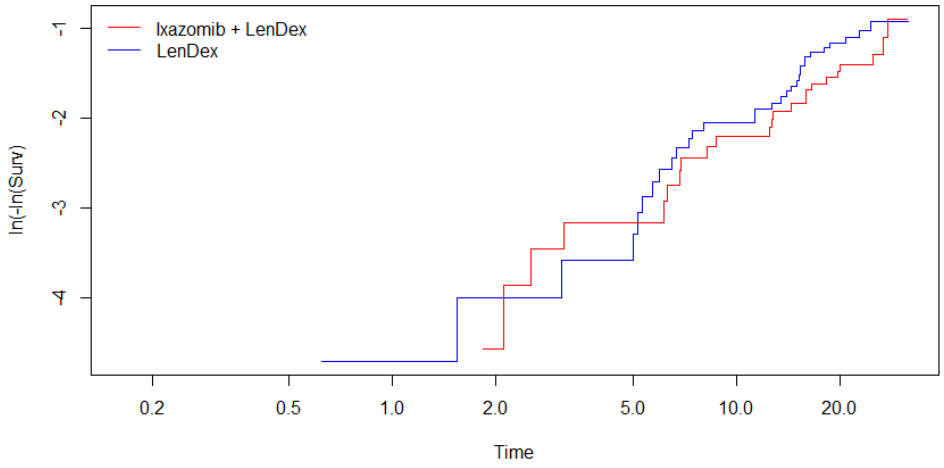
**Figure 9: Q-Q curve for ToT, 2+ prior lines population**




**Key:** AFT, accelerated failure time; IXALENDEX, ixazomib, lenalidomide and dexamethasone; ToT, time on treatment

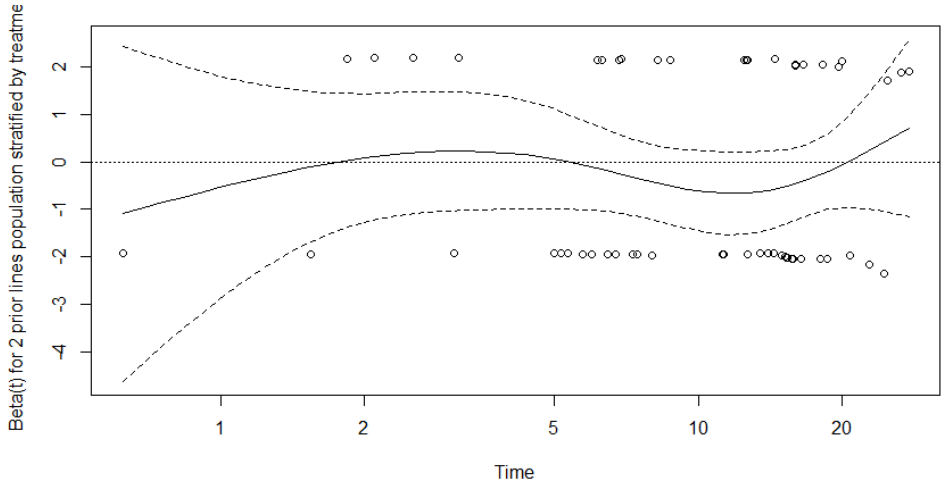
## OS - 2 prior

**Figure 10: LCHP plot for OS, 2-prior lines population**




**Key:** LCHP, log cumulative hazard plot; LenDex, lenalidomide and dexamethasone; OS, overall survival

**Figure 11: Schoenfeld residuals plot for OS, 2-prior lines population**

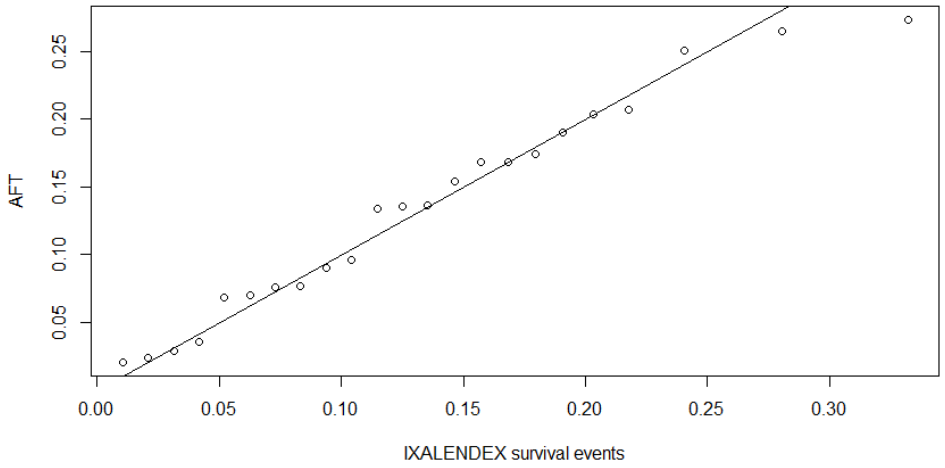



**Key:** OS, overall survival

**Table 8: Schoenfeld residuals OS 2-prior lines (IA2)**

| Population | Time p-value | Log(Time) p-value | Time^2 p-value |
|---|---|---|---|
| OS 2 prior lines | 0.787 | 0.97 | 0.561 |
| **Key:** OS, overall survival | | | |

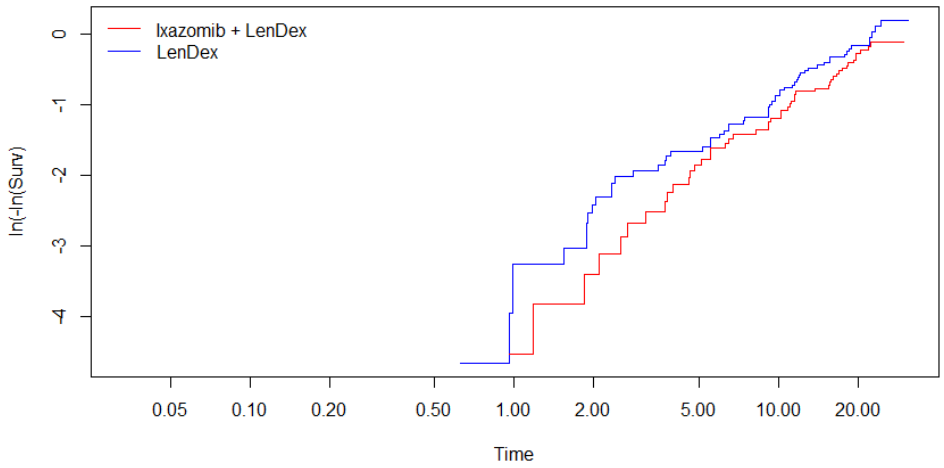
**Figure 12: Q-Q curve for OS, 2-prior lines population**




**Key:** AFT, accelerated failure time; IXALENDEX, ixazomib, lenalidomide and dexamethasone; OS, overall survival

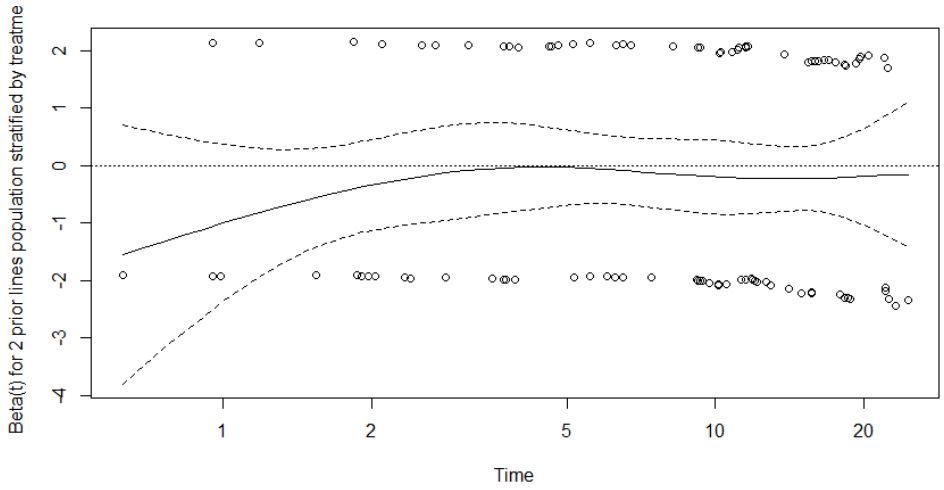
PFS - 2 prior

**Figure 13: LCHP plot for PFS, 2-prior lines population**




**Key:** LCHP, log cumulative hazard plot; LenDex, lenalidomide and dexamethasone; PFS, progression free survival

**Figure 14: Schoenfeld residuals for PFS, 2-prior lines population**

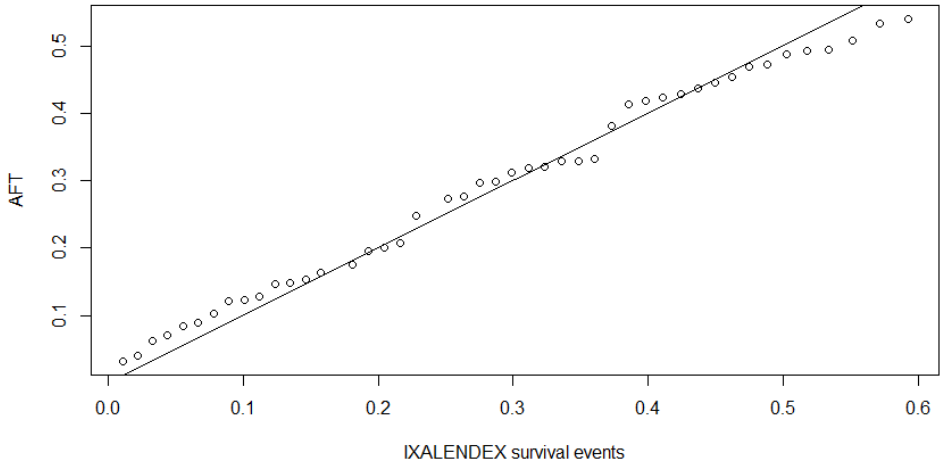



**Key:** PFS, progression free survival

**Table 9: Schoenfeld residuals PFS 2-prior lines (IA2)**

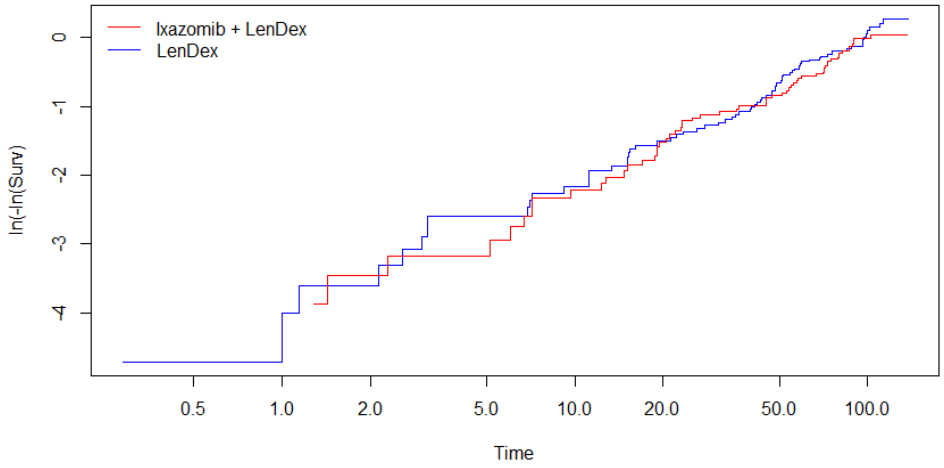
| Population | Time p-value | Log(Time) p-value | Time^2 p-value |
|---|---|---|---|
| PFS 2 prior lines | 0.786 | 0.522 | 0.976 |
| **Key:** PFS, progression free survival | | | |

**Figure 15: Q-Q curves for PFS, 2-prior lines population**



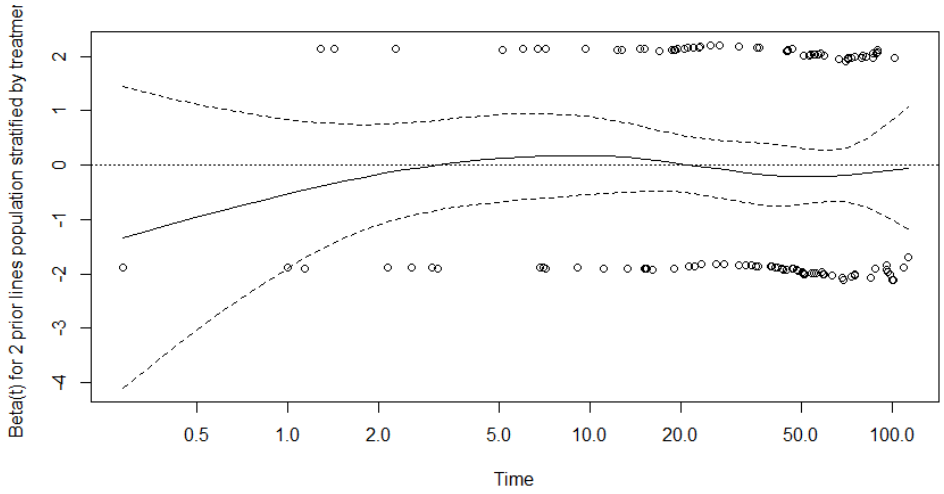

**Key:** AFT, accelerated failure time; IXALENDEX, ixazomib, lenalidomide and dexamethasone; PFS, progression free survival

**Figure 16: LCHP plot for ToT, 2-prior lines population**




**Key:** LCHP, log cumulative hazard plot; LenDex, lenalidomide and dexamethasone; ToT, time on treatment

**Figure 17: Schoenfeld residuals plot for ToT, 2-prior lines population**

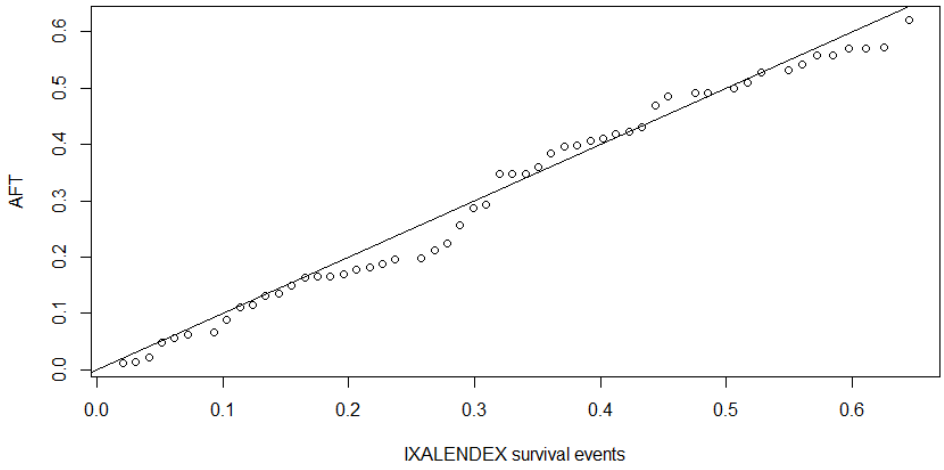



**Key:** ToT, time on treatment

**Table 10: Schoenfeld residuals ToT 2-prior lines (IA2)**

| Population | Time p-value | Log(Time) p-value | Time^2 p-value |
|---|---|---|---|
| TOT 2 prior lines | 0.752 | 0.991 | 0.684 |
| **Key:** PFS, progression free survival | | | |

**Figure 18: Q-Q curve for ToT, 2-prior lines population**




**Key:** IXALENDEX, ixazomib, lenalidomide and dexamethasone; ToT, time on treatment

**A8.PRIORITY QUESTION:** For OS, PFS, and ToT (Appendix 1 of ACD response, section 2.1.2.1) please tabulate the “mean of covariate” values used in in the adjusted parametric models for both the 2+ prior subgroup

and the 2 prior subgroup. Please define the procedure described as “mean of covariates method” and describe why it was chosen over the alternatives.

**Response:** The “mean of covariates method”, or Average Covariate Method (ACM) is a method for applying risk equations to a population. Using this method, the mean value of a risk factor over the model population is calculated and used as input to the risk equations to derive a single risk or hazard for the represented population at each evaluation point. It is used as an alternative to Patient-Level Simulation (PLS), sometimes referred to as “Corrected Group Prognosis” (CGP) which models each combination of risk factors present within individuals of the population, and mean values are only calculated on the output.

As the population of the informing trial was the same as what was being modelled and outcome-influencing differences are applied uniformly over the population of interest, ACM was the method of choice.

**Table 11: Proportion of patients attributing each risk factor of the 2+ prior lines and 2 prior lines sub-population in the IA2 data cut.**

| | 2+ Prior Lines | 2 Prior Lines |
|---|---|---|
| Prior Lines = 2 or 3 | 100.00% | 92.79% |
| Cytogenetics = High Risk | 19.53% | 17.79% |
| ISS = Stage III | 12.79% | 10.10% |
| Age > 65 years | 52.86% | 50.96% |
| Light chain myeloma = Yes | 21.21% | 18.27% |
| Relapsed and refractory = Yes | 26.94% | 23.08% |
| Primary refractory = Yes | 7.07% | 8.17% |
| Proteasome inhibitor = Yes | 76.43% | 77.88% |
| Immunomodulation agent = Yes | 68.01% | 66.83% |
| ECOG performance score = 2 | 8.42% | 8.65% |
| ASCT undertaken = Yes | 56.23% | 59.62% |
| History of bone lesions = Yes | 73.06% | 75.96% |
| Renal dysfunction = Yes | 13.80% | 10.58% |
| Asian = Yes | 9.09% | 8.17% |
| Gender = male | 56.23% | 58.65% |
| Race = white | 82.49% | 84.13% |

A9.Referring to section 3.2.5 of the ACD response

a. Please present the statistical analyses that lead to only a subset of the patient characteristics being presented in Table 2 and Table 3 of section 3.2.5 of the ACD response.

**Response:**
The subset of patient and disease characteristics presented in Tables 2 and 3 of the ACD response were selected based on clinical importance rather than a statistical analysis. Due to concerns over potential imbalances in disease and patient characteristics confounding the

results within the 2 prior and 3 prior lines alone unstratified subgroups, Takeda consulted with a series of UK multiple myeloma experts who identified cytogenetic risk, age and international staging system (ISS) stage as the key prognostic variables within the trial data and hence these were presented within the ACD response:

Age is important as older myeloma patients may be in poorer general health and unable to tolerate strong or sustained chemotherapy. In the CRUK survival statistics, five-year survival for myeloma decreases with increasing age. Five-year net survival in men ranges from 74% in 15-49 year olds to 24% in 80-99 year olds, for patients diagnosed with myeloma in England during 2009-2013. In women, five-year survival ranged from 74% to 26% in the same age groups.[1] In addition, a retrospective analysis of 2,695 myeloma patients by the UK HMRN registry demonstrated that median survival from diagnosis was [redacted] (all patients) and this decreased with increasing age (Table 12 Figure 19), with median survival ranging from [redacted]. As shown in Table 2 of the ACD response, there is an imbalance in the distribution of young (≤ 65 years) and old (>75 years) patients across the MM-1 study arms, which will likely confound the relative overall efficacy seen within the unstratified, individual lines of therapy.

**Table 12: HMRN dataset: overall survival from diagnosis by sex, age and International Staging System (ISS) score**

[redacted]

**Figure 19: HMRN dataset: overall survival from diagnosis by age group**

Myeloma is also characterised by chromosomal instability and the presence of high risk cytogenetic abnormalities is known to have a negative impact on prognosis[2] It is widely published and recognised within both UK and International guidelines that cytogenetic results provide important prognostic information in myeloma.[3-7] In addition, the International Staging System (ISS) is a risk stratification algorithm based on two parameters; high serum β2-microglobulin level reflects high tumour mass and reduced renal function, and low serum albumin in myeloma is mainly caused by inflammatory cytokines such as interleukin [redacted] secreted by the myeloma microenvironment. The ISS score identifies three patient groups with different prognoses; the median overall survival (OS) was [redacted] in the ISS Stage I, [redacted] in the ISS Stage II, [redacted] in the ISS Stage III groups (P<.001). Although cytogenetics results were not available for analysis, the HMRN registry also confirms the prognostic significance of ISS stage. In patients with a known ISS score, median OS decreased with more advanced ISS stage, with survival ranging from [redacted] for ISS Stage I to [redacted] for ISS Stage III (Table 12, Figure 20).

**Figure 20: HMRN dataset: overall survival from diagnosis by ISS group**

NICE guidelines recognise the prognostic value of high risk cytogenetics and the ISS. NICE guideline [8] recommends performing fluorescence in-situ hybridisation (FISH) testing to identify the adverse risk abnormalities and to use these abnormalities alongside International Staging System (ISS) scores to identify people with high-risk myeloma. In Figure 2 of the ACD response, it is evident that there is a disproportionate distribution across the arms of both standard and high-risk cytogenetic abnormalities in 3rd line alone and 4th line alone unstratified subgroups, with also an apparent imbalance in ISS stage in the 4th line alone subgroup. Therefore, consistent with age, the key prognostic factors could impact on and confound the interpretation of results.

In conclusion, age, cytogenetic risk and ISS stage were selected for presentation in Tables 2 and 3 based on UK clinical experts recommendation, which is consistent with both published literature and UK and International guidelines. These results highlight the potential confounding effects of key prognostic factors and the limitations of any unadjusted analyses within the individual lines of therapy.

b. Please outline why the set of characteristics in Table 2 and Table 3 of section 3.2.5 differ from those of section 2.1.2.1 of Appendix 1 for the 2+ prior subgroup, and from those of the economic model for the 2 prior subgroup.

**Response:** The characteristics within Table 2 and Table 3 of section 3.2.5 are based on clinical insight of the most important risk factors within this disease area. The characteristics outlined in section 2.1.2.1 of Appendix 1 and the economic model are those that were found to be significant risk factors specific to the endpoint being measured, based on a backwards stepwise iteration method outlined in the initial submission.

c. Please present the statistical analyses including the log rank tests used to "detect significant differences in clinical end points between treatments" and the results of the various backward iterations that lead to only a subset of the patient characteristics being considered for the IA2 2+ prior subgroup.

**Response:** Table 13 to Table 15 outline the statistical analysis including the log rank tests used to detect significant differences in clinical end points between treatments for the 2+ prior lines subpopulation (IA2 cut).

**Table 13: Baseline risk factors and log rank significance for OS for the IA2 2+ prior line sub-population**

| Level 1 | | | Level 2 | | | P-value (log rank) |
|---|---|---|---|---|---|---|
| Variant | Median (mths) | Mean (mths) | Variant | Median (mths) | Mean (mths) | |
| IXALENDEX = Yes | NA | 26.77 | LENDEX = Yes | NA | 24.84 | 0.09 |
| High risk cytogenetics = Yes | 27.56 | 23.95 | High risk cytogenetics = No | NA | 26.26 | 0.15 |
| ISS Stage III | 24.94 | 22.7 | ISS Stage I or II | NA | 26.32 | 0.02* |
| Age > 65 years | NA | 24.4 | Age <= 65 years | NA | 27.34 | 0.01* |
| Light chain myeloma = Yes | NA | 25.07 | Light chain myeloma = No | NA | 25.97 | 0.75 |
| Relapsed and refractory = Yes | NA | 27.07 | Relapsed and refractory = No | NA | 25.27 | 0.21 |
| Primary refractory = Yes | NA | 25.44 | Primary refractory = No | NA | 25.85 | 0.95 |
| Proteasome inhibitor = Exposed | NA | 25.45 | Proteasome inhibitor = Naive | NA | 26.80 | 0.45 |
| Immunomodulation agent = Exposed | NA | 25.94 | Immunomodulation agent = Naive | NA | 25.64 | 0.81 |
| ECOG performance status = 2 | NA | 23.05 | ECOG performance status = 0/1 | NA | 26.13 | 0.13 |
| ASCT undertaken = Yes | NA | 26.62 | ASCT undertaken = No | NA | 24.81 | 0.06 |
| History of bone lesions = Yes | NA | 25.37 | History of bone lesions = No | NA | 26.52 | 0.16 |
| Renal dysfunction = Yes | NA | 23.90 | Renal dysfunction = No | NA | 25.94 | 0.57 |
| Race = Asian | NA | 18.90 | Race = Non-Asian | NA | 25.54 | 0.08 |
| *NA: Indicates median not reached; *: Significant to p < 0.05* | | | | | | |

**Table 14: Baseline risk factors and log rank significance for PFS for the IA2 2+ prior line sub-population**

| Level 1 | | | Level 2 | | | P-value (log rank) |
|---|---|---|---|---|---|---|
| Variant | Median (mths) | Mean (mths) | Variant | Median (mths) | Mean (mths) | |
| IXALENDEX = Yes | 21.98 | 19.92 | LENDEX = Yes | 12.98 | 15.88 | 0.00* |
| High risk cytogenetics = Yes | 13.86 | 16.92 | High risk cytogenetics = No | 18.60 | 18.19 | 0.54 |
| ISS Stage III | 18.46 | 17.11 | ISS Stage I or II | 18.27 | 18.04 | 0.64 |
| Age > 65 years | 19.68 | 18.34 | Age <= 65 years | 15.64 | 17.36 | 0.54 |
| Light chain myeloma = Yes | 10.18 | 15.34 | Light chain myeloma = No | 19.12 | 18.71 | 0.06 |
| Relapsed and refractory = Yes | 17.91 | 18.11 | Relapsed and refractory = No | 18.60 | 17.81 | 0.88 |
| Primary refractory = Yes | 20.04 | 20.74 | Primary refractory = No | 18.27 | 17.68 | 0.35 |
| Proteasome inhibitor = Exposed | 17.91 | 17.53 | Proteasome inhibitor = Naive | 20.50 | 18.92 | 0.32 |
| Immunomodulation agent = Exposed | 18.43 | 17.44 | Immunomodulation agent = Naive | 18.60 | 18.71 | 0.54 |
| ECOG performance status = 2 | 18.60 | 17.21 | ECOG performance status = 0/1 | 18.46 | 18.13 | 0.69 |
| ASCT undertaken = Yes | 18.60 | 18.72 | ASCT undertaken = No | 17.02 | 16.90 | 0.24 |
| History of bone lesions = Yes | 17.91 | 17.65 | History of bone lesions = No | 19.61 | 18.56 | 0.48 |
| Renal dysfunction = Yes | 17.02 | 16.34 | Renal dysfunction = No | 18.43 | 18.11 | 0.39 |
| Race = Asian | 17.02 | 13.60 | Race = Non-Asian | 18.43 | 17.95 | 0.86 |
| *NA: Indicates median not reached; *: Significant to p < 0.05* | | | | | | |

**Table 15: Baseline risk factors and log rank significance for TOT for the IA2 2+ prior line sub-population**

| Level 1 | | | Level 2 | | | P-value (log rank) |
|---|---|---|---|---|---|---|
| Variant | Median (mths) | Mean (mths) | Variant | Median (mths) | Mean (mths) | |
| IXALENDEX = Yes | 17.74 | 18.34 | LENDEX = Yes | 12.65 | 15.50 | 0.04* |
| High risk cytogenetics = Yes | 13.49 | 16.36 | High risk cytogenetics = No | 15.90 | 16.97 | 0.99 |

| | | | | | | |
|---|---|---|---|---|---|---|
| ISS Stage III | 11.50 | 13.04 | ISS Stage I or II | 16.39 | 17.45 | 0.02* |
| Age > 65 years | 13.11 | 16.12 | Age <= 65 years | 16.79 | 17.79 | 0.28 |
| Light chain myeloma = Yes | 10.78 | 14.16 | Light chain myeloma = No | 16.82 | 17.65 | 0.03* |
| Relapsed and refractory = Yes | 15.01 | 17.69 | Relapsed and refractory = No | 15.38 | 16.57 | 0.51 |
| Primary refractory = Yes | 18.40 | 18.15 | Primary refractory = No | 14.77 | 16.77 | 0.62 |
| Proteasome inhibitor = Exposed | 14.26 | 16.94 | Proteasome inhibitor = Naive | 17.35 | 16.80 | 0.94 |
| Immunomodulation agent = Exposed | 14.13 | 16.23 | Immunomodulation agent = Naive | 16.82 | 18.51 | 0.15 |
| ECOG performance status = 2 | 10.32 | 14.24 | ECOG performance status = 0/1 | 15.90 | 17.16 | 0.26 |
| ASCT undertaken = Yes | 16.39 | 17.46 | ASCT undertaken = No | 13.26 | 16.15 | 0.32 |
| History of bone lesions = Yes | 15.67 | 16.89 | History of bone lesions = No | 13.68 | 16.72 | 0.91 |
| Renal dysfunction = Yes | 10.84 | 12.41 | Renal dysfunction = No | 16.36 | 17.45 | 0.01* |
| Race = Asian | NA | 14.23 | Race = Non-Asian | 13.90 | 16.63 | 0.14 |
| *NA: Indicates median not reached; *: Significant to p < 0.05* | | | | | | |

Table 16 to Table 18 outlines the result of the backwards stepwise method for determining covariates for the 2+ prior lines subpopulation (IA2 cut).

**Table 16: Backwards stepwise iteration for OS for the IA2 2+ prior line sub-population**

| Characteristic | I1 | I2 | I3 | I4 | I5 | I6 | I7 | I8 | I9 | I10 |
|---|---|---|---|---|---|---|---|---|---|---|
| High risk cytogenetics = Yes | 0.020 | 0.020 | 0.020 | 0.017 | 0.034 | 0.044 | 0.057 | 0.073 | 0.133 | |
| ISS Stage III | 0.007 | 0.007 | 0.007 | 0.007 | 0.008 | 0.010 | 0.010 | 0.016 | 0.017 | 0.020 |
| Age > 65 years | 0.017 | 0.017 | 0.017 | 0.017 | 0.008 | 0.008 | 0.008 | 0.015 | 0.018 | 0.015 |
| Light chain myeloma = Yes | 0.483 | 0.484 | 0.486 | 0.485 | 0.359 | | | | | |
| Relapsed and refractory = Yes | 0.082 | 0.081 | 0.082 | 0.079 | 0.064 | 0.062 | 0.083 | | | |
| Primary refractory = Yes | 0.889 | 0.889 | | | | | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Proteasome inhibitor = Exposed | 0.794 | 0.787 | 0.794 | | | | | | | |
| Immunomodulation agent = Exposed | 0.978 | | | | | | | | | |
| ECOG performance status = 2 | 0.536 | 0.535 | 0.529 | 0.514 | | | | | | |
| History of bone lesions = Yes | 0.101 | 0.098 | 0.096 | 0.092 | 0.081 | 0.081 | 0.072 | 0.078 | | |
| Race = Asian | 0.104 | 0.102 | 0.102 | 0.101 | 0.093 | 0.105 | | | | |
| *In: Iteration n* | | | | | | | | | | |

**Table 17: Backwards stepwise iteration for PFS for the IA2 2+ prior line sub-population**

| Characteristic | I1 | I2 | I3 | I4 | I5 | I6 | I7 | I8 | I9 | I10 | I11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| High risk cytogenetics = Yes | 0.353 | 0.349 | 0.353 | 0.357 | 0.283 | 0.307 | 0.338 | 0.287 | | | |
| ISS Stage III | 0.401 | 0.434 | 0.430 | 0.433 | 0.440 | 0.478 | | | | | |
| Light chain myeloma = Yes | 0.038 | 0.032 | 0.032 | 0.032 | 0.031 | 0.030 | 0.034 | 0.027 | 0.033 | 0.039 | 0.050 |
| Relapsed and refractory = Yes | 0.855 | 0.839 | 0.849 | | | | | | | | |
| Primary refractory = Yes | 0.383 | 0.361 | 0.361 | 0.360 | 0.336 | 0.362 | 0.359 | | | | |
| Proteasome inhibitor = Exposed | 0.552 | 0.470 | 0.460 | 0.452 | | | | | | | |
| Immunomodulation agent = Exposed | 0.484 | 0.407 | 0.373 | 0.379 | 0.455 | | | | | | |
| ECOG performance status = 2 | 0.967 | | | | | | | | | | |
| ASCT undertaken = Yes | 0.210 | 0.193 | 0.195 | 0.200 | 0.212 | 0.211 | 0.158 | 0.204 | 0.180 | 0.193 | |
| History of bone lesions = Yes | 0.202 | 0.207 | 0.205 | 0.199 | 0.182 | 0.206 | 0.209 | 0.214 | 0.248 | | |
| Race = Asian | 0.904 | 0.892 | | | | | | | | | |

*In: Iteration n*

**Table 18: Backwards stepwise iteration for TOT for the IA2 2+ prior line sub-population**

| Characteristic | I1 | I2 | I3 | I4 | I5 | I6 | I7 | I8 | I9 | I10 |
|---|---|---|---|---|---|---|---|---|---|---|
| High risk cytogenetics = Yes | 0.386 | 0.384 | 0.402 | 0.352 | | | | | | |
| ISS Stage III | 0.016 | 0.016 | 0.015 | 0.014 | 0.015 | 0.020 | 0.021 | 0.003 | 0.004 | 0.004 |
| Light chain myeloma = Yes | 0.043 | 0.042 | 0.043 | 0.035 | 0.043 | 0.043 | 0.042 | 0.020 | 0.013 | 0.013 |
| Relapsed and refractory = Yes | 0.150 | 0.149 | 0.155 | 0.148 | 0.156 | 0.200 | | | | |
| Primary refractory = Yes | 0.428 | 0.428 | 0.439 | | | | | | | |
| Proteasome inhibitor = Exposed | 0.766 | 0.767 | | | | | | | | |
| Immunomodulation agent = Exposed | 0.176 | 0.176 | 0.152 | 0.166 | 0.174 | | | | | |
| ECOG performance status = 2 | 0.116 | 0.112 | 0.114 | 0.121 | 0.122 | 0.138 | 0.160 | 0.272 | | |
| History of bone lesions = Yes | 0.986 | | | | | | | | | |
| Renal dysfunction = Yes | 0.122 | 0.118 | 0.122 | 0.160 | 0.155 | 0.139 | 0.188 | | | |
| Race = Asian | 0.132 | 0.132 | 0.136 | 0.137 | 0.143 | 0.091 | 0.116 | 0.134 | 0.124 | |
| *In: Iteration n* | | | | | | | | | | |

d. In light of the final covariates differing for the IA2 2 prior subgroup please present the corresponding statistical analyses for the IA2 2 prior subgroup.

**Response:** Table 19 to Table 21 outline the statistical analysis including the log rank tests used to detect significant differences in clinical end points between treatments for the 2 prior lines subpopulation (IA2 cut).

**Table 19: Baseline risk factors and log rank significance for OS for the IA2 2 prior line sub-population**

| Level 1 | | | Level 2 | | | P-value (log rank) |
|---|---|---|---|---|---|---|
| Variant | Median (mths) | Mean (mths) | Variant | Median (mths) | Mean (mths) | |
| IXALENDEX = Yes | NA | 26.35 | LENDEX = Yes | NA | 25.39 | 0.36 |
| High risk cytogenetics = Yes | NA | 22.86 | High risk cytogenetics = No | NA | 26.13 | 0.39 |
| ISS Stage III | 24.94 | 20.97 | ISS Stage I or II | NA | 26.43 | 0.01* |
| Age > 65 years | NA | 24.23 | Age <= 65 years | NA | 27.39 | 0.02* |
| Light chain myeloma = Yes | NA | 24.29 | Light chain myeloma = No | NA | 26.21 | 0.58 |
| Relapsed and refractory = Yes | NA | 27.55 | Relapsed and refractory = No | NA | 25.34 | 0.20 |
| Primary refractory = Yes | NA | 24.15 | Primary refractory = No | NA | 25.90 | 0.89 |
| Proteasome inhibitor = Exposed | NA | 25.65 | Proteasome inhibitor = Naive | NA | 26.52 | 0.69 |
| Immunomodulation agent = Exposed | NA | 25.81 | Immunomodulation agent = Naive | NA | 25.96 | 0.80 |
| ECOG performance status = 2 | NA | 22.42 | ECOG performance status = 0/1 | NA | 26.07 | 0.09 |
| ASCT undertaken = Yes | NA | 26.52 | ASCT undertaken = No | NA | 24.64 | 0.10 |
| History of bone lesions = Yes | NA | 25.39 | History of bone lesions = No | NA | 26.80 | 0.20 |
| Renal dysfunction = Yes | 27.56 | 23.33 | Renal dysfunction = No | NA | 26.04 | 0.39 |
| Race = Asian | NA | 18.84 | Race = Non-Asian | NA | 25.62 | 0.16 |
| *NA: Indicates median not reached; *: Significant to p < 0.05* | | | | | | |

**Table 20: Baseline risk factors and log rank significance for PFS for the IA2 2 prior line sub-population**

| Level 1 | | | Level 2 | | | P-value (log rank) |
|---|---|---|---|---|---|---|
| Variant | Median (mths) | Mean (mths) | Variant | Median (mths) | Mean (mths) | |
| IXALENDEX = Yes | 19.32 | 18.74 | LENDEX = Yes | 15.64 | 17.08 | 0.24 |
| High risk cytogenetics = Yes | 15.67 | 15.89 | High risk cytogenetics = No | 18.27 | 18.31 | 0.77 |
| ISS Stage III | 14.92 | 15.69 | ISS Stage I or II | 18.27 | 18.35 | 0.34 |
| Age > 65 years | 18.43 | 18.01 | Age <= 65 years | 16.59 | 17.75 | 1.00 |
| Light chain myeloma = Yes | 9.72 | 13.59 | Light chain myeloma = No | 19.32 | 19.03 | 0.02* |
| Relapsed and refractory = Yes | 17.91 | 17.29 | Relapsed and refractory = No | 18.27 | 17.91 | 0.69 |
| Primary refractory = Yes | 19.68 | 17.83 | Primary refractory = No | 17.91 | 18.06 | 0.79 |
| Proteasome inhibitor = Exposed | 18.27 | 18.36 | Proteasome inhibitor = Naive | 16.59 | 17.10 | 0.62 |
| Immunomodulation agent = Exposed | 17.91 | 17.20 | Immunomodulation agent = Naive | 18.60 | 19.24 | 0.40 |
| ECOG performance status = 2 | 18.43 | 16.43 | ECOG performance status = 0/1 | 17.91 | 17.78 | 0.62 |
| ASCT undertaken = Yes | 18.27 | 18.38 | ASCT undertaken = No | 16.59 | 16.90 | 0.28 |
| History of bone lesions = Yes | 16.59 | 17.79 | History of bone lesions = No | 23.26 | 17.53 | 0.45 |
| Renal dysfunction = Yes | 15.90 | 12.85 | Renal dysfunction = No | 18.43 | 18.60 | 0.05 |
| Race = Asian | 15.70 | 13.65 | Race = Non-Asian | 18.27 | 18.21 | 0.61 |
| *NA: Indicates median not reached; *: Significant to p < 0.05* | | | | | | |

**Table 21: Baseline risk factors and log rank significance for TOT for the IA2 2 prior line sub-population**

| Level 1 | | | Level 2 | | | P-value (log rank) |
|---|---|---|---|---|---|---|
| Variant | Median (mths) | Mean (mths) | Variant | Median (mths) | Mean (mths) | |
| IXALENDEX = Yes | 16.82 | 17.73 | LENDEX = Yes | 13.67 | 16.75 | 0.95 |
| High risk cytogenetics = Yes | 13.40 | 15.26 | High risk cytogenetics = No | 16.79 | 17.32 | 0.73 |
| ISS Stage III | 12.19 | 12.23 | ISS Stage I or II | 16.82 | 17.80 | 0.09 |
| Age > 65 years | 13.22 | 16.10 | Age <= 65 years | 17.31 | 18.37 | 0.77 |
| Light chain myeloma = Yes | 9.53 | 13.30 | Light chain myeloma = No | 17.25 | 17.94 | 0.80 |
| Relapsed and refractory = Yes | 16.82 | 16.51 | Relapsed and refractory = No | 16.13 | 17.03 | 0.98 |
| Primary refractory = Yes | 18.20 | 16.17 | Primary refractory = No | 16.36 | 17.20 | 0.98 |
| Proteasome inhibitor = Exposed | 16.36 | 17.77 | Proteasome inhibitor = Naive | 14.74 | 15.34 | 0.09 |
| Immunomodulation agent = Exposed | 15.90 | 16.62 | Immunomodulation agent = Naive | 16.82 | 18.43 | 0.55 |
| ECOG performance status = 2 | 9.87 | 12.89 | ECOG performance status = 0/1 | 16.79 | 17.47 | 0.17 |
| ASCT undertaken = Yes | 16.82 | 17.56 | ASCT undertaken = No | 13.26 | 16.02 | 0.88 |
| History of bone lesions = Yes | 15.67 | 16.86 | History of bone lesions = No | 20.21 | 16.92 | 0.02* |
| Renal dysfunction = Yes | 10.14 | 11.11 | Renal dysfunction = No | 16.82 | 17.81 | 0.35 |
| Race = Asian | NA | 13.83 | Race = Non-Asian | 16.13 | 17.07 | 0.00* |
| *NA: Indicates median not reached; *: Significant to p < 0.05* | | | | | | |

Table 22 to Table 24 outline the result of the backwards stepwise method for determining covariates for the 2+ prior lines subpopulation (IA2 cut).

**Table 22: Backwards stepwise iteration for OS for the IA2 2 prior line sub-population**

| Characteristic | I1 | I2 | I3 | I4 | I5 | I6 | I7 | I8 | I9 | I10 |
|---|---|---|---|---|---|---|---|---|---|---|
| High risk cytogenetics = Yes | 0.103 | 0.099 | 0.102 | 0.105 | 0.092 | 0.091 | 0.131 | 0.141 | 0.120 | |
| ISS Stage III | 0.002 | 0.002 | 0.002 | 0.002 | 0.002 | 0.002 | 0.001 | 0.002 | 0.001 | 0.002 |
| Age > 65 years | 0.006 | 0.005 | 0.006 | 0.005 | 0.006 | 0.006 | 0.003 | 0.003 | 0.004 | 0.005 |
| Light chain myeloma = Yes | 0.760 | 0.760 | 0.768 | | | | | | | |
| Relapsed and refractory = Yes | 0.246 | 0.232 | 0.231 | 0.226 | 0.215 | 0.200 | 0.176 | 0.192 | | |
| Primary refractory = Yes | 0.820 | 0.822 | | | | | | | | |
| Proteasome inhibitor = Exposed | 0.768 | 0.769 | 0.781 | 0.768 | | | | | | |
| Immunomodulation agent = Exposed | 0.710 | 0.711 | 0.709 | 0.720 | 0.686 | | | | | |
| ECOG performance status = 2 | 0.783 | 0.781 | 0.756 | 0.698 | 0.673 | 0.633 | | | | |
| History of bone lesions = Yes | 0.086 | 0.085 | 0.080 | 0.078 | 0.080 | 0.081 | 0.046 | 0.035 | 0.035 | 0.050 |
| Renal dysfunction = Yes | 0.970 | | | | | | | | | |
| Race = Asian | 0.216 | 0.212 | 0.209 | 0.212 | 0.201 | 0.215 | 0.221 | | | |
| *In: Iteration n* | | | | | | | | | | |

**Table 23: Backwards stepwise iteration for PFS for the IA2 2 prior line sub-population**

| Characteristic | I1 | I2 | I3 | I4 | I5 | I6 | I7 | I8 | I9 | I10 | I11 | I12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| High risk cytogenetics = Yes | 0.498 | 0.500 | 0.469 | 0.518 | 0.498 | 0.515 | | | | | | |
| ISS Stage III | 0.322 | 0.309 | 0.274 | 0.234 | 0.212 | 0.220 | 0.237 | 0.262 | 0.285 | | | |
| Light chain myeloma = Yes | 0.015 | 0.025 | 0.021 | 0.023 | 0.023 | 0.025 | 0.028 | 0.027 | 0.025 | 0.036 | 0.050 | 0.023 |
| Relapsed and refractory = Yes | 0.829 | 0.597 | 0.629 | 0.666 | | | | | | | | |
| Primary refractory = Yes | 0.676 | 0.731 | | | | | | | | | | |
| Proteasome inhibitor = Exposed | 0.465 | 0.657 | 0.692 | | | | | | | | | |
| Immunomodulation agent = Exposed | 0.424 | 0.365 | 0.370 | 0.320 | 0.333 | 0.386 | 0.371 | 0.356 | | | | |
| ECOG performance status = 2 | 0.905 | | | | | | | | | | | |
| ASCT undertaken = Yes | 0.200 | 0.315 | 0.338 | 0.320 | 0.334 | 0.286 | 0.280 | 0.301 | 0.268 | 0.229 | | |
| History of bone lesions = Yes | 0.370 | 0.423 | 0.437 | 0.418 | 0.397 | 0.409 | 0.436 | | | | | |
| Renal dysfunction = Yes | 0.371 | 0.196 | 0.204 | 0.215 | 0.224 | 0.201 | 0.188 | 0.154 | 0.180 | 0.153 | 0.104 | |
| Race = Asian | 0.680 | 0.635 | 0.604 | 0.551 | 0.543 | | | | | | | |
| *In: Iteration n* | | | | | | | | | | | | |

**Table 24: Backwards stepwise iteration for TOT for the IA2 2+ prior line sub-population**

| Characteristic | I1 | I2 | I3 | I4 | I5 | I6 | I7 | I8 | I9 | I10 | I11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| High risk cytogenetics = Yes | 0.267 | 0.262 | 0.256 | 0.247 | 0.266 | 0.391 | | | | | |
| ISS Stage III | 0.022 | 0.020 | 0.017 | 0.015 | 0.018 | 0.013 | 0.013 | 0.008 | 0.009 | 0.016 | 0.033 |
| Age > 65 years | 0.187 | 0.185 | 0.183 | 0.177 | 0.217 | 0.207 | 0.214 | 0.211 | 0.183 | | |
| Light chain myeloma = Yes | 0.091 | 0.090 | 0.087 | 0.079 | 0.078 | 0.073 | 0.088 | 0.097 | 0.095 | 0.093 | |
| Relapsed and refractory = Yes | 0.754 | 0.756 | | | | | | | | | |
| Primary refractory = Yes | 0.959 | | | | | | | | | | |
| Proteasome inhibitor = Exposed | 0.183 | 0.182 | 0.191 | 0.224 | 0.210 | 0.342 | 0.443 | | | | |
| Immunomodulation agent = Exposed | 0.348 | 0.349 | 0.360 | 0.295 | 0.285 | 0.328 | 0.286 | 0.230 | | | |
| ECOG performance status = 2 | 0.405 | 0.406 | 0.420 | 0.418 | 0.361 | | | | | | |
| History of bone lesions = Yes | 0.535 | 0.536 | 0.509 | 0.481 | | | | | | | |
| Renal dysfunction = Yes | 0.199 | 0.197 | 0.210 | 0.220 | 0.179 | 0.093 | 0.089 | 0.094 | 0.109 | 0.069 | 0.024 |
| Race = Asian | 0.532 | 0.533 | 0.539 | | | | | | | | |
| *In: Iteration n* | | | | | | | | | | | |

e. Please also present the central estimates and p-values for the treatment effect covariate and each of the patient characteristics covariates for each of the adjusted parameterised curves for the IA2 OS, PFS and TOT curves, separately for the 2+ prior and the 2 prior.

**Response:** Table 25 to Table 30 present the central estimates and p-values for the treatment effect covariate and each of the patient characteristics covariates for each of the adjusted parameterised curves. The disparity between the means in this question compared with the means in response to B1 arises as these tables reflect the full extrapolation, whereas values in BI are model outputs and reflect the time horizon considered in the model.

**Table 25: Covariate central estimates and significance for OS for the IA2 2+ prior line sub-population**

| Fit | LEN+DEX | | IXA+LEN+DEX | | Treatment | ISS Stage III | Age > 65 years |
|---|---|---|---|---|---|---|---|
| | Median | Mean | Median | Mean | p-value | | |
| Exponential | 44.06 | 63.00 | 66.80 | 92.09 | 0.0559 | 0.0205 | 0.0153 |
| Weibull | 38.06 | 47.71 | 53.86 | 67.41 | 0.0516 | 0.0203 | 0.0154 |
| Gompertz | 37.46 | 40.86 | 50.16 | 52.70 | 0.0501 | 0.0188 | 0.0136 |
| Log normal | 46.09 | 86.00 | 69.31 | 111.49 | 0.0473 | 0.1087 | 0.0087 |
| Log Logistic | 40.79 | 72.79 | 59.02 | 94.97 | 0.0494 | 0.0375 | 0.0106 |
| Generalised Gamma | 41.20 | 64.28 | 60.05 | 88.92 | 0.0529 | 0.0471 | 0.0141 |

**Key:** DEX, dexamethasone; IA, interim analysis; ISS, International Staging System; IXA, ixazomib; LEN, lenalidomide; OS, overall survival

**Table 26: Covariate central estimates and significance for PFS for the IA2 2+ prior line sub-population**

| Fit | LEN+DEX | | IXA+LEN+DEX | | Treatment | Light chain myeloma |
|---|---|---|---|---|---|---|
| | Median | Mean | Median | Mean | p-value | |
| Exponential | 13.95 | 20.13 | 22.14 | 31.94 | 0.0045 | 0.0562 |
| Weibull | 14.12 | 18.52 | 21.65 | 28.39 | 0.0028 | 0.0499 |
| Gompertz | 14.20 | 18.39 | 21.93 | 27.27 | 0.0035 | 0.0532 |
| Log normal | 13.37 | 27.17 | 21.03 | 41.18 | 0.0047 | 0.0062 |
| Log Logistic | 13.26 | 28.26 | 21.05 | 41.96 | 0.0034 | 0.0087 |
| Generalised Gamma | 13.34 | 30.45 | 20.93 | 44.88 | 0.0054 | 0.0059 |

**Key:** DEX, dexamethasone; IA, interim analysis; IXA, ixazomib; LEN, lenalidomide; PFS< progression free survival

**Table 27: Covariate central estimates and significance for TOT for the IA2 2+ prior line sub-population**

| Fit | LEN+DEX | | IXA+LEN+DEX | | Treatment | ISS Stage III | Light chain myeloma |
|---|---|---|---|---|---|---|---|
| | Median | Mean | Median | Mean | p-value | | |
| Exponential | 13.30 | 19.19 | 18.08 | 26.08 | 0.0288 | 0.0040 | 0.0123 |
| Weibull | 13.33 | 19.09 | 18.08 | 25.88 | 0.0291 | 0.0042 | 0.0127 |
| Gompertz | 13.29 | 19.22 | 18.07 | 26.15 | 0.0290 | 0.0041 | 0.0124 |
| Log normal | 12.35 | 31.67 | 17.58 | 42.66 | 0.0411 | 0.0120 | 0.0105 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Log Logistic | 12.61 | 30.95 | 17.62 | 40.59 | 0.0348 | 0.0136 | 0.0068 |
| Generalised Gamma | 13.13 | 19.82 | 17.97 | 27.13 | 0.0303 | 0.0052 | 0.0136 |
| **Key:** DEX, dexamethasone; IA, interim analysis; ISS, International Staging System; IXA, ixazomib; LEN, lenalidomide; ToT, time on treatment | | | | | | | |

**Table 28: Covariate central estimates and significance for OS for the IA2 2 prior line sub-population**

| Fit | LEN+DEX | | IXA+LEN+DEX | | Treatment | ISS Stage III | Age > 65 years | History of bone lesions |
|---|---|---|---|---|---|---|---|---|
| | Median | Mean | Median | Mean | p-value | | | |
| Exponential | 50.14 | 71.20 | 69.52 | 95.26 | 0.0958 | 0.0018 | 0.0042 | 0.0461 |
| Weibull | 42.47 | 53.40 | 56.40 | 70.74 | 0.0834 | 0.0023 | 0.0050 | 0.0496 |
| Gompertz | 40.75 | 43.63 | 51.12 | 53.20 | 0.0834 | 0.0015 | 0.0035 | 0.0451 |
| Log normal | 52.28 | 93.06 | 68.49 | 110.35 | 0.1210 | 0.0097 | 0.0021 | 0.0395 |
| Log Logistic | 45.47 | 78.84 | 60.29 | 96.34 | 0.0991 | 0.0060 | 0.0036 | 0.0576 |
| Generalised Gamma | 47.45 | 75.99 | 62.58 | 94.77 | 0.1063 | 0.0062 | 0.0057 | 0.0480 |
| **Key:** DEX, dexamethasone; IA, interim analysis; ISS, International Staging System; IXA, ixazomib; LEN, lenalidomide; OS, overall survival | | | | | | | | |

**Table 29: Covariate central estimates and significance for PFS for the IA2 2 prior line sub-population**

| Fit | LEN+DEX | | IXA+LEN+DEX | | Treatment | Light chain myeloma |
|---|---|---|---|---|---|---|
| | Median | Mean | Median | Mean | p-value | |
| Exponential | 15.92 | 22.97 | 20.19 | 29.13 | 0.2616 | 0.0268 |
| Weibull | 15.95 | 20.95 | 19.92 | 26.16 | 0.2293 | 0.0229 |
| Gompertz | 16.10 | 20.65 | 20.14 | 25.30 | 0.2437 | 0.0245 |
| Log normal | 15.13 | 31.33 | 19.75 | 39.87 | 0.2165 | 0.0121 |
| Log Logistic | 15.21 | 31.97 | 19.40 | 39.34 | 0.2446 | 0.0084 |
| Generalised Gamma | 15.20 | 28.97 | 19.72 | 37.04 | 0.2204 | 0.0130 |
| **Key:** DEX, dexamethasone; IA, interim analysis; IXA, ixazomib; LEN, lenalidomide; PFS, progression free survival | | | | | | |

**Table 30: Covariate central estimates and significance for TOT for the IA2 2 prior line sub-population**

| Fit | LEN+DEX | | IXA+LEN+DEX | | Treatment | ISS Stage III | Renal dysfunction |
|---|---|---|---|---|---|---|---|
| | Median | Mean | Median | Mean | p-value | | |
| Exponential | 14.96 | 21.59 | 17.19 | 24.80 | 0.3992 | 0.0303 | 0.0218 |
| Weibull | 14.90 | 22.03 | 17.15 | 25.36 | 0.4061 | 0.0327 | 0.0241 |
| Gompertz | 14.96 | 21.58 | 17.19 | 24.79 | 0.3995 | 0.0303 | 0.0222 |
| Log normal | 14.31 | 38.74 | 16.30 | 43.01 | 0.5206 | 0.0151 | 0.0314 |
| Log Logistic | 14.74 | 37.68 | 16.37 | 40.87 | 0.5718 | 0.0344 | 0.0398 |
| Generalised Gamma | 15.03 | 20.99 | 17.37 | 24.24 | 0.3801 | 0.0535 | 0.0280 |

**Key:** DEX, dexamethasone; IA, interim analysis; ISS, International Staging System; IXA, ixazomib; LEN, lenalidomide; ToT, time on treatment

## Section B: Clarification on cost-effectiveness data

B1. Please tabulate the mean durations of the OS, PFS and ToT parameterised curves for the IA1 for the 1 prior and the 2+ prior and for the IA2 for the 1 prior (if available), the 2 prior and the 2+ prior (see table below). Please also provide the medians of the unadjusted KM curves alongside these (5 tables).

**Response:** Table 31 and Table 32 present the mean OS, PFS and ToT for the IA2 data cut for the 2+ prior IXA+LEN+DEX and LEN+DEX arms, respectively. Table 33 and Table 34 present the mean OS, PFS and ToT for the IA2 data cut for the 2-prior IXA+LEN+DEX and LEN+DEX arms, respectively. These estimates were obtained from the updated model sent in response to the ACD. The 1 prior data has not been analysed using the IA2 data as this population is not relevant for the positioning of ixazomib going forward (see our response to the ACD and submission of new evidence/analyses of 19th May 2017). The data associated with the IA1 data are not presented as per the discussion in the overview.

**Table 31: Mean OS, PFS and ToT over a lifetime horizon for each parametric curve in the 2+ prior lines population IA2 data (IXA+LEN+DEX)**

| | OS | | PFS | | ToT | |
|---|---|---|---|---|---|---|
| | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** |
| Exponential | 87.47 | 92.99 | 31.82 | 31.99 | 25.77 | 26.23 |
| Weibull | 65.59 | 68.04 | 28.38 | 28.43 | 25.81 | 26.03 |
| Log normal | 111.39 | 112.16 | 42.23 | 41.25 | 43.56 | 42.90 |
| Log logistic | 94.50 | 95.62 | 42.91 | 42.03 | 41.43 | 40.80 |
| Gompertz | 53.21 | 53.05 | 27.32 | 27.30 | 26.69 | 26.30 |
| Gamma | 106.25 | 89.65 | 41.30 | 44.96 | 26.75 | 27.29 |
| KM median | Not reached | | 22.00 | | 17.74 | |

**Key:** DEX, dexamethasone; IXA, ixazomib; KM, Kaplan-Meier; LEN, lenalidomide; OS, overall survival; PFS, progression free survival; ToT, time on treatment

**Table 32: Mean OS, PFS and ToT over a lifetime horizon for each parametric curve in the 2+ prior lines population IA2 data (LEN+DEX)**

| | OS | | PFS | | ToT | |
|---|---|---|---|---|---|---|
| | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** |
| Exponential | 61.15 | 62.31 | 20.16 | 20.09 | 19.32 | 19.07 |
| Weibull | 47.42 | 47.26 | 18.60 | 18.50 | 19.34 | 18.97 |
| Log normal | 86.79 | 85.39 | 27.86 | 27.11 | 32.45 | 31.47 |
| Log logistic | 73.71 | 72.24 | 29.02 | 28.21 | 31.92 | 30.78 |
| Gompertz | 41.53 | 40.56 | 18.47 | 18.37 | 19.73 | 19.10 |
| Gamma | 47.42 | 63.70 | 27.08 | 30.39 | 19.90 | 19.70 |
| KM median | Not reached | | 12.98 | | 12.66 | |

**Key:** DEX, dexamethasone; IXA, ixazomib; KM, Kaplan-Meier; LEN, lenalidomide; OS, overall survival; PFS, progression free survival; ToT, time on treatment

**Table 33: Mean OS, PFS and ToT over a lifetime horizon for each parametric curve in the 2-prior lines population IA2 data (IXA+LEN+DEX)**

| | OS | | PFS | | ToT | |
|---|---|---|---|---|---|---|
| | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** |
| Exponential | 83.75 | 101.65 | 28.86 | 28.86 | 24.23 | 24.93 |
| Weibull | 64.93 | 75.40 | 26.10 | 25.94 | 25.00 | 25.49 |
| Log normal | 111.11 | 115.35 | 41.01 | 39.48 | 44.45 | 43.31 |
| Log logistic | 94.38 | 100.81 | 40.46 | 38.96 | 41.59 | 41.11 |
| Gompertz | 52.26 | 55.57 | 25.46 | 25.11 | 25.17 | 24.92 |
| Gamma | 96.40 | 99.94 | 36.86 | 36.67 | 23.40 | 24.35 |
| KM median | Not reached | | 15.90 | | 16.82 | |

**Key:** DEX, dexamethasone; IXA, ixazomib; KM, Kaplan-Meier; LEN, lenalidomide; OS, overall survival; PFS, progression free survival; ToT, time on treatment

**Table 34: Mean OS, PFS and ToT over a lifetime horizon for each parametric curve in the 2-prior lines population IA2 data (LEN+DEX)**

| | OS | | PFS | | ToT | |
|---|---|---|---|---|---|---|
| | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** |
| Exponential | 66.97 | 66.75 | 23.05 | 23.16 | 21.93 | 21.49 |
| Weibull | 52.59 | 50.45 | 21.14 | 21.10 | 22.57 | 21.92 |
| Log normal | 96.73 | 89.11 | 32.06 | 31.61 | 40.13 | 38.49 |
| Log logistic | 80.69 | 75.52 | 33.06 | 32.24 | 38.76 | 37.48 |
| Gompertz | 44.58 | 41.84 | 20.93 | 20.79 | 22.66 | 21.48 |
| Gamma | 81.45 | 72.15 | 28.76 | 29.23 | 21.15 | 20.88 |
| KM median | Not reached | | 11.90 | | 13.67 | |

**Key:** DEX, dexamethasone; KM, Kaplan-Meier; LEN, lenalidomide; OS, overall survival; PFS, progression free survival; ToT, time on treatment

B2. Please present the AIC and BIC for the unadjusted OS, PFS and TOT curves of the IA2 analysis separately for the 2 prior subgroup and the 2+ prior subgroup.

**Response:** Table 35, Table 36 and Table 37 present the AIC and BIC for the unadjusted OS, PFS and ToT for the IA2 analysis in the 2+ prior lines population. Table 38, Table 39 and Table 40 present the AIC and BIC for the unadjusted OS, PFS and ToT for the IA2 analysis in the 2-prior lines population.

**Table 35: AIC and BIC Unadjusted curves OS 2+ prior lines IA2 data**

| Model | N | ll(null) | ll(model) | df | AIC | BIC |
|---|---|---|---|---|---|---|
| Exponential | 297 | -413.6863259 | -412.2354881 | 2 | 828.4709761 | 835.8584404 |
| Weibull | 297 | -412.1170569 | -410.5882362 | 3 | 827.1764725 | 838.2576689 |
| Gompertz | 297 | -413.2224561 | -411.7146893 | 3 | 829.4293785 | 840.510575 |
| Lognormal | 297 | -411.2384505 | -409.5423918 | 3 | 825.0847835 | 836.16598 |
| Log logistic | 297 | -411.6246937 | -410.0478906 | 3 | 826.0957812 | 837.1769776 |
| Gamma | 297 | -411.1864381 | -409.522738 | 4 | 827.045476 | 841.8204045 |

**Key:** AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; df, degrees of freedom; N, number; OS, overall survival

**Table 36: AIC and BIC Unadjusted curves PFS 2+ prior lines IA2 data**

| Model | N | ll(null) | ll(model) | df | AIC | BIC |
|---|---|---|---|---|---|---|
| Exponential | 297 | -639.5079224 | -635.5837527 | 2 | 1275.167505 | 1282.55497 |
| Weibull | 297 | -638.2264386 | -633.8757209 | 3 | 1273.751442 | 1284.832638 |
| Gompertz | 297 | -639.3386697 | -635.207383 | 3 | 1276.414766 | 1287.495963 |
| Lognormal | 297 | -634.4455465 | -630.6098833 | 3 | 1267.219767 | 1278.300963 |
| Log logistic | 297 | -636.6533927 | -632.5983508 | 3 | 1271.196702 | 1282.277898 |
| Gamma | 297 | -634.4383267 | -630.6018857 | 4 | 1269.203771 | 1283.9787 |

**Key:** AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; df, degrees of freedom; N, number; PFS, progression free survival

**Table 37: AIC and BIC Unadjusted curves ToT 2+ prior lines IA2 data**

| Model | N | ll(null) | ll(model) | df | AIC | BIC |
|---|---|---|---|---|---|---|
| Exponential | 297 | -1064.605 | -1062.627 | 2 | 2129.253 | 2136.641 |
| Weibull | 297 | -1064.599 | -1062.626 | 3 | 2131.252 | 2142.333 |
| Gompertz | 297 | -1064.567 | -1062.608 | 3 | 2131.216 | 2142.297 |
| Lognormal | 297 | -1070.774 | -1068.903 | 3 | 2143.806 | 2154.887 |
| Log logistic | 297 | -1066.059 | -1064.163 | 3 | 2134.326 | 2145.408 |
| Gamma | 297 | -1064.539 | -1062.561 | 4 | 2133.122 | 2147.897 |

**Key:** AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; df, degrees of freedom; N, number; ToT, time on treatment

**Table 38: AIC and BIC Unadjusted curves OS 2-prior lines IA2 data**

| Model | N | ll(null) | ll(model) | df | AIC | BIC |
|---|---|---|---|---|---|---|
| Exponential | 208 | -287.6662361 | -287.2717193 | 2 | 578.5434385 | 585.2185147 |
| Weibull | 208 | -286.7665997 | -286.3350516 | 3 | 578.6701031 | 588.6827174 |
| Gompertz | 208 | -287.3482553 | -286.9226291 | 3 | 579.8452581 | 589.8578724 |
| Lognormal | 208 | -286.4146397 | -286.0399609 | 3 | 578.0799219 | 588.0925361 |
| Log logistic | 208 | -286.5324839 | -286.0946817 | 3 | 578.1893633 | 588.2019776 |
| Gamma | 208 | -286.3258565 | -285.9314714 | 4 | 579.8629428 | 593.2130951 |

**Key:** AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; df, degrees of freedom; N, number; OS, overall survival

**Table 39: AIC and BIC Unadjusted curves PFS 2-prior lines IA2 data**

| Model | N | ll(null) | ll(model) | df | AIC | BIC |
|---|---|---|---|---|---|---|
| Exponential | 208 | -445.6927044 | -445.0327166 | 2 | 894.0654333 | 900.7405095 |
| Weibull | 208 | -444.7269631 | -443.9831813 | 3 | 893.9663626 | 903.9789768 |
| Gompertz | 208 | -445.5252209 | -444.8218131 | 3 | 895.6436261 | 905.6562404 |
| Lognormal | 208 | -443.3616891 | -442.4419684 | 3 | 890.8839367 | 900.896551 |
| Log logistic | 208 | -443.9553741 | -443.1959393 | 3 | 892.3918786 | 902.4044928 |
| Gamma | 208 | -443.2130367 | -442.3447885 | 4 | 892.689577 | 906.0397293 |

**Key:** AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; df, degrees of freedom; N, number; PFS, progression free survival

**Table 40: AIC and BIC Unadjusted curves ToT 2-prior lines IA2 data**

| Model | N | ll(null) | ll(model) | df | AIC | BIC |
|---|---|---|---|---|---|---|
| Exponential | 208 | -739.7423903 | -739.579245 | 2 | 1483.15849 | 1489.833566 |
| Weibull | 208 | -739.5827813 | -739.4254385 | 3 | 1484.850877 | 1494.863491 |
| Gompertz | 208 | -739.7216692 | -739.5613126 | 3 | 1485.122625 | 1495.135239 |
| Lognormal | 208 | -745.6752931 | -745.5207342 | 3 | 1497.041468 | 1507.054083 |
| Log logistic | 208 | -741.8952109 | -741.8013121 | 3 | 1489.602624 | 1499.615238 |
| Gamma | 208 | -739.4522751 | -739.2814023 | 4 | 1486.562805 | 1499.912957 |

**Key:** AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; df, degrees of freedom; N, number; ToT, time on treatment

B3. Within the economic model please clarify if E21 (CovariateAdj_mainsettings) in Main Settings worksheet only directly determines E46 (Adjusted) in Parameters worksheet, and the Adjusted variable directly determines everything else thereafter? Or does E21 directly determine values in addition to E46 (Adjusted) in the Parameters worksheet?

**Response:** E21 in the Main Settings sheet only directly determines E46 (Adjusted) in the Parameters worksheet and the visual basic macro whereby the adjusted sheets are hidden or unhidden.

B4. The Main Settings worksheet E55 is described as “Total number of week payer is responsible for treatment costs. Please find input on the results sheet”. The ERG cannot identify this element in the Results worksheet and would welcome clarification on this.

**Response:** This has been left in from previous model versions. The input is next to the text in Cells E55:F55.

B5. Please outline the role of the TxEffectSubgrps variable within the model and its direct effects upon other variables in the model. How does this differ from applying the adjusted curves?

**Response:** This has been left in from previous model versions and does not link anywhere in the model.

B6. The values of Table 9 in Appendix 1 are not aligned with those of cells D156:G175 of the TRAEs worksheet of the economic model.

a. Please clarify which is correct.

**Response:** The model is correct (cells D156:G175) – Table 41 provides the updated version of Table 9 in Appendix 1.

**Table 41: Cycle probabilities associated with AEs 2+ prior lines (IA2)**

| Grade 3+ treatment emergent AEs | Average duration of AEs (days) | LEN+DEX | | | IXA+LEN+DEX cycle probability |
|---|---|---|---|---|---|
| | | No of events* | Rate | Cycle Probability | |
| Anaemia | 42.08 | ***49*** | 0.2955 | 0.0056 | 0.0025 |
| Cardiac failure | 11.31 | ***3*** | 0.0181 | 0.0003 | 0.0003 |
| Deep vein thrombosis | 11.40 | ***2*** | 0.0121 | 0.0002 | 0.0001 |
| Diarrhoea | 31.44 | ***2*** | 0.0121 | 0.0002 | 0.0019 |
| Fatigue | 63.33 | ***7*** | 0.0422 | 0.0008 | 0.0008 |
| Upper respiratory tract infection/Pulmonary-related | 15.40 | ***2*** | 0.0121 | 0.0002 | 0.0003 |
| Ischaemic heart disease | 4.20 | ***2*** | 0.0121 | 0.0002 | 0.0000 |
| Nausea | 20.60 | ***0*** | 0.0015 | 0.0000 | 0.0003 |

| Grade 3+ treatment emergent AEs | Average duration of AEs (days) | LEN+DEX | | | IXA+LEN+DEX cycle probability |
|---|---|---|---|---|---|
| | | No of events* | Rate | Cycle Probability | |
| Neutropenia | 15.08 | ***68*** | 0.4101 | 0.0078 | 0.0058 |
| Peripheral neuropathy | 50.00 | ***1*** | 0.0060 | 0.0001 | 0.0001 |
| Pneumonia | 19.59 | ***28*** | 0.1689 | 0.0032 | 0.0018 |
| Pulmonary embolism | 56.53 | ***4*** | 0.0241 | 0.0005 | 0.0005 |
| Rash-related | 26.14 | ***1*** | 0.0060 | 0.0001 | 0.0013 |
| Renal failure | 37.05 | ***10*** | 0.0603 | 0.0012 | 0.0003 |
| Thrombocytopaenia | 21.13 | ***9*** | 0.0543 | 0.0010 | 0.0046 |
| Vomiting | 4.75 | ***2*** | 0.0121 | 0.0002 | 0.0001 |
| New primary malignancy | 40.33 | ***1*** | 0.0060 | 0.0001 | 0.0001 |
| Key: AEs, adverse events; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide | | | | | |

b. Please provide the equivalent data to the TRAEs worksheet cells D130:E149 for the IA2 data cut for the TMM-1 trial as a whole.

**Response:** Table 42 presents the equivalent data to the TRAEs worksheet cells D130:E149 for the IA2 data cut for the TMM-1 trial ITT population.

**Table 42: TRAE for ITT using IA2 data**

| **TOURMALINE TRAE data** | **IXA+LEN+DEX** | **LEN+DEX** |
|---|---|---|
| | **N** | **N** |
| N | 358 | 362 |
| Average treatment exposure in months | 15.03382928 | 14.57474446 |
| Patient-years of exposure | 448.5092402 | 439.6714579 |
| Anaemia | 45 | 70 |
| Cardiac failure | 13 | 10 |
| Deep vein thrombosis | 3 | 3 |

| | | |
|---|---|---|
| Diarrhoea | 31 | 9 |
| Fatigue | 15 | 10 |
| Upper respiratory tract infection/Pulmonary-related | 4 | 4 |
| Ischaemic heart disease | 3 | 3 |
| Nausea | 6 | 0 |
| Neutropenia | 196 | 155 |
| Peripheral neuropathy | 2 | 1 |
| Pneumonia | 46 | 50 |
| Pulmonary embolism | 9 | 9 |
| Rash-related | 21 | 6 |
| Renal failure | 6 | 22 |
| Thrombocytopaenia | 86 | 25 |
| Vomiting | 4 | 2 |
| New primary malignancy | 1 | 1 |
| **Key:** DEX, dexamethasone; ITT, intention to treat; IXA, ixazomib; LEN, lenalidomide; N, number; TRAE, treatment related adverse events | | |

c. The average duration of AEs appears to be draw from the previous model and is not arm specific. Please outline the reasons for this.

**Response:** The average duration of AEs presented in the model was obtained from the original IA1 analysis. This was not updated in line with the rest of the model due to time restrictions and prioritisation of inputs that were considered to have a direct impact on results. Table 43 presents the average duration of AEs for the ITT population using IA2 data.

**Table 43: Average duration of TRAEs in the ITT population using IA2 data**

| | Mean days | Standard deviation |
|---|---|---|
| Anaemia | 50.25 | 99.16 |
| Cardiac failure | 10.53 | 10.58 |
| Deep vein thrombosis | 37.33 | 66.25 |
| Diarrhoea | 42.37 | 72.91 |
| Fatigue | 80.58 | 80.31 |
| Upper respiratory tract infection/Pulmonary-related | 12.50 | 8.73 |
| Ischemic heart disease | 3.83 | 2.93 |
| Nausea | 19.60 | 23.03 |
| Neutropenia | 14.08 | 18.94 |
| Peripheral neuropathy | 52.50 | 44.55 |
| Pneumonia | 16.52 | 21.76 |
| Pulmonary embolism | 58.28 | 68.64 |
| Rash-related | 26.64 | 26.31 |
| Renal failure | 31.68 | 51.83 |
| Thrombocytopenia | 25.25 | 38.48 |
| Vomiting | 3.75 | 4.92 |
| New primary malignancy flag | 30.00 | NA |
| **Key:** IA, interim analysis; ITT, intention to treat; NA, not available; TRAE, treatment related adverse events | | |

B7. **PRIORITY QUESTION:** In discontinuation data in Table 16 of Appendix 1, the distributions of the total patient numbers for each category in terms of progression status appear to fall into one of three categories:

- Progression measured before end of data cut
- Progression free measured at end of data cut
- Progression status not available at end of data cut

a. Please confirm if this interpretation for the progression column is correct.

**Response:** This interpretation is correct

b. Please fill in the patient numbers for the other columns for the IA2 data cut.

**Response:** Please note the following assumptions when compiling the table:

- Patients are marked as progressed if there was an assessment for progression for the patient within the period date of randomisation to date of data cut off.
- If patient was not progressed, patients marked as progression free if there was an assessment for pre-progression (i.e. vGPR, CR, PR, SD) for the patient within the period date of randomisation to date of data cut off
- If patient was neither progressed or progression free, patient's progression status marked as not available.

**Table 44: Events and censors for the 2+ prior line sub-population (IA2 data cut) stratified by reason for discontinuation, progression status at IA2 cut off point and treatment arm**

| | Prog. | AE | Withdr. | S. Term. | Pr. Viol. | Other | Censor |
|---|---|---|---|---|---|---|---|
| IA2 LEN+DEX (Total) | N = 57 | N = 30 | N = 13 | N = 1 | N = 1 | N = 1 | N = 46 |
| 1. Prog measured before IA2 | N=57 | N=4 | N=1 | N=0 | N=0 | N=0 | N=4 |
| 2. Measured prog free at IA2 | N=0 | N=20 | N=8 | N=1 | N=0 | N=1 | N=42 |
| 3. Prog status at IA2 n.a. | N=0 | N=6 | N=4 | N=0 | N=1 | N=0 | N=0 |
| IA2 IXA+LEN+DEX (Total) | N = 46 | N = 24 | N = 14 | N = 1 | N = 0 | N = 3 | N = 60 |
| 1. Prog measured before IA2 | N=46 | N=3 | N=0 | N=0 | .. | N=0 | N=1 |
| 2. Measured prog free at IA2 | N=0 | N=19 | N=9 | N=1 | .. | N=3 | N=59 |
| 3. Prog status at IA2 n.a. | N=0 | N=2 | N=5 | N=0 | .. | N=0 | N=0 |
| Prog: Progression; AE: Adverse Event; Withdr: Withdrawal from Study; S Term: Sponsor Termination; Pr Viol: Protocol Violation; IA2: Interim Analysis 2 | | | | | | | |

c. Please confirm if patients in the third category of progression status not available at end of data cut were treated as censored in the construction of the PFS Kaplan Meier curves.

**Response:** Patients whose progression status was not available at the end of the data cut were treated as censors within the PFS endpoint unless the patient had died prior to the end of the data cut.

d. Please also outline which if any of the patient numbers involve LOCF and to what degree and why LOCF is necessary for these patients. This may be submitted after the main clarification response.

**Response:** Please refer to response B7b for information on how the patient numbers are compiled and as such there is an element of LOCF in the majority of patients. Due to the nature of the analysis, this information will be submitted in due course (expected to be submitted to NICE by end of July).

B8. **PRIORITY QUESTION:** Please outline which events in Table 16 of Appendix 1 are treated as discontinuation events and which are treated as censoring events within the DOT curves of the model.

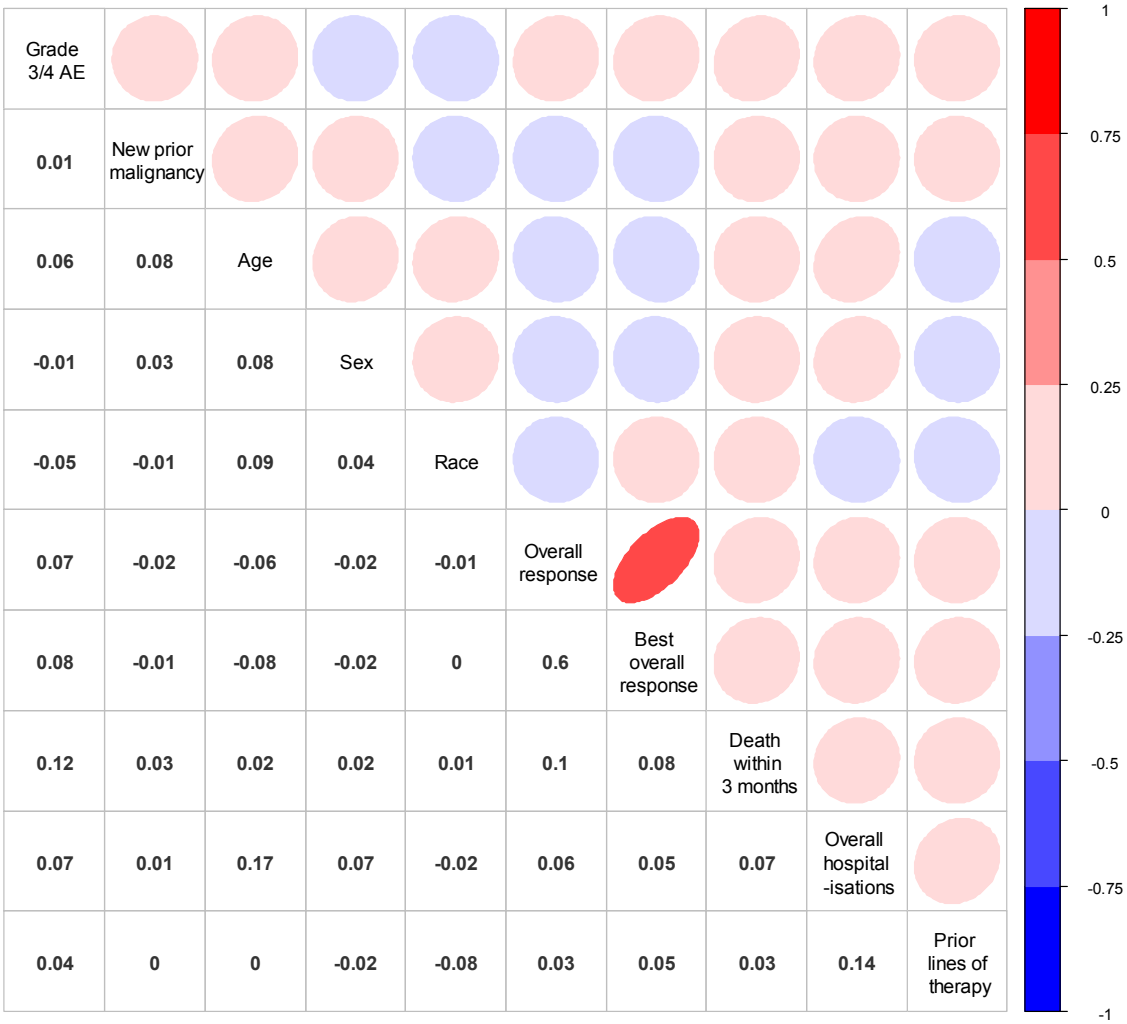
**Response:** In the duration of therapy (DOT) endpoint, all events are treated as a discontinuation event regardless of whether they were classified as discontinuation or a censor within the time on treatment (TOT) endpoint.

B9. **PRIORITY QUESTION:** Referring Appendix 1 Section 2.1.3.1

a. Please present the correlation data alluded to in this section, including that for variables that were considered as candidates but not included in the final model.

**Response:** Correlation was explored between the predictors which had been selected for inclusion within the utility regression model. Substantial correlation was observed only between best overall response assessment and overall response assessment (captured at the time of the EQ-5D measurement), and it is believed that the latter may be a better measure of assessment as this may vary over a patient's follow-up time and is recorded at the same time as the EQ-5D measurement, hence best overall response assessment was not included in the final statistical model. All other covariates were taken through to inclusion in the statistical model. One variable (new prior malignancies [0 vs. 1+]) was dropped during the stepwise selection process. A correlation plot is presented in Figure 21 which shows little correlation between any of the pairwise comparisons except best and overall response assessments (according to Pearson's product moment correlation coefficient values).

**Figure 21: Correlation plot**




**Key:** AE, adverse event.
**Notes:** Correlation is shown between all potential predictors; circles represent little or no correlation; ellipses represent stronger correlation. Red represents positive correlation; blue represents negative correlation. Figures represent Pearson's Product Moment Correlation Coefficients.

b. The text suggests that the list of covariates that were included, as listed in Table 11, was decided a priori rather than through statistical tests. Please confirm whether this was the case, and justify this. What reasons did the clinicians give for not exploring line of therapy as a covariate?

**Response:** The covariates included in the statistical model were identical to those included in the original utility regression model (as reported in the manufacturer's submission). Initial variable selection was based upon clinical expert opinion regarding prognostic factors believed to impact quality of life (QoL). The variables were pre-specified for the original utility analysis based on the requirements for the economic analysis plan. Utilities were required for the different health states in the model (by response; by progression status and for end-of-life) and for events in the model (e.g. experience of adverse events). The final model retained only those variables which resulted in statistically significantly different utilities.

Statistical exploration of correlation was performed on the selected list of predictors to ensure that multicollinearity was not a significant problem. As part of the ACD, the ERG had suggested inclusion of additional covariates such as age, prior lines of therapy in the statistical model; as such, age was explored in the updated utility regression model as part of the ACD response. Prior lines of therapy have also been included as part of this response and results are presented within the answer to question B11, but was not found to improve statistical model fit.

c. Please present the results of each of the forwards and backwards stepwise selection approach and the statistical tests which resulted in the final model.

**Response:** A model fitted to the data including the variable - prior lines of therapy – is reported as part of the response to B11 (Priority Questions). Inclusion of this predictor worsened the model goodness-of-fit - the Akaike Information Criterion (AIC) increased and so this variable would not be taken forward to the final statistical model during the stepwise selection process. AIC results for each of the models fitted during the stepwise selection algorithm are presented in Table 45. The stepwise selection algorithm (performed using statistical software, R) was applied to the saturated model (i.e. inclusion of all predictors as shown in Table 45) and the procedure dropped and added variables independently in each iteration (dependent on statistical significance and improved model fit according to the AIC). This process resulted in the model with the final list of predictors (top row of Table 45). Whilst age was not considered to improve model fit, inclusion of this variable yielded the 2nd best fitting model and the difference in AIC values is negligible. Hence, combined with the fact that this may also be a clinically relevant variable, age was kept in the statistical model.

**Table 45: Model goodness-of-fit**

| Grade 3/4 AE | Gender | Race | Hospitalisations | Death within 3 months | Overall response assessment | Age | New prior malignancy | Prior lines of therapy* | AIC |
|---|---|---|---|---|---|---|---|---|---|
| ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | **-7372.5** |
| ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | **-7371.3** |
| ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | -7370.7 |
| ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | -7370.5 |
| ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | -7369.5 |
| ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | -7369.3 |
| ✓ | ✓ | | ✓ | ✓ | ✓ | | | | -7369.1 |
| ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | -7367.5 |
| ✓ | | ✓ | ✓ | ✓ | ✓ | | | | -7365.2 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ✓ | ✓ | ✓ | | ✓ | ✓ | | | | -7347.3 |
| | ✓ | ✓ | ✓ | ✓ | ✓ | | | | -7346.3 |
| ✓ | ✓ | ✓ | ✓ | ✓ | | | | | -7334.5 |
| ✓ | ✓ | ✓ | ✓ | | ✓ | | | | -7331.3 |
| **Key:** AE, adverse event; AIC, Akaike Information Criterion; * included in statistical model as part of the clarification responses. | | | | | | | | | |

d. What was the time window for hospitalisations? Is the definition of hospitalisations the same as that for the hospitalisation patient count data of the Hospitalisation worksheet of the model?

**Response:** The variable 'total number of hospitalisations' was a measure of the overall number of hospitalisations per patient (i.e. not time-dependent). A hospitalisation is defined as at least one overnight stay in a general ward unit, ICU, palliative care unit, and/or hospice. The variable was then dichotomised into at least one vs no hospitalisations. There was no time window applicable as the variable was not measured around the time of the EQ-5D record. In the economic model, an admission was defined where the length of stay was at least one overnight stay. In addition, hospitalisations which overlapped (i.e. on the same date) and shared the same type of hospitalisation, were merged and considered as one hospitalisation.

e. What is the reference age for the age coefficient?

**Response:** No reference category for age is applicable in the statistical regression model, as age is included as a continuous predictor. The coefficient for age indicates how much the utility score is expected to decrease when age increases by one unit (i.e. one year) (interpretation is consistent with that from linear regression modelling adjusting for a continuous covariate).

f. What was the number of EQ-5D responses in the IA2 analysis:
   - With PD
   - With both PD and within 3 months of death
   - With hospitalisation
   - With both hospitalisation and within 3 months of death

**Response:** A total of 651 unique patients were included in the regression model (after excluding patients and records with missing covariate data). The number of records/patients for each of the scenarios is as follows:

- With PD – 1110 records (382 patients)
- With both PD and within 3 months of death – 57 records (44 patients)
- With hospitalisation – 3676 records (286 patients)
- With both hospitalisation and within 3 months of death – 86 records (47 patients)

B10. **PRIORITY QUESTION:** It is difficult to read across between the original and the revised EQ-5D analyses. Please present the equivalent of Table 12 in Appendix 1 for the IA1 data cut. This may be submitted after the main clarification response

**Response:** As stated in the Section 1 (Overview), all new analyses submitted post-ACD relates to use of the more mature dataset (IA2) and this has superseded the analyses using the less mature datacut (IA1). Given this, we are not clear of the rationale for the requests for an updated utility regression analysis on the IA1 datacut. We believe the analyses based on the IA2 datacut should be considered as completely separate to the earlier analyses based on IA1, and so reference to analysis based on IA1 is of low relevance for consideration of the new evidence.

B11. **PRIORITY QUESTION** Is the revised EQ-5D analysis based on IA2 all patient data or IA2 2+ prior patient data? If it is based upon all patient data, what effect does including the number of previous treatments as a covariate (1 prior and 2+ prior with 1 prior as the reference) have upon the estimates in Table 12 of Appendix 1 and what is the p-value for this covariate? What effect upon the estimates does removing:

- age as a covariate have?
- death within 3 months as a covariate have?
- sex and race as covariates have?

**Response:** The revised EQ-5D analysis based on IA2 data submitted in the ACD response was based on all patients. Results when including the number of prior therapies in the statistical model are presented in Table 46.

**Table 46: Statistical regression output including the number of prior lines of therapy**

| Parameter | Coefficient | Standard Error | 95% Lower Confidence Limit | 95% Upper Confidence Limit | Abs(t-value) | p-value |
|---|---|---|---|---|---|---|
| Intercept | 0.808 | 0.067 | 0.677 | 0.939 | 12.11 | <0.001* |
| Grade 3/4 AE (ref=0) ≥1 | -0.031 | 0.006 | -0.043 | -0.020 | 5.30 | <0.001* |
| Age (years) | <0.001 | <0.001 | -0.003 | 0.001 | 0.88 | 0.378 |
| Gender (ref=female) Male | 0.055 | 0.018 | 0.020 | 0.090 | 3.07 | 0.002* |
| Race (ref=non-white) White | -0.059 | 0.026 | -0.111 | -0.007 | 2.24 | 0.026* |
| Total number of hospitalisations (ref=0) ≥1 | -0.091 | 0.018 | -0.127 | -0.054 | 4.92 | <0.001* |
| Death within 3 months (ref=No) Yes | -0.106 | 0.016 | -0.137 | -0.074 | 6.58 | <0.001* |
| Overall response assessment (ref=VGPR+) | 0.001 | 0.005 | -0.008 | 0.011 | 0.27 | <0.001* (0.784) |

| | | | | | | |
|---|---|---|---|---|---|---|
| PR<br>SD<br>PD | -0.011<br>-0.038 | 0.008<br>0.007 | -0.026<br>-0.051 | 0.005<br>-0.025 | 1.37<br>5.74 | (0.169)<br>(<0.001) |
| **Prior lines of therapy (ref=1)**<br>**2+** | **-0.003** | **0.018** | **-0.038** | **0.033** | **0.14** | **0.891** |
| Key: Abs, absolute; AE, adverse event; PD, progressive disease; PR, partial response; ref, reference; SD, stable disease; SE, standard error; VGPR+, very good partial response; * statistically significant at 5% level.<br>Notes: VGPR+ includes CR, PR, sCR and VGPR. | | | | | | |

The variable representing prior lines of therapy is not statistically significant (i.e. there is insufficient evidence to suggested QoL improves/worsens between patients who have received 1 prior therapy vs. those receiving 2+ prior therapies). In addition, this variable was not taken forward to the final model when implementing the stepwise algorithm.

Model output is for each of the scenarios is presented below (Table 47) as follows:

- Model 1: Results from IA2 data cut (as presented in Table 12 Appendix 1 of the ACD response document)
- Model 2: Removal of age as a covariate
- Model 3: Removal of death within 3 months as a covariate
- Model 4: Removal of sex and race

**Table 47: Statistical model output from proposed scenarios**

| | Model 1 | | | Model 2 | | | Model 3 | | | Model 4 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Coef** | **SE** | **p-val** | **Coef** | **SE** | **p-val** | **Coef** | **SE** | **p-val** | **Coef** | **SE** | **p-val** |
| **Intercept** | 0.806 | 0.066 | <0.001* | 0.754 | 0.027 | <0.001* | 0.809 | 0.067 | <0.001* | 0.794 | 0.064 | <0.001* |
| **Grade 3/4 AE (ref=0)** ≥1 | -0.031 | 0.006 | <0.001* | -0.031 | 0.006 | <0.001* | -0.034 | 0.006 | <0.001* | -0.031 | 0.006 | <0.001* |
| **Age (years)** | -0.001 | 0.001 | 0.379 | Excluded | | | <-0.001 | <0.001 | 0.380 | -0.001 | <0.001 | 0.308 |
| **Gender (ref=female)** Male | 0.055 | 0.018 | 0.002* | 0.055 | 0.018 | 0.002* | 0.053 | 0.018 | 0.003* | Excluded | | |
| **Race (ref=non-white)** White | -0.059 | 0.026 | 0.026* | -0.061 | 0.026 | 0.020* | -0.061 | 0.027 | 0.021* | Excluded | | |
| **Total number of hospitalisations (ref=0)** ≥1 | -0.091 | 0.018 | <0.001* | -0.094 | 0.018 | <0.001* | -0.094 | 0.018 | <0.001* | -0.087 | 0.018 | <0.001* |
| **Death within 3 months (ref=No)** Yes | -0.106 | 0.016 | <0.001* | -0.106 | 0.016 | <0.001* | Excluded | | | -0.105 | 0.016 | <0.001* |
| **Overall response assessment (ref=VGPR+)** PR | 0.001 | 0.005 | <0.001* (0.784) | 0.001 | 0.005 | <0.001* (0.778) | 0.002 | 0.005 | <0.001* (0.741) | 0.001 | 0.005 | <0.001* (0.780) |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SD | -0.011 | 0.008 | (0.169) | -0.011 | 0.008 | (0.175) | -0.012 | 0.008 | (0.138) | -0.011 | 0.008 | (0.169) |
| PD | -0.038 | 0.007 | (<0.001*) | -0.038 | 0.007 | (<0.001*) | -0.042 | 0.007 | (<0.001*) | -0.038 | 0.007 | (<0.001*) |

**Key:** AE, adverse event; coef, coefficient; SE, standard error; PD, progressive disease; PR, partial response; ref, reference; SD, stable disease; VGPR, very good partial response; * statistically significant at 5% level.

B12. **PRIORITY QUESTION:** What was the mean baseline EQ-5D value in the TMM-1 trial among all patients and among the subgroups (1 prior, 2+ prior and 2 prior)?

**Response:** Of the 651 patients included in the statistical regression model, 612 had a SCREENING visit – the mean utility values are as follows:

- All patients: 0.663 (n=612)
- 2+ prior: 0.640 (n=250)
- 2 prior: 0.664 (n=171)

The 1 prior data has not been analysed using the IA2 data as this population is not relevant for the positioning of ixazomib going forward (see our response to the ACD and submission of new evidence/analyses of 19th May 2017).

B13. Please present the arithmetic underlying the calculation of VGPR+ 0.689, PR 0.690, SD 0.678 and PD 0.650 quality of life values on page 31 of Appendix 1, documenting the inputs to this. This may be presented within an excel spreadsheet. Please outline how these relate to the values in Table 12 of Appendix 1.

**Response:** Coefficients from regression model output (Table 12 in Appendix 1 of the ACD response) are used to estimate the expected utility value for each overall response assessment category and is based on the mean values of each predictor:

- Age: 65.3
- Proportion of at least one grade 3/4 adverse event: 0.11
- Proportion male patients: 0.57
- Proportion white patients: 0.89
- Proportion within 3 months of death: 0.01
- Proportion at least one hospitalisations: 0.39

Combining these values with the regression model output results in the mean utility values as presented in Table 12 (Appendix 1) of the ACD response.

B14. The number of hospice admissions in cell D54 of the Hospitalisations worksheet is not aligned with those of cells D13, D24, D35 and D46 of the Hospitalisations worksheet. Please account for this. The average length of Hospice stay differs somewhat from the original company submission. Please account for this.

**Response:** D54 corresponds to the number of hospice admissions across the ITT population. Whereas D13, D24, D35 and D46 correspond with the number of events in the 2+ prior lines population. The ITT population was used to obtain a more robust average of length of stay as, for example with the length of stay associated with hospice admissions, there were a small number of patients providing these data within the 2+ prior and 2 prior subgroups.

The original model used data from the IA1 data cut. The updated model uses data from the IA2 data cut. In validating the average length of hospice stay it came to our attention that the code was double counting a small number of hospitalisations.

Table **48** presents the number and length of stay of hospitalisations for acute care, palliative care, intensive care unit and hospice admissions for the ITT population using IA2 data.

**Table 48: Hospitalisations across both IXA+LEN+DEX and LEN+DEX using IA2 data**

| Type | Events | Length of stay in days | Standard deviation |
|---|---|---|---|
| Acute | 475 | 3697 | 9.64 |
| Palliative | 73 | 833 | 16.01 |
| ICU | 31 | 626 | 25.68 |
| Hospice | 24 | 137 | 4.56 |
| Key: ICU, intensive care unit | | | |

Table 49 presents the correct numbers for D10:E13 within the model on the 'Hospitalisations' sheet.

**Table 49: Hospitalisations associated with LEN+DEX in the pre-progression health state**

| | 2+ Prior Lines Number of events | 2 Prior Lines Number of events |
|---|---|---|
| Acute care unit admission | 89 | 68 |
| Palliative care unit admission | 11 | 9 |
| ICU admissions | 4 | 3 |
| Hospice admission | 5 | 5 |
| Key: DEX, dexamethasone; ICU, intensive care unit; LEN, lenalidomide | | |

Table 50 presents the correct numbers for D21:E21 within the model on the 'Hospitalisations' sheet.

**Table 50: Hospitalisations associated with IXA+LEN+DEX in the pre-progression health state**

| | 2+ Prior Lines Number of events | 2 Prior Lines Number of events |
|---|---|---|
| Acute care unit admission | 96 | 62 |
| Palliative care unit admission | 7 | 1 |
| ICU admissions | 1 | 1 |
| Hospice admission | 0 | 0 |
| Key: DEX, dexamethasone; ICU, intensive care unit; IXA, ixazomib; LEN, lenalidomide | | |

Table 51 presents the correct numbers for D32:E35 within the model on the 'Hospitalisations' sheet.

**Table 51: Hospitalisations associated with LEN+DEX in the post-progression health state**

| | 2+ Prior Lines Number of events | 2 Prior Lines Number of events |
|---|---|---|
| Acute care unit admission | 38 | 28 |
| Palliative care unit admission | 12 | 3 |
| ICU admissions | 3 | 2 |
| Hospice admission | 1 | 0 |
| Key: DEX, dexamethasone; ICU, intensive care unit; LEN, lenalidomide | | |

Table 52 presents the correct numbers for D43:E46 within the model on the 'Hospitalisations' sheet.

**Table 52: Hospitalisations associated with IXA+LEN+DEX in the post-progression health state**

| | 2+ Prior Lines Number of events | 2 Prior Lines Number of events |
|---|---|---|
| Acute care unit admission | 20 | 12 |
| Palliative care unit admission | 11 | 7 |
| ICU admissions | 3 | 0 |
| Hospice admission | 0 | 0 |
| Key: DEX, dexamethasone; ICU, intensive care unit; IXA, ixazomib; LEN, lenalidomide | | |

B15. **PRIORITY QUESTION:** Please provide the data in cells D8:E22 of the PostProgression worksheet split by arm. Please augment this with the arm and subgroup specific values (4 values) for patient years of follow-up post-progression.

**Response:** Table 53 presents the number of patients receiving each subsequent therapy by arm and by subgroup using the IA2 data.

**Table 53: Subsequent therapy data by arm and by subgroup using IA2 data**

| | 2+ prior lines | | | 2 prior | | |
|---|---|---|---|---|---|---|
| | All patients | LEN+DEX | IXA+LEN+DEX | All patients | LEN+DEX | IXA+LEN+DEX |
| Sample size | 297 | 149 | 148 | 208 | 111 | 97 |
| Number of patients progressing at 2nd interim analysis | 151 | 83 | 68 | 105 | 58 | 47 |
| Number of patients receiving at least 1 subsequent therapy | 99 | 53 | 46 | 75 | 37 | 38 |
| Therapy | | | | | | |
| Bendamustine + Prednisolone | 11 | 5 | 6 | 9 | 5 | 4 |
| Cyclophosphamide | 41 | 23 | 18 | 31 | 16 | 15 |
| Doxorubicin | 9 | 5 | 4 | 7 | 3 | 4 |
| Bortezomib | 53 | 26 | 27 | 43 | 21 | 22 |
| Carfilzomib | 6 | 3 | 3 | 3 | 1 | 2 |
| Lenalidomide | 21 | 9 | 12 | 17 | 7 | 10 |
| Melphalan | 18 | 9 | 9 | 12 | 2 | 10 |
| Pomalidomide | 20 | 13 | 7 | 15 | 12 | 3 |
| Thalidomide | 12 | 6 | 6 | 10 | 4 | 6 |
| Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide | | | | | | |

**Section C: Textual clarifications and additional points**

C1. Please clarify whether the values in Table 8 of Appendix are restricted to the periods when on IXA+LEN+DEX or LEN+DEX treatment, or include AEs after discontinuation of IXA+LEN+DEX or LEN+DEX treatment.

**Response:** The AEs within this table are TRAEs and are included if the start date of the AE occurring for a patient falls between (and including) the date treatment started and the date treatment ended.

C2. Please provide a copy of the CSR for the IA2 data cut; i.e. the equivalent of reference 42 of the original submission for the 2nd interim analysis.

**Response:** Please find attached to this response document the CSR for IA2, entitiled CSR IA2

C3. If available, please provide the report underlying the summary of the EQ-5D analysis of Appendix 1 section 2.1.3.1.

**Response:** No separate report is available as the updated utility regression analyses were conducted as part of the new evidence submission and hence the write up was performed directly as part of the appendix of new evidence/analyses submitted with the ACD response on 19th May 2017.

# 3. References


1. Cancer Research UK. Myeloma survival statistics http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/survival#ref-12017 [
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3. Sonneveld P, Avet-Loiseau H, Lonial S, Usmani S, Siegel D, Anderson KC, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood. 2016;127(24):2955-62.
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5. Bird JM, Owen RG, D'Sa S, Snowden JA, Pratt G, Ashcroft J, et al. Guidelines for the diagnosis and management of multiple myeloma 2011. Br J Haematol. 2011;154(1):32-75.
6. Pratt G, Jenner M, Owen R, Snowden JA, Ashcroft J, Yong K, et al. Updates to the guidelines for the diagnosis and management of multiple myeloma. Br J Haematol. 2014;167(1):131-3.
7. Kumar SK, Callander NS, Alsina M, Atanackovic D, Biermann JS, Chandler JC, et al. Multiple Myeloma, Version 3.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017;15(2):230-69.
8. National Institute for Health and Care Excellence. Myeloma: diagnosis and management https://www.nice.org.uk/guidance/ng35/chapter/Recommendations#laboratory-investigations2016 [

# Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma [ID807] - Response to 2nd set of clarification questions on Takeda's ACD response

**Submitted by Takeda UK Ltd.**

**Single Technology Appraisal (STA)**
**National Institute of Health and Care Excellence (NICE)**

Submitted 28th June 2017

# Table of Contents

# List of Tables

# List of Abbreviations

| | |
|---|---|
| ACD | Appraisal consultation document |
| AE | Adverse event |
| DEX | Dexamethasone |
| ERG | Evidence Review Group |
| IXA | Ixazomib |
| KM | Kaplan-Meier |
| LEN | Lenalidomide |
| NICE | National Institute for Health and Care Excellence |
| OS | Overall survival |
| PD | Progressive disease |
| PFS | Progression-free survival |
| PR | Partial response |
| SD | Stable disease |
| STA | Single technology appraisal |
| ToT | Time on treatment |
| VGPR | Very good partial response |

# 1. Overview

This document contains Takeda's response to the follow-up clarification questions from the evidence review group (ERG) and NICE that were sent to Takeda on Monday 19th June.

# 2. Response to clarification questions

Please find below responses by Takeda to each of the questions raised by the ERG, Warwick Evidence, and the technical team at NICE.

> **B1:** The 1-prior group and the IA1 remain relevant to this question in order to assess whether the company position is that adjusting for covariates increases or decreases the gains from ixazomib when the trial is split by each of the stratifications at randomisation and by each of the data cuts. "Please tabulate the mean durations of the OS, PFS and ToT parameterised curves for the IA1 for the 1 prior and the 2+ prior" in the table format requested (adjusted and unadjusted).

**Response:** In response to question B1, the mean overall survival (OS), progression free survival (PFS) and time on treatment (ToT) are presented assuming the same distribution across all outcomes. This is specified for interpretation of results as the distribution applied to the OS outcome impacts both the mean PFS and the mean ToT over the lifetime horizon. Therefore, for the first row of each table, results are presented assuming an exponential distribution for OS, PFS and ToT. To maintain consistency with this approach, the results presented in the original clarification response are summarised below with any changes highlighted in bold. As shown, this assumption impacts mainly the ToT estimates and changes these estimates only slightly.

Table 1 and Table 2 present the mean OS, PFS and ToT for the IA2 data cut for the 2+ prior IXA+LEN+DEX and LEN+DEX arms, respectively. Table 3 and Table 4 present the mean OS, PFS and ToT for the IA2 data cut for the 2-prior IXA+LEN+DEX and LEN+DEX arms, respectively. These estimates were obtained from the updated model sent in response to the Appraisal Consultation Document (ACD).

**Table 1: Mean OS, PFS and ToT over a lifetime horizon for each parametric curve in the 2+ prior lines population IA2 data (IXA+LEN+DEX)**

| | OS | | PFS | | ToT | |
|---|---|---|---|---|---|---|
| | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** |
| Exponential | 87.47 | 92.99 | 31.82 | 31.99 | 25.77 | 26.23 |
| Weibull | 65.59 | 68.04 | 28.38 | 28.43 | 25.81 | 26.03 |
| Log normal | 111.39 | 112.16 | 42.23 | 41.25 | 43.56 | 42.90 |
| Log logistic | 94.50 | 95.62 | 42.91 | 42.03 | 41.43 | 40.80 |
| Gompertz | 53.21 | 53.05 | 27.32 | 27.30 | **26.49** | **26.19** |
| Gamma | 106.25 | 89.65 | 41.30 | 44.96 | 26.75 | 27.29 |
| KM median | Not reached | | 22.00 | | 17.74 | |

**Key:** DEX, dexamethasone; IXA, ixazomib; KM, Kaplan-Meier; LEN, lenalidomide; OS, overall survival; PFS, progression free survival; ToT, time on treatment

**Table 2: Mean OS, PFS and ToT over a lifetime horizon for each parametric curve in the 2+ prior lines population IA2 data (LEN+DEX)**

| | OS | | PFS | | ToT | |
|---|---|---|---|---|---|---|
| | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** |
| Exponential | 61.15 | 62.31 | 20.16 | 20.09 | 19.32 | 19.07 |
| Weibull | 47.42 | 47.26 | 18.60 | 18.50 | 19.34 | 18.97 |
| Log normal | 86.79 | 85.39 | 27.86 | 27.11 | 32.45 | 31.47 |
| Log logistic | 73.71 | 72.24 | 29.02 | 28.21 | 31.92 | 30.78 |
| Gompertz | 41.53 | 40.56 | 18.47 | 18.37 | 19.69 | **19.08** |
| Gamma | **81.67** | 63.70 | 27.08 | 30.39 | 19.90 | 19.70 |
| KM median | Not reached | | 12.98 | | 12.66 | |

**Key:** DEX, dexamethasone; IXA, ixazomib; KM, Kaplan-Meier; LEN, lenalidomide; OS, overall survival; PFS, progression free survival; ToT, time on treatment

**Table 3: Mean OS, PFS and ToT over a lifetime horizon for each parametric curve in the 2-prior lines population IA2 data (IXA+LEN+DEX)**

| | OS | | PFS | | ToT | |
|---|---|---|---|---|---|---|
| | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** |
| Exponential | 83.75 | 101.65 | 28.86 | 28.86 | 24.23 | 24.93 |
| Weibull | 64.93 | 75.40 | 26.10 | 25.94 | 25.00 | 25.49 |
| Log normal | 111.11 | 115.35 | 41.01 | 39.48 | 44.45 | 43.31 |
| Log logistic | 94.38 | 100.81 | 40.46 | 38.96 | 41.59 | 41.11 |
| Gompertz | 52.26 | 55.57 | 25.46 | 25.11 | **25.02** | **24.86** |
| Gamma | 96.40 | 99.94 | 36.86 | 36.67 | 23.40 | 24.35 |
| KM median | Not reached | | 15.90 | | 16.82 | |

**Key:** DEX, dexamethasone; IXA, ixazomib; KM, Kaplan-Meier; LEN, lenalidomide; OS, overall survival; PFS, progression free survival; ToT, time on treatment

**Table 4: Mean OS, PFS and ToT over a lifetime horizon for each parametric curve in the 2-prior lines population IA2 data (LEN+DEX)**

| | OS | | PFS | | ToT | |
|---|---|---|---|---|---|---|
| | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** |
| Exponential | 66.97 | 66.75 | 23.05 | 23.16 | 21.93 | 21.49 |
| Weibull | 52.59 | 50.45 | 21.14 | 21.10 | 22.57 | 21.92 |
| Log normal | 96.73 | 89.11 | 32.06 | 31.61 | 40.13 | 38.49 |
| Log logistic | 80.69 | 75.52 | 33.06 | 32.24 | 38.76 | 37.48 |
| Gompertz | 44.58 | 41.84 | 20.93 | 20.79 | **22.54** | **21.41** |
| Gamma | 81.45 | 72.15 | 28.76 | 29.23 | 21.15 | 20.88 |
| KM median | Not reached | | 11.90 | | 13.67 | |

**Key:** DEX, dexamethasone; KM, Kaplan-Meier; LEN, lenalidomide; OS, overall survival; PFS, progression free survival; ToT, time on treatment

Table 5 and Table 6 present the mean OS, PFS and ToT for the IA1 data cut for the 2+ prior IXA+LEN+DEX and LEN+DEX arms, respectively.

Table **7** and Table 8 present this information for the 1 prior line population using the IA1 data cut. The 2 prior lines population was not analysed using IA1 data and, as such, these data are not available within the original nor the current version of the model.

**Table 5: Mean OS, PFS and ToT over a lifetime horizon for each parametric curve in the 2+ prior lines population IA1 data (IXA+LEN+DEX)**

| | OS | | PFS | | ToT | |
|---|---|---|---|---|---|---|
| | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** |
| Exponential | 95.84 | 102.56 | 32.83 | 33.24 | 27.60 | 27.89 |
| Weibull | 60.60 | 64.06 | 26.06 | 26.17 | 29.08 | 28.98 |
| Log normal | 117.46 | 118.17 | 42.39 | 41.21 | 57.32 | 56.38 |
| Log logistic | 91.92 | 94.48 | 41.15 | 40.28 | 50.76 | 49.92 |
| Gompertz | 42.35 | 43.48 | 24.10 | 24.00 | 29.68 | 29.51 |
| Gamma | 113.01 | 106.95 | 43.95 | 47.75 | 35.34 | 33.86 |
| KM median | Not reached | | Not reached | | 18.20 | |

**Key:** DEX, dexamethasone; IXA, ixazomib; KM, Kaplan-Meier; LEN, lenalidomide; OS, overall survival; PFS, progression free survival; ToT, time on treatment

**Table 6: Mean OS, PFS and ToT over a lifetime horizon for each parametric curve in the 2+ prior lines population IA1 data (LEN+DEX)**

| | OS | | PFS | | ToT | |
|---|---|---|---|---|---|---|
| | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** |
| Exponential | 62.57 | 65.73 | 19.06 | 19.13 | 20.20 | 13.98 |
| Weibull | 41.76 | 43.19 | 16.30 | 16.27 | 21.05 | 21.15 |
| Log normal | 90.85 | 90.20 | 27.25 | 26.48 | 42.97 | 42.24 |
| Log logistic | 69.79 | 70.39 | 27.15 | 26.53 | 38.72 | 37.91 |
| Gompertz | 33.09 | 33.69 | 15.98 | 15.89 | 21.90 | 21.84 |
| Gamma | 86.28 | 78.64 | 28.54 | 32.19 | 25.09 | 24.24 |
| KM median | Not reached | | 12.91 | | 12.91 | |

**Key:** DEX, dexamethasone; KM, Kaplan-Meier; LEN, lenalidomide; OS, overall survival; PFS, progression free survival; ToT, time on treatment

**Table 7: Mean OS, PFS and ToT over a lifetime horizon for each parametric curve in the 1 prior line population IA1 data (IXA+LEN+DEX)**

| | OS | | PFS | | ToT | |
|---|---|---|---|---|---|---|
| | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** |
| Exponential | 90.71 | 97.16 | 28.05 | 28.52 | 24.16 | 24.68 |
| Weibull | 61.08 | 65.20 | 22.69 | 22.59 | 21.11 | 21.43 |
| Log normal | 123.74 | 122.41 | 38.51 | 37.05 | 39.32 | 39.18 |
| Log logistic | 94.57 | 95.74 | 36.64 | 35.26 | 34.94 | 34.68 |
| Gompertz | 43.58 | 45.86 | 20.77 | 20.44 | 18.87 | 19.09 |
| Gamma | 115.04 | 109.70 | 33.28 | 26.02 | 20.81 | 21.11 |
| KM median | Not reached | | 20.62 | | 17.26 | |

**Key:** DEX, dexamethasone; IXA, ixazomib; KM, Kaplan-Meier; LEN, lenalidomide; OS, overall survival; PFS, progression free survival; ToT, time on treatment

**Table 8: Mean OS, PFS and ToT over a lifetime horizon for each parametric curve in the 1 prior line population IA1 data (LEN+DEX)**

| | OS | | PFS | | ToT | |
|---|---|---|---|---|---|---|
| | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** | **Unadjusted** | **Adjusted** |
| Exponential | 107.98 | 113.35 | 25.35 | 25.81 | 25.13 | 25.24 |
| Weibull | 72.19 | 75.68 | 20.77 | 20.66 | 21.77 | 21.73 |
| Log normal | 140.23 | 139.76 | 36.96 | 36.12 | 44.82 | 44.86 |
| Log logistic | 106.73 | 107.40 | 34.82 | 33.98 | 37.79 | 37.37 |
| Gompertz | 48.45 | 50.38 | 19.25 | 18.96 | 19.31 | 19.25 |
| Gamma | 131.36 | 126.10 | 31.55 | 24.40 | 21.38 | 21.29 |
| KM median | Not reached | | 16.57 | | 17.05 | |

**Key:** DEX, dexamethasone; KM, Kaplan-Meier; LEN, lenalidomide; OS, overall survival; PFS, progression free survival; ToT, time on treatment

**B10:** The request is due to the difficulty in reading across from the original analysis and the current analysis. Values have changed by a reasonable amount. A response to this question will enable an informal assessment of the extent to which the changes are due to the move from the IA1 to the IA2 data cut and the extent to which the changes are due to the revised functional form.

**Response:** The updated utility regression model results based on the IA1 data cut are presented in Table 9. Similar trends are observed for both the IA1 and IA2 data. The model fitted was identical to that fitted to the IA2 data (as presented in Table 12 in Appendix 1 of the ACD response document).

**Table 9: Utility coefficients for parameters obtained using the EQ-5D from the TOURMALINE-MM1 trial (IA1)**

| Parameter | Coefficient | Standard Error | 95% Lower Confidence Limit | 95% Upper Confidence Limit | Abs(t-value) | p-value |
|---|---|---|---|---|---|---|
| Intercept | 0.810 | 0.066 | 0.681 | 0.939 | 12.332 | <0.001* |
| Grade 3/4 AE (ref=0) | | | | | 3.935 | |
| ≥1 | -0.029 | 0.007 | -0.044 | -0.015 | | <0.001* |
| Age (years) | -0.001 | 0.001 | -0.003 | 0.001 | 1.002 | 0.317 |
| Gender (ref=female) | | | | | | |
| Male | 0.061 | 0.018 | 0.026 | 0.096 | 3.394 | <0.001* |
| Race (ref=non-white) | | | | | | |
| White | -0.051 | 0.026 | -0.102 | <0.001 | 1.979 | 0.048* |
| Total number of hospitalisations (ref=0) | | | | | | |
| ≥1 | -0.091 | 0.019 | -0.128 | -0.055 | 4.915 | <0.001* |
| Death within 3 months (ref=No) | | | | | | |
| Yes | -0.130 | 0.021 | -0.171 | -0.089 | 6.146 | <0.001* |
| Overall response assessment (ref=VGPR+) | | | | | | <0.001* |
| PR | -0.007 | 0.006 | -0.019 | 0.005 | 1.180 | (0.238) |
| SD | -0.028 | 0.009 | -0.046 | -0.010 | 3.093 | (<0.002) |
| PD | -0.046 | 0.009 | -0.063 | -0.029 | 5.302 | (<0.001) |

Key: Abs, absolute; AE, adverse event; PD, progressive disease; PR, partial response; ref, reference; SD, stable disease; SE, standard error; VGPR+, very good partial response; * statistically significant at 5% level.

Notes: VGPR+ includes CR, PR, sCR and VGPR.

The ERG would also be grateful for some further clarification around the response to questions B7 and B15:

1. The B7 response states that “Patients are marked as progressed if there was an assessment for progression for the patient within the period date of randomisation to date of data cut-off “. Please clarify if it would be more accurate for this to state “Patients are marked as progressed if there was an assessment for progression for the patient within the period date of randomisation to date of data cut-off at which the patient was assessed as having progressed “.

**Response:** This revised statement is correct.

2. The B7 response also states that “If patient was not progressed, patients marked as progression free if there was an assessment for pre-progression (i.e. very good partial response (VGPR), complete response (CR), partial response (PR), stable disease (SD)) for the patient within the period of randomisation to date of data cut-off” Is this essentially saying that each of the following applied to these patients?

    - They were measured as VGPR, CR, PR, SD at some point prior to the data cut-off, and
    - the time point when VGPR, CR, PR, SD was measured could be at any date prior to the data cut-off, and
    - they did not have any subsequent measure of progression at which the patient was assessed as having progressed prior to the data cut-off

**Response:** This is correct, patients would be categorised as pre-progression if they have had one or more pre-progression assessments in the period (date of randomisation to date of cut off) without any post-progression assessments in that same period.

3. Within the PFS Kaplan-Meier curve would these patients be treated as progression free up to the data cut-off and then censored at the data cut off?

**Response**: This is correct for cases where patients do not die prior to the data cut off. Patients who die will receive a PFS event at the time of death.

4. The B7 response also states that “If patient was neither progressed or progression free, patients progression status marked as not available”. Is this patient group essentially those without any measurement of VGPR, CR, PR, SD or progression within the period of randomisation to date of data cut-off or is this patient group wider than this?

**Response** This is correct (those without any measurement of VGPR, CR, PR, SD or progression within the period of randomisation to date of data cut-off).

5. B15: Table 53 answers the first part of B15 but not the second part “Please augment this with the arm and subgroup specific values (4 values) for patient years of follow-up post-progression.” Please supply the 4 values requested.

**Response:** This table has been modified (see Table 10 of this response) to incorporate patient years of follow-up post-progression. The values requested mirror that as outlined for hospitalisations in the model**.**

**Table 10: Subsequent therapy data by arm and by subgroup using IA2 data**

| | 2+ prior lines | | | 2 prior | | |
|---|---|---|---|---|---|---|
| | **All patients** | **LEN+DEX** | **IXA+LEN+DEX** | **All patients** | **LEN+DEX** | **IXA+LEN+DEX** |
| Sample size | 297 | 149 | 148 | 208 | 111 | 97 |
| Number of patients progressing at 2nd interim analysis | 151 | 83 | 68 | 105 | 58 | 47 |
| Patient years of follow-up post-progression | 106.72 | 62.34 | 44.38 | 77.57 | 43.78 | 33.79 |
| Number of patients receiving at least 1 subsequent therapy | 99 | 53 | 46 | 75 | 37 | 38 |
| Therapy | | | | | | |
| Bendamustine + Prednisolone | 11 | 5 | 6 | 9 | 5 | 4 |
| Cyclophosphamide | 41 | 23 | 18 | 31 | 16 | 15 |
| Doxorubicin | 9 | 5 | 4 | 7 | 3 | 4 |
| Bortezomib | 53 | 26 | 27 | 43 | 21 | 22 |
| Carfilzomib | 6 | 3 | 3 | 3 | 1 | 2 |
| Lenalidomide | 21 | 9 | 12 | 17 | 7 | 10 |
| Melphalan | 18 | 9 | 9 | 12 | 2 | 10 |
| Pomalidomide | 20 | 13 | 7 | 15 | 12 | 3 |
| Thalidomide | 12 | 6 | 6 | 10 | 4 | 6 |

Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide

**Title:** Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed refractory multiple myeloma – **Addendum following the new analyses submitted by the Company**

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**Declared competing interests of the authors**

The authors have no conflicts of interest.

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**Rider on responsibility for report**

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

**This report should be referenced as follows:** Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed refractory multiple myeloma: A Single Technology Appraisal. Warwick Evidence, 2017.

**Contributions of authors:** Xavier Armoiry (Senior Research Fellow) conducted the critique of clinical effectiveness evidence and co-ordinated the project; Ewen Cummins (Health Economist) conducted, reviewed and critiqued the cost-effectiveness evidence; Martin Connock (Senior Research Fellow) conducted the critique of clinical effectiveness evidence and undertook additional analyses and Aileen Clarke (Professor of Public Health and Health Services Research) co-ordinated the project and provided comments on the report.

**Word count:** 28453.

**Please note that:** Sections redacted in black are ‘academic in confidence’ (AIC) or ‘commercial in confidence’ (CIC).

**TABLE OF CONTENT**

## *LIST OF ABBREVIATIONS*

| | |
|---|---|
| ASCO | American Society of Clinical Oncology |
| BORD | Bortezomib + Dexamethasone |
| BORT | Bortezomib |
| BSC | Best Supportive Care |
| CARF | Carfilzomib |
| CEAF | Cost-effectiveness Acceptability Frontier |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence Interval |
| CR | Complete Response |
| CS | Company Submission |
| CYCLO | Cyclophosphamide |
| DEX | Dexamethasone |
| DoR | Duration of response |
| ECOG | Eastern Cooperative Oncology Group |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| EQ-5D | EuroQol – 5 Dimensions |
| ERG | Evidence Review Group |
| FAD | Final Appraisal Determination |

| | |
|---|---|
| FDA | U.S.Food and Drug Administration |
| HR | Hazard Ratio |
| HRQoL | Health Related Quality of Life |
| ICER | Incremental Cost-Effectiveness Ratio |
| IV | Intravenous |
| IXA | Ixazomib |
| IXAL | Ixazomib + Lenalidomide + Dexamethasone |
| KM | Kaplan Meier |
| LEN | Lenalidomide |
| LEND | Lenalidomide + Dexamethasone |
| LYG | Life Years Gained |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NMA | Network Meta-Analysis |
| OR | Odds Ratio |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| PANO | Panobinostat |
| PFS | Progression-Free Survival |
| POM | Pomalidomide |
| PPS | Post-Progression Survival |

| | |
|---|---|
| PR | Partial Response |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PSS | Personal Social Services |
| QALY | Quality Adjusted Life Years |
| QoL | Quality of Life |
| RCT | Randomised Controlled Trial |
| RoB | Risk of Bias |
| RR | Response rates |
| RRMM | Relapsed Refractory Multiple Myeloma |
| SD | Standard Deviation |
| SPC | Summary of Product Characteristics |
| TMM-1 | Tourmaline MM1 trial (pivotal trial) |
| TTNT | Time to next treatment |
| TTP | Time To Progression |
| UK | United Kingdom |
| VGPR | Very Good Partial Response |

## *LIST OF FIGURES*

*LIST OF TABLES*

# 1 CLINICAL EFFECTIVENESS

## 1.1 Classification of the Tourmaline MM-1 participants according to the number of prior therapies

The second submission centres on the 2+ prior therapies population (that is IXA LEN DEX as a third or fourth line intervention). Two procedures were used to classify patients according to the number of prior therapies. Trial investigators determined prior status according to whether patients had received one prior or "two or three priors", and this was used to stratify patients into two subgroups at randomisation. In addition, the number of lines of prior therapy was determined by "blinded Sponsor medical review" of prior therapy data. This generated three subgroups: 1 prior, 2 prior, and 3 prior. The two classifications did not match, thereby introducing uncertainty into the actual population modelled. Potential reasons for numerical discrepancies between classifications were not discussed. The submission uses the investigator classification in cost effectiveness analysis and argues that this has the benefit of retaining randomised stratification and is more likely to reflect a "real world". However the ERG note that a potential dis-benefit is misclassification of the number of prior therapies and thereby the exact characteristics of the population of interest; also the ERG is not convinced that the trial investigator's classification would necessarily better reflect real world UK practice.

In response to the ERG's clarification requests after the first and second submissions Takeda provided response data based on IA2 results and the Blinded Sponsor medical review classification. There were some inconsistencies between the two clarification responses; the ERG is uncertain as to how these arose. The clarification data supplied are summarised in Table 1.

**Table 1- Patient numbers for response based on IA2 and medical review classification of priors**

| SUB GROUP | RESPONSE | IXA LEN DEX | | LEN DEX | |
|---|---|---|---|---|---|
| | | CR 1 | CR 2 | CR 1 | CR 2 |
| 2 PRIOR | ORR | 77 | 76 | 78 | 77 |
| 2 PRIOR | VGPR+ | 49 | 50 | 42 | 46 |
| 2 PRIOR | CR | 16 | 18 | 6 | 9 |
| | *PR* | *51* | *53* | *72* | *68* |
| 3 PRIOR | ORR | 32 | 33 | 21 | 21 |
| 3 PRIOR | VGPR+ | 20 | 20 | 7 | 8 |
| 3 PRIOR | CR | 4 | 4 | 1 | 1 |
| | *PR* | *28* | *29* | *20* | *20* |
| 2 or 3 prior | VGPR+ | *69* | *70* | *49* | *54* |
| *2 or 3 prior* | *PR* | *79* | *82* | *92* | *88* |

CR 1 = response to the clarification request after the first submission. CR 2 = response to the clarification request after the second submission. ORR= overall response rate; VGPR+ = very good partial response or better; CR = complete response; PR = partial response calculated assuming PR = ORR – CR. Numbers for the " 2 or 3" prior group are derived by addition of 2 prior + 3 prior.

The number of patients in the prior therapy subgroups as defined by the two classification systems is summarised in Table 1. Relative to the "blinded medical review" the investigator classification generates fewer 1 prior patients (425 versus 441) and more 2 or 3 prior LEN DEX patients (149 versus 136). The impact of these relatively modest numerical discrepancies will depend on the response rates in the various subgroups and on any differences in the distribution of patient covariates used in adjustment of modelled survival curves. Thus these discrepancies in classification introduce additional uncertainty into the appropriateness of covariate values used for survival curve adjustment.

Table 2 summarises the number of patients and percentage achieving a VGPR+ response according to prior subgroup and method of classification; the estimates for the Blinded Review classification are based on data supplied in Takeda's second clarification response.

**Table 2 Patient numbers for VGPR+ based on IA2 and medical review classification of priors**

| | Investigator classification | | "Blinded Sponsor medical review" classification | |
|---|---|---|---|---|
| | IXA LEN DEX | LEN DEX | IXA LEN DEX | LEN DEX |
| All | 360 [185] 51.4% | 362 [159] 43.9% | 360 [185] 51.4% | 362 [159] 43.9% |
| 1 prior | 212 [105] 49.4% | 213 [105] 49.4% | 224 [115] | 217 [104] |
| 2 or 3 prior | 148 [80] 54% | 149 [54] 36.2% | 136 [70] 51.5% | 145 [54] 37.2% |
| 2 prior | NR | NR | 97 [50] 51.5% | 111 [46] 41.4% |
| 3 prior | NR | NR | 39 [20] 51.3% | 34 [8] 23.5% |
| Square brackets enclose the numbers of patients experiencing a VGPR+ response. The percentages refer to the percentage achieving VGPR in that subgroup | | | | |

The investigator classification for the "2 or 3 prior" population moderately favours IXA LEN DEX versus LEN DEX as far as VGPR+ response rates are concerned (i.e. a 17.8% advantage versus a 14.3% advantage) as opposed to the medical review classification. If the first clarification response data for the Medical Review classification are used instead of the second clarification response data the advantage of selecting the investigator classification will be greater.

In summary the ERG conclude that there is uncertainty about which patients in Tourmaline should be classified as members of a 2+ prior population, and as a corollary which covariates would be appropriate for adjustment of survival curves.

## 1.2 Comparison of ixazomib with panobinostat regimen in people after 3 prior therapies

In the final scope, Panobinostat with Bortezomib and Dexamethasone was noted as a relevant comparator of Ixazomib for people who have had at least 2 therapies.

In the submission, the company claimed that Panobinostat in combination with Bortezomib and Dexametasone is recommended as third line treatment, but not often used in clinical practice, and concluded that Panobinostat is not a relevant comparator for third line treatment.

In the original report, the ERG considered that the exclusion of Panobinostat-Bortezomib-Dexamethasone was not entirely justified and that this regimen should be included.

In the appraisal consultation document (ACD), the position of Panobinostat in the treatment pathway was discussed and the committee concluded that Panobinostat is mainly used only after three previous therapies. The Committee concluded that it would have preferred to see a comparison of Ixazomib with Panobinostat for people who have had three previous therapies, in addition to the comparison with lenalidomide. Following the consultation, the Company indicated to NICE that, they intended to include an exploratory analysis of Ixazomib + Lenalidomide + dexamethasone versus the panobinostat regimen in patients who had received three previous therapies. They said that the analysis would include evaluation of the impact on the ICER and if it could be done, might need to use proxy 2+ prior therapy data due to limitations in the availability of specific three prior therapy data for the comparator panobinostat.
In their response to the ACD submitted on 19th May 2017, the Company did not provide any analysis using Panobinostat at third or fourth line. Indeed, they disagreed with the Committee that Panobinostat could be a relevant comparator since they suggested that a Lenalidomide based regimen would be used earlier than a Panobinostat regimen.

While the ERG agrees that Lenalidomide would be generally used earlier that the Panobinostat regimen, there may be situations in clinical practice where these two regimens could be used in people who have had three previous therapies. Therefore, the ERG considers that an exploratory analyses with a Panobinostat regimen as a relevant comparator should have been undertaken in people with three prior therapies.

The ERG agree with the Company there is no specific data on the outcomes of a Panobinostat regimen in the specific three prior therapy group. This means that an exploratory analysis with panobinostat would need to use proxy 2+ prior therapies.

Although the Company has not presented any exploratory analysis using Panobinostat as a relevant comparator in the ACD response, the ERG has noted that these clinical outcomes were in fact presented by the Company in their original submission. Indeed while the Company considered Panobinostat not to be a relevant comparator in the 2+ prior therapies within the original submission, they presented the NMA results in this subgroup as part of their response to the ERG's clarification questions.

As illustrated in the network plot presented on Figure 1, the comparison between IXA-LEN-DEX and PANO-BORT-DEX was made using the IXA-LEN-DEX vs. LEN-DEX comparison from the TMM-1 RCT[1] and the LEN-DEX vs PANO-BORT-DEX comparison.

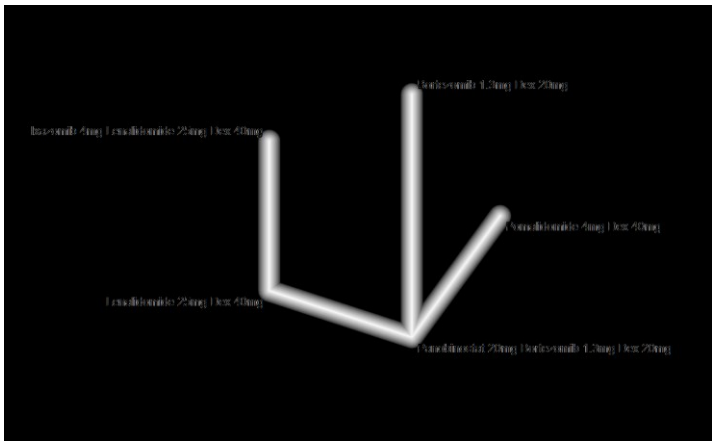


**Figure 1- Network Plot: Overall Survival: 2+ Prior Therapies: SMC Data utilised RCT only: Dose Specific: Primary Publications Data (company submission, clarification questions)**

Although there is no RCT for LEN-DEX vs. PANO-BORT-DEX, the Company identified a study that compared these two regimen using a matching adjusted indirect treatment comparison of survival outcomes using patient-level data. [2] The ERG has verified that this study only used data from patients with 2-3 prior lines of treatment.

On a methodological standpoint, as we emphasized in our initial report, this NMA suffers from the same limitations as that submitted for people with at least one prior therapy, owing to the inclusion of non-RCT data.

The results of the Company's NMA for PFS, and OS in the 2+prior therapies group are presented in Table 3.

**Table 3- NMA results in the 2+ prior therapy group**

| Outcome | Ixazomib+len+dex vs. len+dex<br>Hazard Ratio (95% CrI) | Ixazomib+len+dex vs. Pano-bort+dex<br>Hazard Ratio (95% CrI) | Source |
|---|---|---|---|
| PFS | 0.59 (0.4, 0.84) | 0.62 (0.38, 0.96) | Takeda's clarification response, word document named "A11a NICE OS 2+Prior All studies (all RCTs) Primary Dose Specific SMC included (not ref 33)", Page 3 of 7A11a NICE PFS 2+ Prior All studies (all RCTs) Primary Dose Specific, Page 3 of 8 |
| OS | 0.64 (0.35, 1.09) | 0.76 (0.38, 1.37) | Takeda's clarification response, word document named "A11a NICE OS 2+Prior All studies (all RCTs) Primary Dose Specific SMC included (not ref 33)", Page 3 of 7 |

These exploratory results suggest a very slightly reduced effectiveness for IXA-LEN-DEX relative to PANO-BORT-DEX compared to that of IXA-LEN-DEX relative to LEN-DEX on the risk of progression or death (HR for progression or death of 0.62 vs. 0.59 respectively).

Regarding the risk of death, the reduction of effectiveness is even more marked (HR for death of 0.76 vs 0.64 respectively), the benefit from IXA-LEN-DEX is not statistically different when compared to that from PANO-BORT-DEX.

Given the time constraints, the ERG has not explored the impact of these results on the ICER further. However, owing to the reduced clinical effectiveness, one can assume that the ICER of IXA-LEN-DEX relative to PANO-BORT-DEX is likely to be much higher compared to that of IXA-LEN-DEX relative to LEN-DEX.

## 1.3 Relevance of the analysis in the two prior therapies group

The Company provided a scenario analysis in the 2 prior therapies only sub-group. It was undertaken following a comment within the ACD which suggested that the Committee

had expressed a preference for a scenario analysis in this subgroup after adjustment for different baseline characteristics.

In the original ERG report, we emphasized that the Company undertook a cost-effectiveness analysis in the 2+ prior therapies group (third or fourth line) although the Company would position IXA-LEN-DEX mainly as third line therapy.

We also pointed out that the greater benefit of ixazomib in the 2+ prior therapies population seemed largely driven by an increased benefit of ixazomib in heavily pre-treated patients (fourth line) and less by the group of people with 2 prior therapies (third line).

This is the reason why we proposed an exploratory analysis to evaluate the cost-effectiveness of ixazomib in the 2 prior therapies subgroup (third line only).

During the Appraisal committee meeting, the Company indicated that they did not agree with this analysis on the grounds that the presumed greater clinical effectiveness of IXA-LEN-DEX at fourth line compared to third line was actually due to imbalance in key prognostic factors between the unstratified third and fourth line subgroups. This was emphasized on pages 16-17 of the new CS.

The ERG agree that, based on this additional information provided in Table 2, there are severe imbalances within the two subgroups regarding prognostic factors (e.g. age, high cytogenetic risk, ISS stage III), which are likely to substantially contribute to the differences observed between the 2 prior- and 3 prior- therapies subgroups in the HRs for IXA-LEN-DEX vs LEN-DEX.

The ERG regrets that the Company did not provide this information on the imbalance in the distribution of prognostic factors at clarifications response stage of the process.

Had we been aware earlier of this information, we would not have emphasized the point of the presumed difference in clinical benefit between these two subgroups and we would

not have presented an exploratory analysis of the cost-effectiveness in the 2-prior therapies group.

In the Appraisal committee meeting, a point was raised by one of the clinical experts who indicated that although the main positioning of ixazomib would be third line (consistent with the current positioning of LEN-DEX), a significant proportion of patients within the NHS do not receive LEN-DEX before fourth line (after 3 prior therapies). This is because they may be treated in earlier stages by drugs under investigation. Therefore, should ixazomib be recommended within the NHS, one might expect this drug to be used in combination with LEN-DEX if LEN-DEX was offered as a fourth line treatment.

Lastly, the ERG notes that within the TMM-1 trial, randomisation was stratified per number of prior lines, differentiating 1 vs 2-3 prior line of therapies, this explains why, as shown in Table 3 of the new CS, there was no imbalance of key prognostic factors in the stratified 2-3 subgroup.

In summary, the ERG believes that the exploratory analysis presented by the Company in the 2 prior therapies-only subgroup is of limited relevance. Additionally, we will indicate in the cost-effectiveness section that the corresponding results are not plausible.

## 1.4 Use of clinical trial data in modelling PFS and OS

Takeda developed covariate-adjusted parametric models to generate OS and PFS extrapolations beyond the IA2 observed results for the investigator defined 2+ prior therapies population. The ERG makes the following commentary regarding these procedures.

*Covariate adjustment of models*

1] Since it is uncertain whether the investigator-defined 2+ population accurately represents the 2- and 3- prior treated patients in Tourmaline (as indicated in the preceding section), it is uncertain whether the covariate adjustments were appropriate or necessary.

*Progression free survival*

1] There was a lack of clarity between the submitted text and the economic model; it appears that PFS was extrapolated with adjusted accelerated failure time (AFT) generalised gamma (GG) models, while OS extrapolations (which varied in the text and in the model (in text treatment effect = 0.69, in model treatment effect = 0.67159)) used adjusted proportional hazards (PH) Weibull models. This appears to represent an inconsistency in approach. For PFS, the company could have developed a proportional hazards generalised gamma model (e.g. as described by Crowther and Lambert[3]) thereby aligning the method of extrapolation with that for OS. For reasons explained below, the ERG considers that for PFS in the IXA LEN DEX arm, the GG models (whether AFT or PH, adjusted or unadjusted) generate implausible extrapolations.

2] From approximately 10 to 15 years on, Takeda's adjusted GG AFT models for PFS in the IXA LEN DEX arm generate superior survival relative to their adjusted PH Weibull model for OS. Thus the model appears to predict more patients alive un-progressed than total patients alive. It appears that either or both of the PFS and OS models are therefore implausible. This implausibility applies whether PH or AFT gamma models (adjusted or unadjusted) are used to model the IXA LEN DEX arm and is likely to be due to the GG model imposing a continuously decreasing hazard for progression during the extrapolation phase.

Takeda have employed a simple solution to this problem by making the PFS curve identical to that of the OS curve from the point of crossover onward. In the ERG's opinion, this is not a reasonable procedure, since it demands that after crossover all patients who progress die at the same time as they progress (zero post-progression survival). In addition, patients who progress a short time before crossover will also experience very short post progression survival.

3] The company PFS KM data for the IXA LEN DEX arm in the 2+ prior therapies population is superior to that for the 1 prior population (both IA2). This can be seen by comparing Figure 29 from the clarification response 1 and figure 5 from Appendix 1 of the new submission as shown in **Figure 2**.

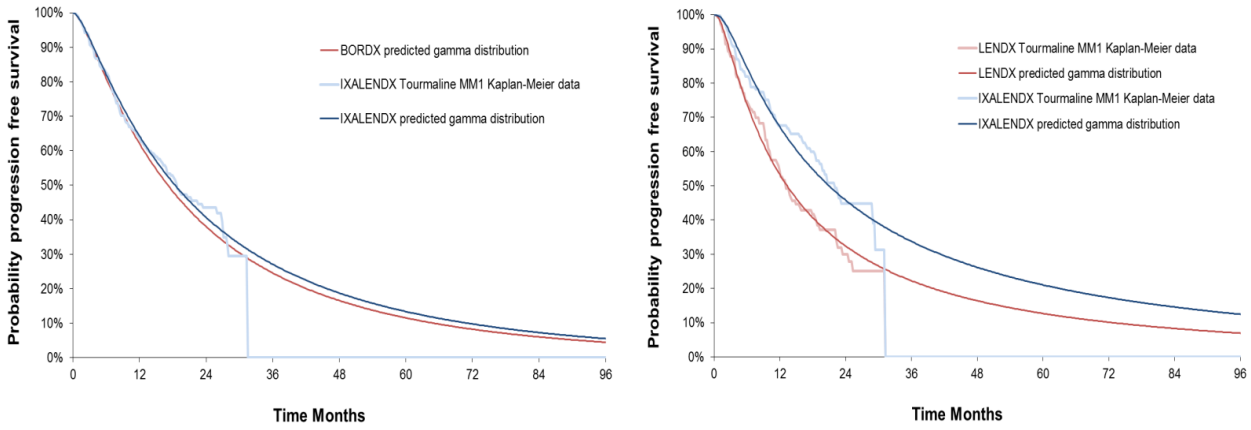



**Figure 2- Comparison of KM plots for PFS 1 prior (left) and 2+ prior (right) therapies populations**.

Note that the upper (blue) lines represent the generalised gamma models for the IXA LEN DEX arms.

The ERG consider it likely that the better performance for the 2+ prior therapies population is clinically implausible. The difference is reflected in the GG models proposed by the company

4] Information criteria (AIC BIC, Table 2 Appendix 1 of the new submission) do not provide a good guide for selection of an appropriate parametric model for PFS in the IXA LEN DEX arm. The company's lognormal, loglogistic and generalised gamma model curves produce implausibly superior survival to OS in extrapolation (see 2 above). Additionally the selected GG model has a poor fit to the observed KM curve from about 13 months onward. The ERG consider that Takeda's Weibull PFS model produces a better fit to the data and a more plausible extrapolation (i.e. one that does not become superior to the OS model). The better fit of the Weibull model to the observed data from

13 months onwards is illustrated in **Figure 3** by plotting cumulative hazard of models versus observed cumulative hazard.

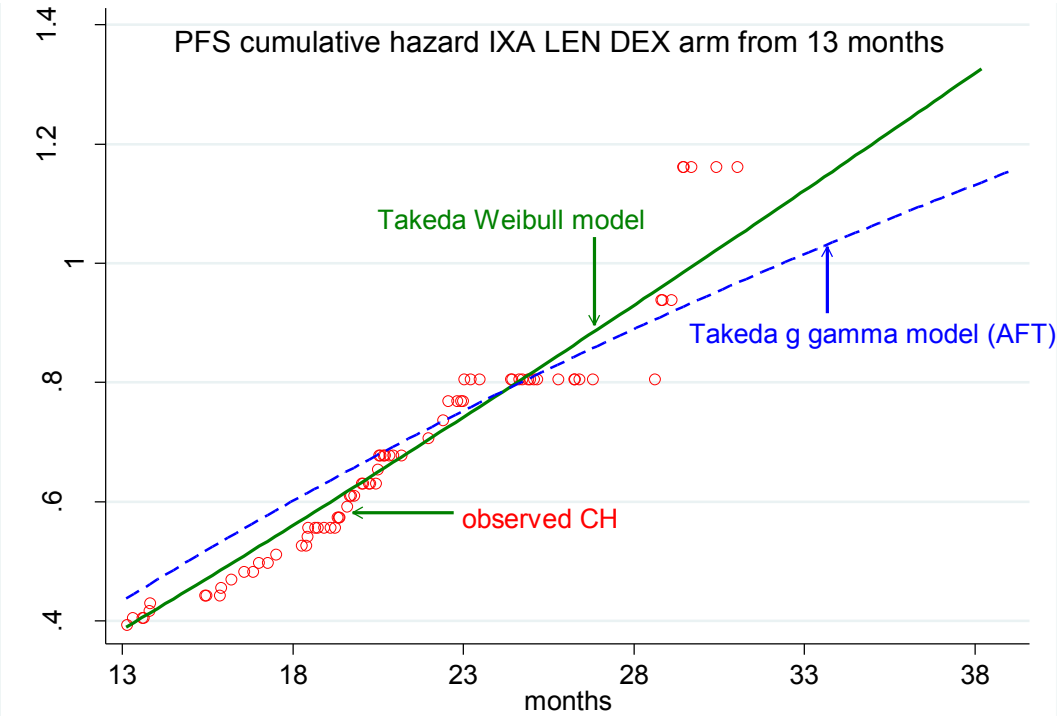



**Figure 3- IXA LEN DEX PFS. The cumulative hazards (CH) for the Takeda GG and Weibull models are compared to the observed cumulative hazard in the IXA LEN DEX arm.**

*Note: in extrapolation the GG model predicts continuously decreasing hazard, whereas the Weibull model predicts a nearly constant hazard.*

*Overall survival*

1] Takeda extrapolated OS beyond the observed data using Weibull models adjusted for covariates. The ERG concurs with the company's choice of Weibull models. The IXA LEN DEX OS curve was obtained by applying a treatment effect to the LEN DEX curve. The ERG's understanding is that this treatment effect was estimated using the Cox's proportional hazards procedure. The ERG notes that the resulting IXA LEN DEX model has a relatively poor fit to the observed data (Figure 10 in Appendix 1 of new submission). **Figure 4** compares the observed cumulative hazard and the Takeda models of CH. For most of the time span the IXA LEN DEX modelled CH appears less than the

observed CH, implying that relative to the observed data the model may over estimate OS. This potential overestimate is extrapolated over a further 22 years (see next point).

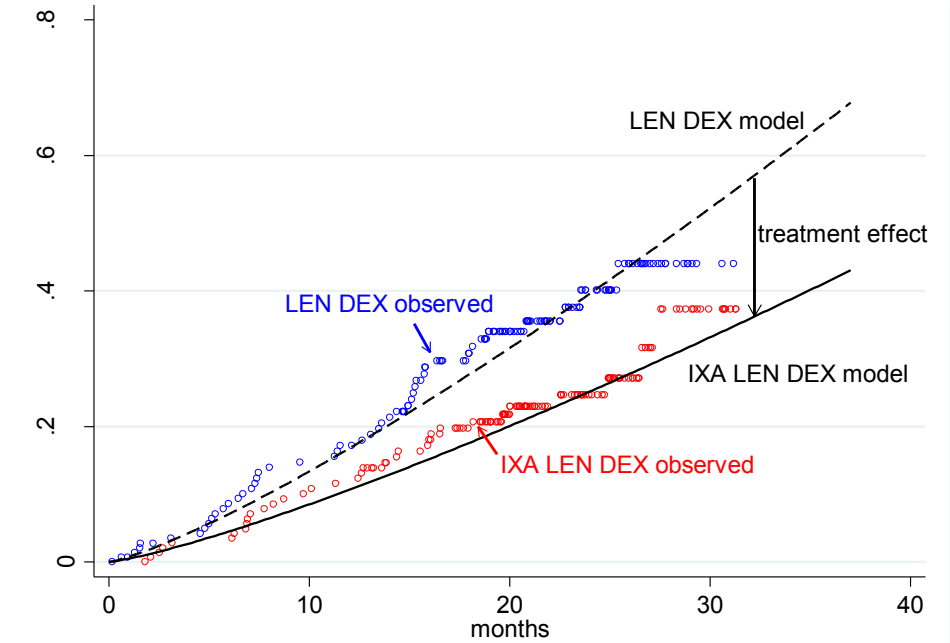



**Figure 4- IXA LEN DEX and LEN DEX OS. Takeda Weibull models cumulative hazard are compared to the observed cumulative hazard.**

2] The Takeda IXA LEN DEX model for OS assumes that the treatment effect is maintained beyond the observed period for the full extrapolation period of ~22 years. The ERG considers it more likely that the treatment effect would gradually dissipate in the long term.

3] Takeda modelling assumes that the influence of covariates, determined from analyses over about 30 months of observation, extends throughout the extrapolations. The ERG considers this a significant assumption.

SUMMARY

1] It is uncertain which Tourmaline patients belong to the 2+ prior therapies population.

2] Because of 1] it is uncertain which covariates should be used if OS and PFS models are to be adjusted

3] Takeda data indicates that number of priors could be an important covariate, but this may not have been fully accommodated in the adjustments included in the Takeda models.

4] Takeda's IXA LEN DEX model for PFS appears implausible because in extrapolation it generates more live non-progressed patients than total patients alive. Correcting for this by making the PFS curve the same as the OS curve is not reasonable because some patients would need to die instantaneously at the time of progression. The reason this difficulty arises is because during extrapolation, Takeda's g gamma PFS model predicts ever decreasing probability of progression, while the Takeda OS model predicts continuously increasing probability for death.

5] For IXA LEN DEX PFS Takeda's adjusted Weibull provides a better fit and a more plausible extrapolation than the generalised gamma model that the company selected.

6] Takeda's OS model for IXA LEN DEX may be over-optimistic in the context of the observed data.

7] For the Weibull IXA LEN DEX OS model Takeda used a treatment effect estimated using data to ~ 30 months and applied this without diminishment for the full 22 years of extrapolation beyond the observed data. It seems more reasonable to expect the treatment effect to gradually diminish during the extrapolation phase.

8] Takeda applied covariate adjustments based on analyses up to ~30 months to the whole of the 22 years of the extrapolation period; this seems a significant assumption in view of the uncertainty about the population and the fact that the number of priors received was not directly used for adjustments.

# 2 COST- EFFECTIVENESS

This section summarises the main changes the company made to the economics in response to the ACD with the resulting company cost-effectiveness estimates. This is followed by:

- a review of some model validation data,
- a brief tabulated summary of the ACD, the company response and an ERG commentary,
- a more detailed review of various aspects of the inputs to and results of the cost effectiveness modelling, and
- ERG exploratory analyses and scenario analyses.

## 2.1 Company revisions to the base case in the light of the ACD

*Treatment effectiveness*

Parameterised curves are fitted to the 2IA data. As in the original submission there is a set of unadjusted curves and a set that are adjusted for various baseline covariates. The company chooses the adjusted curves, in large part due to the information criteria. For the 2+ prior therapies subgroup, the company applies the Weibull, gamma and exponential for OS, PFS and ToT respectively, while for the 2 prior therapies subgroup it applies the exponential for OS, PFS and ToT. Given the ERG clinical review of the 2 prior therapies subgroup, only the detail of the curves of the 2+ prior therapies subgroup is presented in what follows.

**Table 4-** ***AIC and BIC of the adjusted curves: 2+ prior therapies subgroup***

| | | EXP | WEIB | GOMP | LOGN | LOGL | GAMM |
|---|---|---|---|---|---|---|---|
| OS | AIC | 821 | **819** | 822 | 819 | 819 | 820 |
| | BIC | 836 | **838** | 840 | 838 | 837 | 843 |
| PFS | AIC | 1274 | 1272 | 1275 | 1262 | 1266 | **1264** |
| | BIC | 1285 | 1287 | 1290 | 1277 | 1281 | **1282** |
| ToT | AIC | **2122** | 2124 | 2124 | 2137 | 2126 | 2125 |
| | BIC | **2136** | 2142 | 2142 | 2155 | 2145 | 2147 |

The adjustment for baseline covariates is arrived at through an iterative process. The larger set of baseline covariates are included in an initial analysis with the least informative removed sequentially and the analysis rerun, until only statistically significant covariates remain. The OS curves are adjusted for ISS stage III and being aged 65+ years, the PFS curves are adjusted for light chain myeloma and the ToT curves are adjusted for ISS stage III and light chain myeloma. This is slightly different from the baseline covariates of the 1IA data cut analyses. The OS curve was previously only adjusted for age 65+, and the ToT curve was previously adjusted for light chain myeloma and renal dysfunction.

The PFS Kaplan Meier curves and parameterised curves are as below.

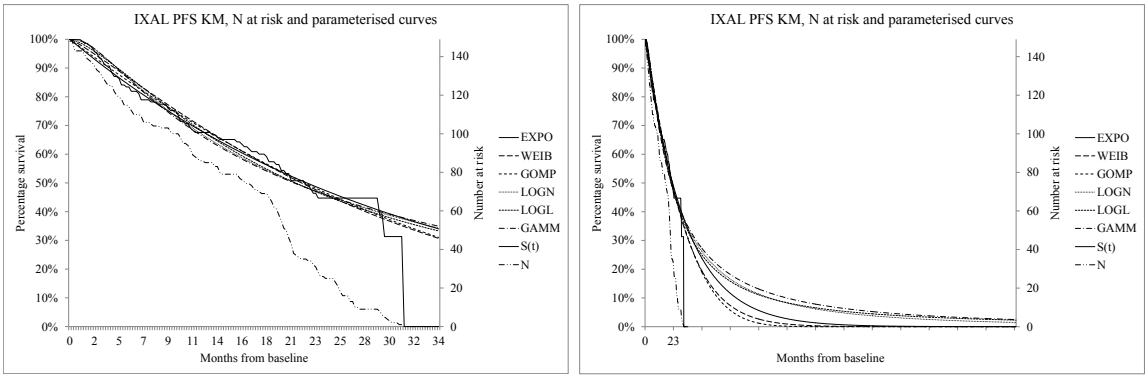



**Figure 5-** ***PFS KM and parameterised curves: IXA+LEN+DEX: 2+ prior therapies subgroup***

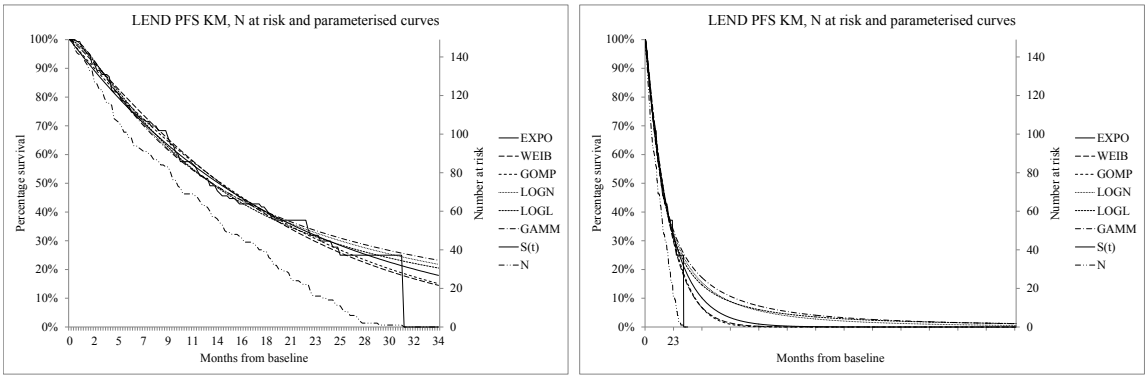



**Figure 6-** ***PFS KM and parameterised curves: LEN+DEX: 2+ prior therapies subgroup***

Unfortunately, due to a glitch in Excel the horizontal axis of the charts with the longer time horizons only labels the first 23 months and the ERG has been unable to correct this in the time available. The x axis markings thereafter indicate approximately 2 year intervals, with the charts going out to 300 months or 25 years.

The gamma, along with the log-normal and the log-logistic curves have quite a long tail out to the right. The exponential, Weibull and Gompertz curves fall more quickly during the period of extrapolation. This is reviewed in greater detail later through analyses which apply Weibulls for the OS, PFS and ToT curves and also needs to be viewed in the context of the OS curves curtailing the PFS curves towards the right hand side.

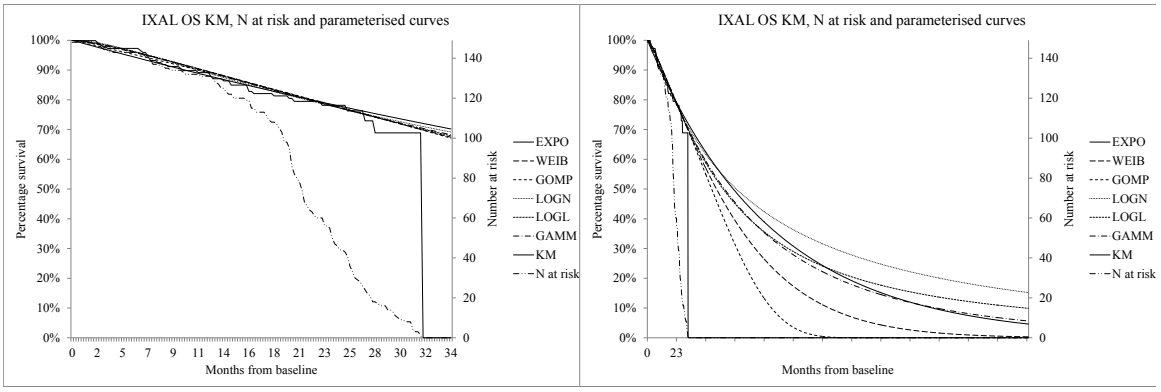



**Figure 7-** ***OS KM and parameterised curves: IXA+LEN+DEX: 2+ prior therapies subgroup***

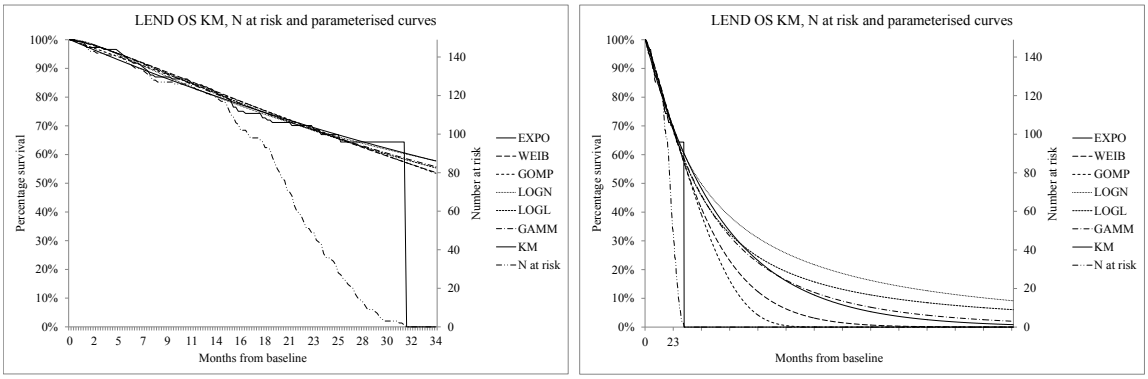



**Figure 8-** ***OS KM and parameterised curves: LEN+DEX: 2+ prior therapies subgroup***

There is relatively little difference between the parameterised OS curves during the trial period although there is considerable divergence thereafter. The gamma, the log-normal and the log-logistic curves all suggest that reasonable proportions of patients remain alive after 25 years. To put this into context, in the UK population aged 66, the proportion surviving to age 91 is around 20% for men and 30% for women and this declines rapidly thereafter to only 16% and 26% surviving to age 92. The flatness of the gamma, the log-normal and the log-logistic curves at 25 years does not appear realistic and if further extrapolated would lead to unfeasible proportions surviving.

There is a surprising amount of divergence between the exponential and the Weibull curves. The exponential suggests that 5% of IXA+LEN+DEX patients survive to 91 years but only 1% of LEN+DEX patients. The Gompertz estimates the shortest overall survival.

Given the immaturity of the OS data with only 23 months of median follow-up at 2IA and a maximum follow up of around 32 months, with consequent considerable uncertainty around the OS curves and the extent to which they might diverge during the extrapolation period.

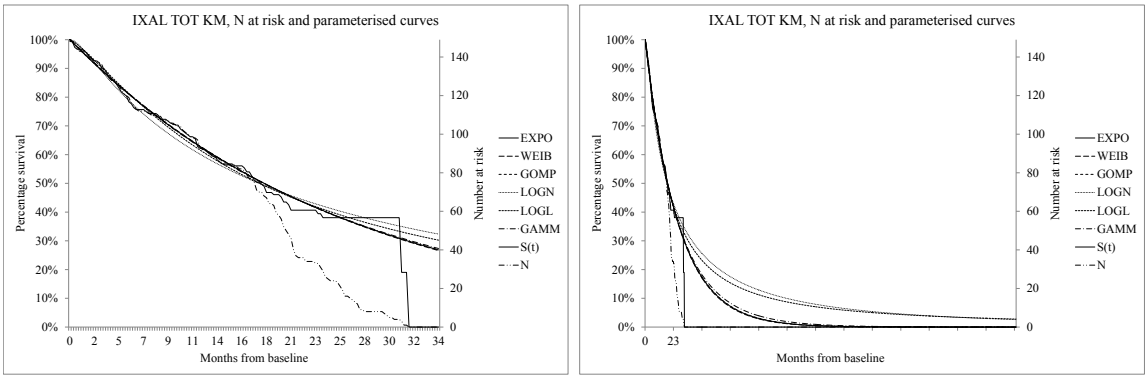



**Figure 9-** ***ToT KM and parameterised curves: IXA+LEN+DEX: 2+ prior therapies subgroup***

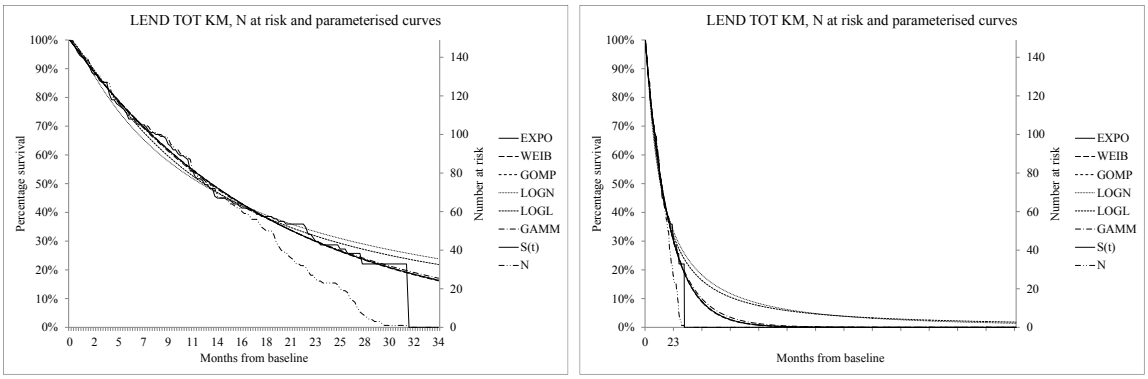



**Figure 10-** ***ToT KM and parameterised curves: LEN+DEX: 2+ prior therapies subgroup***

This results in the following curves for the 2+ prior therapies subgroup.

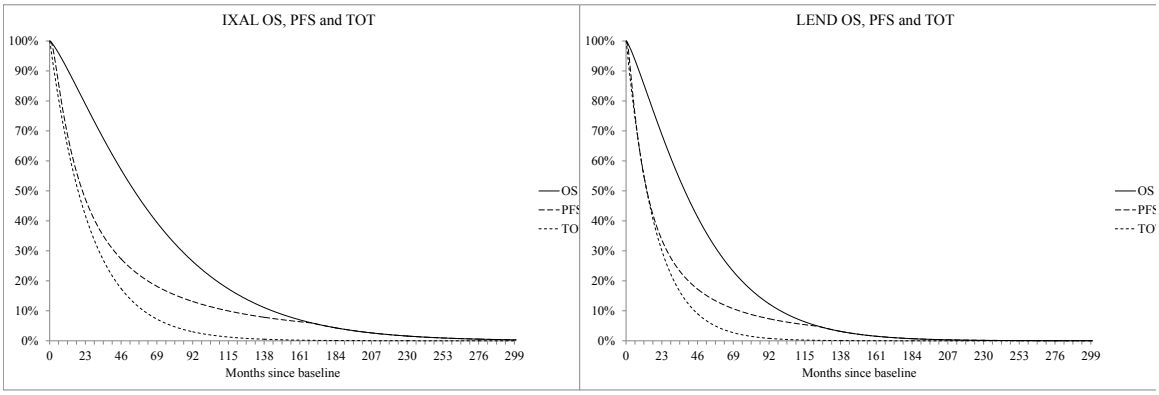



**Figure 11-** ***Base case curves for the 2+ prior therapies subgroup***

As in the previous submission the PFS and ToT curves show little difference during the period of the trial when reasonable numbers of patients remain at risk. It is only during extrapolation that they diverge. This divergence is in part due to the different functional forms assumed for PFS and ToT. If the gamma is applied for both the PFS and the ToT the two curves diverge during extrapolation, however if either the exponential or the Weibull is applied for both PFS and ToT there is relatively little divergence between the two curves during extrapolation, since the PFS curve is pulled in towards the ToT curve. However this needs to be read alongside the section that applies Weibulls for OS, PFS and ToT.

*Best overall response rates*

The best overall response rates have been revised from those of the 1IA data cut to those of the 2IA data cut.

**Table 5-** ***BoR rates: 2+ prior therapies subgroup***

| | Missing | PD | SD | PR | VGPR+ |
|---|---|---|---|---|---|
| 1IA data cut | | | | | |
| IXAL | 9 | 7 (5%) | 13 (9%) | 41 (29%) | 78 (56%) |
| LEND | 15 | 8 (6%) | 26 (19%) | 52 (39%) | 48 (36%) |
| 2IA data cut | | | | | |
| IXAL | 11 | 7 (5%) | 11 (8%) | 39 (28%) | 80 (58%) |
| LEND | 16 | 8 (6%) | 26 (20%) | 45 (34%) | 54 (41%) |

*PD = progression; SD= stable disease; PR= partial response; VGPR+ =very good partial response and more*

In the company base case these BoR rates are applied to the company contemporaneous response quality of life analysis coefficients.

*Quality of life*

The company present the results of a new repeated measures analysis, the key differences from the previous submission are:

- The use of the 2IA data cut,
- Estimates of the quality of life as a function of contemporaneous response rather than as a function of best overall response, and
- Including age, sex and race as covariates.

The coefficients of these and the resulting quality of life values are presented in the detailed ERG review below.

*Resource use after progression*

The company has revised its post progression resource use, updating the estimated proportion of patients who receive subsequent therapy from 41% as described in the 1IA data cut to the 66% of the 2IA data cut. For the patients receiving treatment, the company

states that the PPS costs are weighted by the time spent in PPS which results in weekly costs of £708 for IXA+LEN+DEX and £927 for LEN+DEX. This is reviewed in greater detail in the ERG review below.

*Other resource use*

Concomitant medication costs have been revised from the £31 weekly cost estimate of the 1IA data cut to £36 using the 2IA data cut.

Hospitalisation and adverse event rates have also been revised but these have little impact upon results.

## 2.2 Company revised cost effectiveness estimates

*Company revised base case results*

The company provides a PAS which is a simple [redacted] reduction in the list price, reducing the four weekly cost per pack if ixazomib from £6,336 to [redacted]. This reduces the annual cost of ongoing dosing with ixazomib from £82,651 to [redacted]. All cost effectiveness estimates in this chapter are inclusive of the [redacted] PAS.

For the 2+ prior therapies subgroup the company base case is as below.

**Table 6-** ***Company revised base case: 2+ prior therapies subgroup***

| | Undisc. LY | | | QALYs | | | Costs | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | PFS | PPS | OS | PFS | PPS | Total | Drug | ConMed | Ongoing | Total |
| LEND | 2.289 | 1.626 | 3.914 | 1.647 | 1.106 | 2.726 | £71,452 | £6,717 | £54,199 | £132,369 |
| IXAL | 3.350 | 2.127 | 5.477 | 2.351 | 1.382 | 3.707 | £193,619 | £9,093 | £52,578 | £255,289 |
| Net | 1.061 | 0.501 | 1.562 | 0.704 | 0.276 | 0.981 | £122,166 | £2,376 | -£1,622 | £122,920 |
| ICER | | | | | | | | | | £125,277 |

Ixazomib is estimated to result in an additional 1.6 years survival with two thirds of this gain being realised pre-progression and one third being realised post-progression. This

results in a net 0.981 QALY gain with additional costs of £123k and a cost effectiveness estimate of £125k per QALY.

The probabilistic modelling suggests reasonably similar net costs and QALYs of £122,578 and 0.985 respectively resulting in a central cost effectiveness estimate of £124,428 per QALY and a CEAC as below.

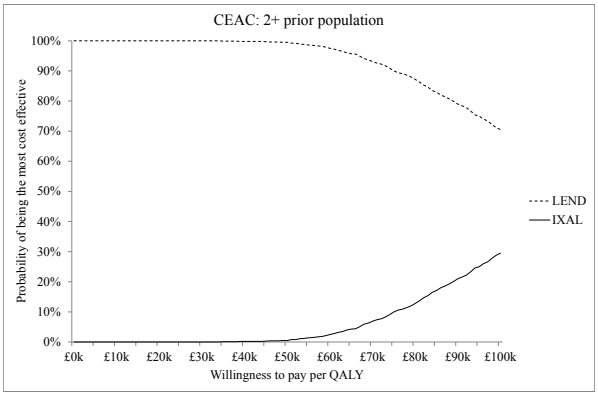



**Figure 12-** ***Company base case CEAC: 2+ prior therapies: With IXA PAS***

For the 2 prior therapies subgroup the company base case is as below.

**Table 7-** ***Company revised base case: 2 prior therapies subgroup***

| | Undisc. LY | | | QALYs | | | Costs | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | PFS | PPS | OS | PFS | PPS | Total | Drug | ConMed | Ongoing | Total |
| LEND | 1.930 | 3.633 | 5.562 | 1.444 | 2.183 | 3.601 | £75,639 | £9,318 | £56,445 | £141,402 |
| IXAL | 2.405 | 6.066 | 8.471 | 1.775 | 3.395 | 5.147 | £186,931 | £13,331 | £53,741 | £254,004 |
| Net | 0.476 | 2.433 | 2.908 | 0.331 | 1.212 | 1.546 | £111,292 | £4,014 | -£2,704 | £112,602 |
| ICER | | | | | | | | | | £72,856 |

For the 2 prior therapies subgroup ixazomib is estimated to result in an additional 2.9 years survival, roughly double that of the 2+ prior therapies subgroup. (This is despite the pre-progression survival gain of 0.5 years being roughly half that of the 2+ prior therapies subgroup). The increased survival is largely due to the net gain of 2.4 years post progression. Given the increased survival gain, the net patient gain also increases to 1.546 QALYs. Since less time is spent in ixazomib treatment, net costs are also lower for the 2

prior therapies group at £112k and the cost effectiveness estimate improves to £72,856 per QALY.

The probabilistic modelling suggests reasonably similar net costs and QALYs of £111,799 and 1.494 respectively resulting in a central cost effectiveness estimate of £74,846 per QALY and a CEAC as below.

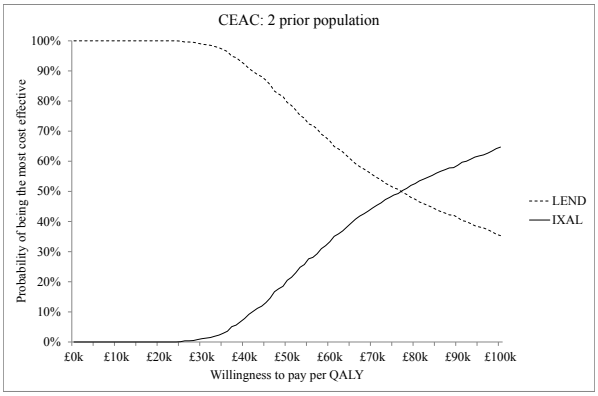



**Figure 13-** ***Company base case CEAC: 2 prior therapies: With IXA PAS***

*Company revised sensitivity analyses*

**Table 8-** ***Company scenario analyses***

| | Δ Cost | Δ QALY | ICER |
|---|---|---|---|
| Base case (PFS: Gamma; ToT: exponential; OS: Weibull) | £123k | 0.981 | £125k |
| Time horizon 15 years | £123k | 0.992 | £124k |
| Time horizon 20 years | £123k | 1.042 | £118k |
| Non-covariate adjusted clinical endpoints | £120k | 0.870 | £138k |
| Cap ToT by PFS | £123k | 0.981 | £125k |
| PFS : Exponential | £121k | 0.979 | £123k |
| PFS : Weibull | £121k | 0.975 | £124k |
| PFS : Gompertz | £121k | 0.972 | £124k |
| PFS : Log-normal | £123k | 0.980 | £125k |
| PFS : Log-logistic | £123k | 0.980 | £125k |
| OS : Exponential | £123k | 1.391 | £88,453 |
| OS : Gompertz | £122k | 0.674 | £180k |
| OS : Log-normal | £124k | 1.203 | £103k |

| | | | |
|---|---|---|---|
| OS : Log-logistic | £124k | 1.094 | £113k |
| OS : Gamma | £123k | 1.205 | £102k |
| ToT : Weibull | £122k | 0.981 | £125k |
| ToT : Gompertz | £123k | 0.981 | £126k |
| ToT : Log-normal | £163k | 0.981 | £166k |
| ToT : Log-logistic | £156k | 0.981 | £159k |
| ToT : Gamma | £127k | 0.981 | £129k |
| IXA+LEN+DEX ToT reduced by 25% | £76,499 | 0.982 | £77,870 |
| Utility source: TMM1 clinical trial | £123k | 0.981 | £125k |
| Utility source: TA171 | £123k | 0.934 | £132k |
| Utility source: TA338 | £123k | 0.888 | £138k |
| Only additional LEN+DEX costed in the IXA+LEN+DEX arm | £123k | 0.981 | £125k |
| Additional LEN+DEX in the IXA+LEN+DEX arm is not costed | £123k | 0.981 | £125k |
| Setting the cost of IXA to £0 | £11,763 | 0.981 | £11,988 |
| Discount rate costs and QALYs: 0% | £132k | 1.206 | £110k |
| Discount rate costs and QALYs: 6% | £117k | 0.857 | £137k |

The scenario analyses around the costs of LEN+DEX do not appear to be correct. This may be due to the company, possibly inadvertently, excising this aspect of the model.

## 2.3 Model validation

*Overall survival observed and extrapolated gains*

The parameterised curves of the company base case for the 2+ prior therapies population suggest a total survival gain for IXA+LEN+DEX compared to LEN+DEX of 1.562 years. As outlined below, the vast majority of the net survival gain, 88%, occurs after the 2IA data cut maximum follow-up of 32 months and is during the extrapolation period of the model. Given the relatively long survival of multiple myeloma patients, immaturity of the overall survival data is an inevitable feature of trials. There is uncertainty about the duration of the treatment effect that should be applied after 32 months, and by implication around the actual survival gains that are likely to be realised.

**Table 9-** ***Modelled survival gains, company base case, 2+ prior therapies***

| | To 32 months | | | From 32 months | | | Total survival gain | | |
|---|---|---|---|---|---|---|---|---|---|
| | PFS | PPS | OS | PFS | PPS | OS | PFS | PPS | OS |
| LEND | 1.363 | 0.747 | 2.110 | 0.926 | 0.879 | 1.804 | 2.289 | 1.626 | 3.914 |
| IXAL | 1.681 | 0.615 | 2.296 | 1.669 | 1.512 | 3.181 | 3.350 | 2.127 | 5.477 |
| net | 0.318 | -0.132 | 0.186 | 0.744 | 0.633 | 1.376 | 1.061 | 0.501 | 1.562 |

*2 prior therapies results*

The estimated PFS, PPS and OS gains for the 2 prior therapies subgroup differ quite markedly from those for the 2 + prior therapies subgroup. While for the 2+ prior therapies subgroup the estimated survival gains are 2:1 PFS to PPS, for the 2 prior therapies subgroup the estimated survival gains are roughly double and less than 1:4 PFS to PPS. In the opinion of the ERG a PPS survival gain of more than four times the PFS survival lacks credibility and appears to be clinically implausible given the known mechanism of action of ixazomib. The 2+ prior therapies subgroup gains and the 2 prior therapies subgroup gains also imply gains for the 3 prior therapies subgroup given the PFS, PPS and OS for the overall population. Simple weighted average calculations suggest the following.

**Table 10-** ***Undiscounted survival gains: IXA+LEN+DEX vs LEN+DEX***

| | N | PFS | PPS | Total |
|---|---|---|---|---|
| 2+ prior therapies | 297 | 1.061 | 0.501 | 1.562 |
| 2 prior therapies | 208 | 0.476 | 2.433 | 2.908 |
| 3 prior therapies | 89 | 2.430 | -4.013 | -1.583 |

Given the different balance between the PFS and PPS modelled survival gains for the 2+ prior and the 2 prior therapies subgroups, the implied gains for the 3 prior therapies subgroup are a large PFS gain, with an even larger PPS loss and a loss in overall survival. These results do not appear to be credible as they arise largely due to the much larger modelled overall survival gain for the 2 prior therapies subgroup, coupled with over 80% of this gain being realised after progression. In the previous section, the ERG also commented that from the clinical effectiveness viewpoint the exploratory analysis presented by the Company for the 2 prior therapies only subgroup is of limited relevance.

*ERG cross check of parameterisation of the curves for the 2IA modelling*

The ERG has cross checked that the parameters for the 2IA data cut 2+ prior therapies subgroup are the same as in the 2IA model submitted during the assessment of the 1st company submission.

ERG cross check of base case results

The ERG has rebuilt the deterministic base case applying the revised company model inputs and assumptions, and gets good agreement with the results of the company model.

**Table 11-** ***ERG rebuild vs company model: 2+ prior therapies subgroup***

| | ERG | | Company | |
|---|---|---|---|---|
| | IXA+LEN+DEX | LEN+DEX | IXA+LEN+DEX | LEN+DEX |
| Costs | £317,779 | £131,585 | £318,031 | £132,369 |
| QALYs | 3.705 | 2.724 | 3.707 | 2.726 |
| Net Costs | £186,195 | | £185,662 | |
| Net QALYs | 0.981 | | 0.981 | |
| ICER | £189,889 | | £189,222 | |

**Table 12-** ***ERG rebuild vs company model: 2 prior therapies subgroup***

| | ERG | | Company | |
|---|---|---|---|---|
| | IXA+LEN+DEX | LEN+DEX | IXA+LEN+DEX | LEN+DEX |
| Costs | £313,170 | £139,960 | £313,937 | £141,402 |
| QALYs | 5.143 | 3.599 | 5.147 | 3.601 |
| Net Costs | £173,210 | | £172,535 | |
| Net QALYs | 1.544 | | 1.546 | |
| ICER | £112,173 | | £111,635 | |

## 2.4 Brief summary of AC, company response and ERG commentary

The ERG reading of the main elements of the ACD, relevant to the revised company economics is summarised below, together with a brief summary of the company response and the ERG economic commentary upon this.

**Table 13-** ***ERG summary of ACD, company response and ERG economic commentary***

| Section | Comment |
|---|---|
| 3.7 | **ACD:** The main population is the 2+ prior patient subgroup. This can be split into the 2 prior subgroup and the 3 prior subgroup. For the 2 prior subgroup the appropriate comparator is LEN+DEX. For the 3 prior subgroup the appropriate comparators are LEN+DEX and PAN+BOR+DEX. The AC would prefer to see an analysis for the 3 prior subgroup using PAN+BOR+DEX as the comparator.<br>**Company:** Comparisons for the 2+ prior subgroup and the 2 prior subgroup of IXA+LEN+DEX versus LEN+DEX are presented. There is no consideration of the 3 prior subgroup or of any comparison with PAN+BOR+DEX.<br>**ERG:** In the light of additional data and the company cost effectiveness estimates for the 2 prior subgroup the ERG agrees with the company that the 2+ prior subgroup is a more sound base for the comparison with LEN+DEX. The ERG has also commented on the lack of comparison with PAN+BOR+DEX in chapter 1 above. |
| 3.12 | **ACD:** Ixazomib may be more effective in the 3 prior subgroup. The experts expected this due to a triplet being more effective than a doublet in a heavily pre-treated population. The AC concluded there was a biologically plausible rationale for this.<br>**Company:** There is no consideration of the 3 prior subgroup or of any comparison with PAN+BOR+DEX.<br>**ERG:** This is reviewed in chapter 1 above. |
| 3.13 | **ACD:** The company notes that analysing the 3 prior subgroup breaks randomisation which was stratified in TMM1 by 1 prior and 2+ prior subgroups.<br>**Company:** The company presents data on the differences in baseline characteristics between the 2 prior subgroup and the 3 prior subgroup.<br>**ERG:** This is reviewed in chapter 1 above. |
| 3.15 | **ACD:** The 2nd interim analysis data cut is preferable to the 1st interim analysis data cut.<br>**Company:** The company revises its analyses to be based upon the 2IA data cut.<br>**ERG:** No comment. |
| 3.16 | **ACD:** The 2+ prior subgroup is appropriate but an analysis of the 2 prior subgroup is required. The latter should adjust for baseline characteristics.<br>**Company:** The company provide an analysis of the 2 prior subgroup adjusted for baseline characteristics. The company also adjusts the 2+ prior subgroup for baseline characteristics.<br>**ERG:** In the light of additional data and the company cost effectiveness estimates for the 2 prior subgroup the ERG agrees with the company that the 2+ prior subgroup is a more sound base for the comparison with LEN+DEX. The adjustment of the 2+ prior subgroup for |

| | |
|---|---|
| | baseline characteristics may be questionable and the company may not have explored relevant covariates. |
| 3.18 | **ACD:** The quality of life decrement for avoiding injections was too large.<br>**Company:** This no longer applies since the only comparator that is considered is LEN+DEX.<br>**ERG:** No comment. |
| 3.19 | **ACD:** Since progression is biologically based, quality of life may not immediately fall at progression. But a higher quality of life value for progressed disease than for stable disease lacks credibility when extrapolated to the longer term and is not credible up to 3 months prior to death.<br>**Company:** A revised quality of life analysis based upon the 2IA data cut suggests a larger quality of life decrement for progressed disease compared to stable disease than the analysis of the 1IA data cut. This is probably due to the longer follow-up being able to capture more of the decline associated with progressive disease.<br>**ERG:** Longer follow up still might suggest further deteriorations in quality of life associated with the first progression. There is no allowance made for further progressions after subsequent treatments. |
| 3.20 | **ACD:** The quality of life values are uncertain, there are no interactions with age or prior treatments and the measure of response is best overall response, which may be optimistic.<br>**Company:** The revised quality of life estimates are based upon measures of response that are contemporaneous to the EQ-5D values. The resulting coefficients have the rates of best overall response applied to them. There is also an age coefficient.<br>**ERG:** Applying the best overall response rates to the coefficients based upon contemporaneous response will be biased. The company also supplies "mean of covariate" estimates which are less optimistic. The age coefficient is quite small and appears to imply a reduction of somewhat less than the decennial fall in UK population norms among those aged 65+. |
| 3.21 | **ACD:** The extrapolated proportion of progression free survival that was spent receiving treatment of 65% for IXA+LEN+DEX and 75% for LEN+DEX differed markedly from that of the trial. The treatment discontinuation rate before progression appeared to be too high. There was a lack of clarity as to how time on treatment was handled compared to progression free survival.<br>**Company:** The company has supplied some additional data on events and censoring within the ToT curves. The revised model estimates are the 62% of PFS in the IXA+LEN+DEX arm incurs treatment costs and 69% in the LEN+DEX arm. |

| | |
|---|---|
| | **ERG:** The construction of the ToT curves is not pre-specified and as reviewed below it is possible that an artificial wedge is being driven between the ToT curve and the PFS curve. The divergence between the ToT curve and the PFS curve may also be largely due to the assumption of different functional forms. The trial data suggests ratios of areas under the ToT and PFS KM curves of 92% for IXA+LEN+DEX and 97% for LEN+DEX. |
| 3.22 | **ACD:** The subsequent costs of treatment should be modelled as weekly costs. The ERG 41% estimate for those receiving subsequent treatment is preferable to the company 24%.<br>**Company:** The company applies a 2IA based estimate of 66% of PPS patients receiving active treatment. It states that weekly costs of £708 for IXA+LEN+DEX and £927 for LEN+DEX are applied.<br>**ERG:** The longer follow-up of the 2IA data cut has quite dramatically increased the proportion of PPS patients receiving treatment. Longer follow up still might increase this further. The company statement about weekly costs is somewhat misleading and should have stated that the company applies a one off cost for PPS patients receiving further active treatment of £78,607 in both the IXA+LEN+DEX arm and the LEN+DEX arm |
| 3.25 | **ACD:** The AC preferred using PFS rather than ToT for costing IXA+LEN+DEX and LED+DEX with modelling of costs subsequent to progression on a weekly basis. The ACD also indicated other preferences which could not be incorporated into the model by the ERG, such as quality of life declining with age.<br>**Company:** The company retains the ToT curves for costing purposes and does not provide a scenario analysis using the PFS curves. The age coefficient of the company 2IA quality of life analysis is applied.<br>**ERG:** The ERG provides base case and full scenario analyses using both the ToT curve and the PFS curve for costing purposes. As reviewed in more detail below, any divergence between ToT and PFS curve occurs during extrapolation and has increased with the 2IA parameterised curves. This extrapolated divergence may be largely a function of the application of different functional forms for ToT and PFS. How the ToT KM curves should be constructed is not pre-specified, and the company has experimented with different definitions of events and censoring events. It is possible that an artificial wedge has been constructed between KM ToT and KM PFS curves. With the caveat that there is uncertainty about the appropriate construction of the ToT KM curves, the ERG acknowledges that there is evidence of some divergence between TOT KM curves and PFS KM curves with ratios of areas under the curves of perhaps around 92% for IXA+LEN+DEX and 97% for LEN+DEX. Lastly, the age coefficient of the company 2IA quality of life analysis seems to suggest a slower decline then the decennial decline in UK population norms. |
| 3.26 | **ACD:** A comparison with panobinostat for the 3 prior subgroup should be presented. |

| | |
|---|---|
| | **Company:** No comparison with panobinostat is presented.<br>**ERG:** This is reviewed in chapter 1 above. |
| 3.27 | **ACD:** End of life does not apply due to the life expectancy for the 2+ patient group being modelled as 3.6 years which exceeds the 24 month criterion.<br>**Company:** The company argues that the AC might be able to consider revised end of life criteria: "The new treatment is given in combination with an existing treatment and both treatments are licensed to be administered until disease progression". IXA+LEN+DEX evaluated against LEN+DEX would fulfil this and so it would be open to the AC to consider end of life for ixazomib. The company has provided scenario analyses around the costs of LEN+DEX but these appear incorrect in the current submission, possibly due to the company inadvertently excising this from the electronic model<br>**ERG:** The ERG assumes that the rationale for the possible new end of life criteria is that the cost of the existing treatment is substantial. The treatment is used in conjunction with the existing treatment, so any extension to PFS incurs the additional costs of the existing treatment during the extension to PFS. To the ERG the possible new end of life criteria argue for setting the costs of LEN+DEX to zero to explore whether without these costs, ixazomib would be cost effective at conventional willingness to pay thresholds. Note also that the possible new end of life criteria are framed in terms of treatments being licensed for administration until progression, which may have a bearing upon the ToT versus PFS costing argument when assessing end of life. This is reviewed in greater detail in chapter 3 below. |

## 2.5 Detailed ERG critique

*Adjusted vs unadjusted curves*

The ACD specified that the 2 prior therapies subgroup analyses should be adjusted for baseline characteristics. The company also adjusts the 2+ prior therapies subgroup parameterised curves for baseline covariates. The final covariates were arrived at by iterative elimination of the worst performing non-significant covariate until only statistically significant covariates at the 5% level remained. This adjustment mainly affects the overall survival curves and improves the cost effectiveness estimate. The information criteria and the mean durations of the adjusted and unadjusted curves can be compared.

The PFS curves are adjusted for light chain myeloma.

**Table 14-** ***PFS parameterised curves AIC and BIC: 2+ prior therapies subgroup***

| | | EXP | WEIB | GOMP | LOGN | LOGL | GAMM |
|---|---|---|---|---|---|---|---|
| Unadjusted | AIC | 1275 | 1274 | 1276 | 1267 | 1271 | 1269 |
| | BIC | 1283 | 1285 | 1287 | 1278 | 1282 | 1284 |
| Adjusted | AIC | 1274 | 1272 | 1275 | 1262 | 1266 | 1264 |
| | BIC | 1285 | 1287 | 1290 | 1277 | 1281 | 1282 |
| Difference | AIC | -1.4 | -1.6 | -1.5 | -5.4 | -4.7 | -5.6 |
| | BIC | 2.3 | 2.1 | 2.2 | -1.7 | -1.0 | -1.9 |

The picture between the AIC and the BIC is mixed for the exponential, the Weibull and the Gompertz curves. Whether the adjusted curves are to be preferred for these judged solely by the information criteria is not clear, but the case for the adjusted curve judged solely by the information criteria appears to be stronger for the log-normal, the log-logistic and the gamma curves.

The mean durations of PFS of the adjusted and unadjusted curves are as follows.

**Table 15-** ***Means months PFS of adjusted and unadjusted curves: 2+ prior therapies subgroup***

| | Unadjusted | | | Adjusted | | | Adj-Unadj |
|---|---|---|---|---|---|---|---|
| | LEND | IXAL | net | LEND | IXAL | net | Gain |
| Exponential | 20 | 32 | 12 | 20 | 32 | 12 | 0.2 |
| Weibull | 19 | 28 | 10 | 19 | 28 | 10 | 0.2 |
| Log normal | 28 | 42 | 14 | 27 | 41 | 14 | -0.2 |
| Log logistic | 29 | 43 | 14 | 28 | 42 | 14 | -0.1 |
| Gompertz | 18 | 27 | 9 | 18 | 27 | 9 | 0.1 |
| Gamma | 27 | 41 | 14 | 30 | 45 | 15 | 0.4 |

The base case applies the gamma curves for PFS, which in common with the log-normal and log-logistic have quite long tails out to the right. Their mean PFSs are somewhat higher than the more commonly applied exponential and Weibull, but there are reasonable differences in the AICs and BICs between the curves.

The mean months of PFS of the unadjusted curves are around 3 to 4 months less than those of the adjusted curves. But the differences between the arms are similar at 14 months for the unadjusted and 15 months for the adjusted, with the adjustment only adding an additional 0.4 months to the net PFS compared to the unadjusted. The effect on the other curves is less, and adjusting PFS for baseline covariates appears to be relatively unimportant.

The OS curves of the 2IA data cut are adjusted for age over 65 years at baseline and ISS stage III. Also note that the final adjusted OS curves of the 1IA data cut were adjusted for age over 65 years, but not for ISS stage III.

**Table 16-** ***OS parameterised curves AIC and BIC: 2+ prior therapies subgroup***

| | | EXP | WEIB | GOMP | LOGN | LOGL | GAMM |
|---|---|---|---|---|---|---|---|
| Unadjusted | AIC | 828 | 827 | 829 | 825 | 826 | 827 |
| | BIC | 836 | 838 | 841 | 836 | 837 | 842 |
| Adjusted | AIC | 821 | 819 | 822 | 819 | 819 | 820 |
| | BIC | 836 | 838 | 840 | 838 | 837 | 843 |
| Difference | AIC | -7.5 | -8.0 | -7.8 | -5.8 | -7.4 | -6.6 |
| | BIC | -0.1 | -0.7 | -0.5 | 1.5 | 0.0 | 0.8 |

The differences in the AICs support the adjusted curves, but there are curiously little differences in the BICs. Of the adjusted curves, the Weibull is applied though the information criteria for it are similar to the log-normal and the log-logistic. The latter two are presumably rejected due to their long tails.

The unadjusted and adjusted OS curves give rise to the following mean months of survival.

**Table 17-** ***Mean months OS of adjusted and unadjusted curves: 2+ prior therapies subgroup***

| | Unadjusted | | | Adjusted | | | Adj-Unadj |
|---|---|---|---|---|---|---|---|
| | LEND | IXAL | net | LEND | IXAL | net | Gain |
| Exponential | 61 | 87 | 26 | 62 | 93 | 31 | 4.4 |
| Weibull | 47 | 66 | 18 | 47 | 68 | 21 | 2.6 |
| Log normal | 87 | 111 | 25 | 85 | 112 | 27 | 2.2 |
| Log logistic | 74 | 95 | 21 | 72 | 96 | 23 | 2.6 |
| Gompertz | 42 | 53 | 12 | 41 | 53 | 12 | 0.8 |
| Gamma | 47 | 106 | 59 | 64 | 90 | 26 | -32.9 |

The Weibull of the base case suggests that adjusting the curves has relatively little impact upon the LEN+DEX mean survival but improves it for IXA+LEN+DEX. Adjusting the curves results in an additional survival gain for IXA+LEN+DEX compared to LEN+DEX of 2.6 months compared to the unadjusted curves.

The proportion of patients in the IXA+LEN+DEX arm that were over 65 years at baseline was 54% compared to 52% for LEN+DEX. Adjusting for this would be expected to improve IXA+LEN+DEX relative to LEN+DEX.

In Table 3 of the May 19th CS, the forest plots of the original CS and CSR of the 2IA data cut all suggest a further possible pre-specified age covariate of >75 years with only 15% in the IXA+LEN+DEX arm being over 75 at baseline compared to 19% in the LEN+DEX arm. The proportion who are older than 75 years might be anticipated to be a stronger determinant of survival during the trial period than the proportion who are older than 65 years. The 4% difference between the arms in the proportion of patients who are older than 75 years is also larger than the 2% difference between the arms in the proportion of patients who are older than 65 years. It is not clear to the ERG why being older than 75 years at baseline was not explored as a possible covariate. Although adjusting for this would be expected to improve LEN+DEX relative to IXA+LEN+DEX.

For completeness, the ToT curves are adjusted for ISS stage III and light chain myeloma with the following AIC and BIC.

**Table 18-** ***ToT parameterised curves AIC and BIC: 2+ prior therapies subgroup***

| | | EXP | WEIB | GOMP | LOGN | LOGL | GAMM |
|---|---|---|---|---|---|---|---|
| Unadjusted | AIC | 2129 | 2131 | 2131 | 2144 | 2134 | 2133 |
| | BIC | 2137 | 2142 | 2142 | 2155 | 2145 | 2148 |
| Adjusted | AIC | 2122 | 2124 | 2124 | 2137 | 2126 | 2125 |
| | BIC | 2136 | 2142 | 2142 | 2155 | 2145 | 2147 |
| Difference | AIC | -7.7 | -7.7 | -7.7 | -7.3 | -8.0 | -7.9 |
| | BIC | -0.3 | -0.3 | -0.3 | 0.1 | -0.6 | -0.5 |

There are parallels with the PFS AIC and BIC, with the AIC favouring the adjusted curves but the BIC being little different between the adjusted and the unadjusted.

**Table 19-** ***Mean months of ToT adjusted and unadjusted curves: 2+ prior therapies subgroup***

| | Unadjusted | | | Adjusted | | | Adj-Unadj |
|---|---|---|---|---|---|---|---|
| | LEND | IXAL | net | LEND | IXAL | net | Gain |
| Exponential | 19 | 26 | 6 | 19 | 26 | 7 | 0.7 |
| Weibull | 19 | 26 | 6 | 19 | 26 | 7 | 0.6 |
| Log normal | 32 | 44 | 11 | 31 | 43 | 11 | 0.3 |
| Log logistic | 32 | 41 | 10 | 31 | 41 | 10 | 0.5 |
| Gompertz | 20 | 27 | 7 | 19 | 26 | 7 | 0.2 |
| Gamma | 20 | 27 | 7 | 20 | 27 | 8 | 0.7 |

As with the PFS, there is only a limited impact of applying the adjusted ToT curves compared to the unadjusted ToT curves.

*Company choices of parameterised curves: Original and current submission*

During the original submission, the company submitted a scenario analysis which applied parameterised curves estimated from the 2IA data cut. The set of parameterised curves are the same as are applied in the current submission; i.e. the 2IA OS log-normal curve of the original submission is identical to the 2IA OS log-normal curve of the current submission. The company chooses a different set of parameterised curves in the current submission than it previously chose for the 2IA sensitivity analysis of its original submission.

**Table 20-** ***Company 2IA data cut parameterised curves: 2+ prior therapies subgroup***

| Submission | Original | Current |
|---|---|---|
| OS curve | Log-Normal | Weibull |
| PFS curve | Log-Normal | Gamma |
| ToT curve | Gamma | Exponential |

The 2IA curves chosen by the company in its current submission result in a cost effectiveness estimate of £125k per QALY. The 2IA curves chosen by the company in its original submission when applied in the model of the current submission result in a cost effectiveness estimate of £106k per QALY.

In the light of this the ERG will undertake scenario analyses that apply the company choices of its original submission.

*Duration of effect and waning*

As previously indicated, the majority of the estimated survival gain of the company base case occurs during extrapolation. Of the estimated 1.56 years additional survival 94% occurs after the median 23 months follow up of the 2IA data cut and 88% occurs after the 32 months longest duration of follow-up and after the end of the 2IA Kaplan Meier curves. The NICE methods guide section 5.7.7 states that:

> "*Alternative scenarios should also be routinely considered to compare the implications of different methods for extrapolation of the results. For example, for duration of treatment effects, scenarios might include when the treatment benefit in the extrapolated phase is: (i) nil; (ii) the same as during the treatment phase and continues at the same level; or (iii) diminishes in the long term*."

Of the three alternatives suggested above the base case corresponds to "*(ii) the same as during the treatment phase and continues at the same level*" and is the most optimistic. To undertake "*(i) nil*", the ERG will present scenario analyses that set the treatment effects equal to zero from 23 months and from the 32 months. To undertake "*(iii)*

*diminishes in the longer term*" the ERG will diminish the treatment effect linearly from 32 months, such that it falls to zero over periods of 1, 2, 5 and 10 years[a].

*Choice of curves and treatment waning*

In the opinion of the ERG the gamma for the PFS may not be a particularly good fit as it suggests an ever falling hazard ratio. This has also been emphasized in section 1 above. The tails of the PFS gammas are also very long out to the right. A consequence of this is that the OS Weibulls, which have shorter tails, curtail the PFS gammas within the modelling. As previously suggested this might argue for Weibulls being applied, to the PFS and perhaps the use of Weibulls for the ToT curves as well.

As already noted, the divergence between the ToT curve and the PFS curve is in large part due to the use of the gamma for the PFS curve and the exponential for the ToT curve. If Weibulls are applied throughout the following curves apply.

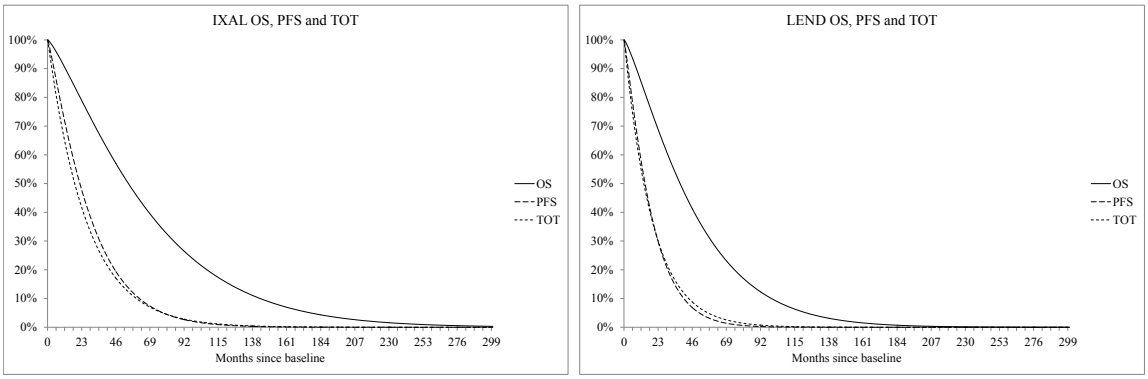



**Figure 14-** ***Weibulls for OS, PFS and ToT: 2+ Prior subgroup***

The primary outcome measure of the trial is PFS. There is somewhat more uncertainty about the OS estimates than the PFS estimates. The model does not impose any functional relationship between PFS and OS during the extrapolation period, or indeed

[a] Implemented in the model as 52, 104, 260 and 520 weeks.

between PFS and TOT. Assuming that all the curves are Weibulls pulls in the PFS curves but leaves the OS curves unaffected. As a consequence, the OS gains are unaffected but the model suggests that a smaller proportion of the patient gains will be during PFS and a larger proportion will be during PPS and after treatment with ixazomib has ceased. Since the quality of life values used by the company for PFS and PPS are not that different, this has only a limited impact upon the net QALY gains.

If drug costs are based upon the TOT curves, there is also relatively little impact upon the net costs and as a consequence the impact upon the cost effectiveness estimate of applying Weibulls throughout is relatively muted. But if the drug costs are based upon the PFS curves, pulling in the PFS curves reduces the net drug costs quite substantially with little effect upon the modelled patient gains, and the cost effectiveness estimate is reduced by a reasonable amount.

The following table illustrates the impact upon survival estimates of moving from the company base case to applying Weibulls throughout.

**Table 21-** ***Company base case vs Weibulls: survival gain estimates***

| | Base case | | Weibulls | | |
|---|---|---|---|---|---|
| Duration Tx effects | PFS | PPS | PFS | PPS | OS |
| Lifetime | 1.061 (68%) | 0.501 (32%) | 0.826 (53%) | 0.736 (47%) | 1.562 |
| 32 mths full, 10yr waning | 0.956 (77%) | 0.287 (23%) | 0.774 (62%) | 0.468 (38%) | 1.242 |
| 32 mths full, 5yr waning | 0.879 (86%) | 0.149 (14%) | 0.734 (71%) | 0.293 (29%) | 1.028 |
| 32 mths full, 2yr waning | 0.808 (101%) | -0.005 (-1%) | 0.669 (83%) | 0.134 (17%) | 0.803 |
| 32 mths full, 1yr waning | 0.776 (110%) | -0.070 (-10%) | 0.628 (89%) | 0.078 (11%) | 0.706 |
| 32 mths | 0.735 (123%) | -0.136 (-23%) | 0.572 (95%) | 0.027 (5%) | 0.599 |

The above show that with a lifetime treatment effect, the OS Weibull and the PFS gamma of the company base case suggests a total survival gain of 1.56 years, with roughly two thirds of the gain being in pre-progression. Even for the company base case, for one third of the survival benefit to occur after progression when patients have cease ixazomib

treatment may raise questions. But this proportion increases to only a little less than half if a PFS Weibull is applied and no adjustment for this is made to the OS curve.
If the full treatment effect is assumed to only apply for 32 months and then to wane to zero over the next two to five years, the curves of the company base case suggest that most if not all of the anticipated survival gains occur pre-progression. The post-progression survival gains fall to 14% of the total survival gains if the treatment effect wanes over the next five years and effectively to zero if the treatment effect wanes over the next two years. But applying a Weibull for the PFS suggests that a five year treatment waning effect after 32 months still results in a net PPS survival gain that is 29% of the total survival gain. Even if the waning effect is only over two years, the net PPS survival gain is 17% of the total survival gain.

The above changes to the survival estimates result in the following cost effectiveness estimates when drug costs are based upon the PFS curves.

**Table 22-** ***Company base case vs Weibulls: Cost effectiveness estimates***

| | Base case | | | Weibulls | | |
|---|---|---|---|---|---|---|
| Duration Tx effects | ΔQALYs | ΔCosts | ICER | ΔQALYs | ΔCosts | ICER |
| Lifetime | 0.981 | £176,649 | £180,166 | 0.975 | £135,174 | £138,741 |
| 32 mths full, 10 year waning | 0.806 | £172,655 | £214,275 | 0.801 | £134,447 | £167,914 |
| 32 mths full, 5 year waning | 0.684 | £169,559 | £247,934 | 0.680 | £132,696 | £195,254 |
| 32 mths full, 2 year waning | 0.550 | £166,428 | £302,895 | 0.546 | £129,390 | £237,367 |
| 32 mths full, 1 year waning | 0.490 | £164,879 | £336,985 | 0.485 | £127,290 | £262,674 |
| 32 mths | 0.422 | £162,874 | £386,560 | 0.416 | £124,340 | £298,850 |

As shown in the above, applying Weibulls throughout has only a relatively muted impact upon the net QALY estimates due to the quality of life values for PFS and PPS being similar. But if there is no waning of treatment effects and drug costs are based upon the PFS curves, as in the above, applying the Weibull for the PFS pulls in the curves reduces the drug costs and so improves the cost effectiveness estimates by a reasonable degree.

The move from an exponential to a Weibull for the ToT curves has relatively little impact, and if drug costs are based upon the ToT curves the cost effectiveness estimates are not much affected.

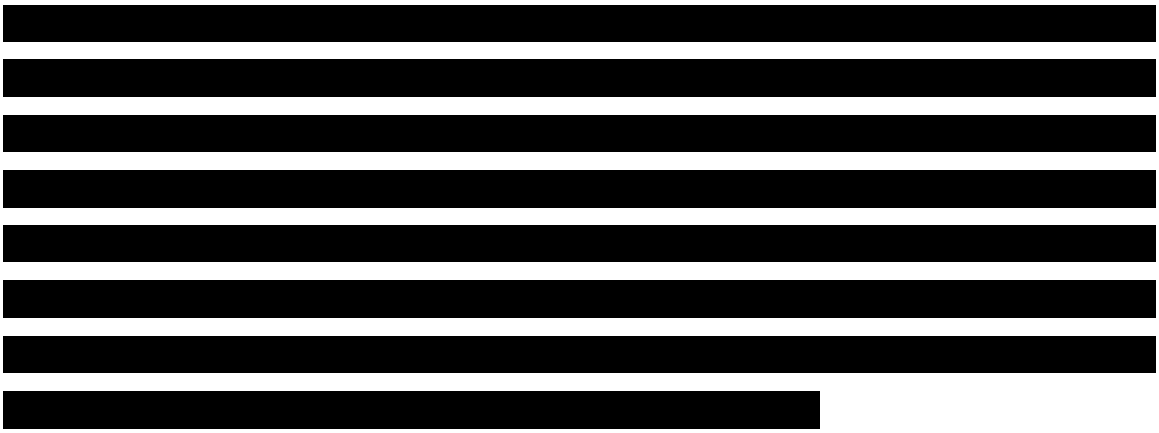
Given the concerns around the balance between the additional survival that occurs in pre-progression to that which occurs post-progression, the Weibulls can be retained for the ToT and PFS curves with the functional forms of the OS curves being varied. This revises the company base case when costed using the PFS curve as follows.

**Table 23-** ***Different OS functional forms with PFS and ToT Weibulls***

| | LY | % PFS | QALY | Cost | ICER |
|---|---|---|---|---|---|
| OS Exponential | 2.522 | 33% | 1.382 | £138k | £99,685 |
| OS Weibull | 1.562 | 53% | 0.974 | £135k | £139k |
| OS Gompertz | 0.992 | 81% | 0.672 | £135k | £202k |
| OS Lognormal | 2.231 | 37% | 1.193 | £138k | £116k |
| OS Log-Logistic | 1.949 | 42% | 1.084 | £138k | £127k |
| OS Gamma | 2.162 | 38% | 1.195 | £138k | £115k |

Examining the exponential, Weibull and gompertz, the highest survival gain is achieved with the exponential at 2.5 years but only a relatively small minority of this, 33%, is experienced during PFS. The Weibull has already been examined and suggests 53% of the additional survival accruing during PFS. The gompertz suggests the smallest overall survival gain of only 0.992 years, but estimates that 81% of this accrues during progression free survival. The AIC and the BIC for the OS exponential, Weibull and gomperts are not that dissimilar.

In the light of the above, if the Weibull is to be retained for OS it may be more reasonable to retain the curves of the company base case throughout than to assume that all curves are Weibulls despite the intuitively appealing effect this has in terms of aligning the ToT curve with the PFS curve. Given the immaturity of the OS data this may be putting the OS "cart" before the PFS "horse", in which case if the Weibulls are preferred for the PFS there may be an argument for considering the gompertz for overall survival.



The above underlines the need to review not only the information criteria of the OS curves, but also to review the modelled balance between PFS survival gains and PPS survival gains and how the assumed duration of treatment effect changes the OS, PFS and PPS survival estimates, when choosing which curves should be applied.

*PFS and ToT KM and parameterised curves [ACD Section 3.21]*

The parameterised PFS and ToT curves show little difference during the period of the trial when reasonable numbers of patients remain at risk. They only really diverge during extrapolation. This can be explored further by juxtaposing the company PFS and ToT Kaplan Meier curves, together with the numbers at risk and the ratio of the areas under the KM curves (AUCs) as below for the 2+ prior therapies subgroup.

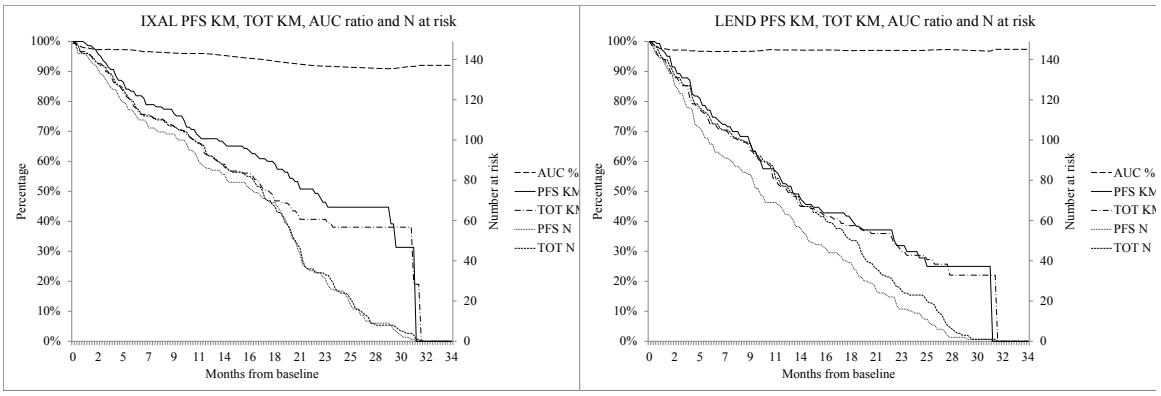



**Figure 15-** ***PFS and ToT KM curves: 2+ prior therapies subgroup***

There is some evidence within the IXA+LEN+DEX Kaplan Meier data that after about one year the ToT curve shows some divergence from the PFS curve, with this divergence looking to be roughly constant over the second year. The curves then come together again, but this is during the period when the numbers at risk begin to fall off. The ratio of the AUCs drops during the first two years to a low of 91% before broadly stabilising, with a slight increase to the end of the data-cut. The parameterised curves of the company base case suggest a similar divergence during this period with the ratio of the AUCs being in line with the 91% of the Kaplan Meier curves. But during the extrapolation period the parameterised curves diverge rather more dramatically, with the ratio of the lifetime AUCs of the parameterised curves being only 62%[b].

There seems to be no evidence within the LEN+DEX Kaplan Meier data for the modelled extent of divergence of the ToT curve from the PFS curve. The ratio of the AUCs shows an initial slight drop but is then broadly stable at 97%. This is in contrast to the parameterised curves of the company base case, which suggest that the curves

[b] Calculated as 2.196 years ToT to 3.553 years PFS. Note also that this is the ratio of the AUCs of the TOT curve to the PFS curve curtailed by the OS curve. The ratios of the uncurtailed curves would be lower than this.

subsequently diverge quite dramatically with the ratio of the lifetime AUCs of the parameterised curves being only 69%[c].

The modelled differences between the ToT curve and the PFS curve occur largely during extrapolation. There appears to be little to no evidence that the ToT curve and the PFS curve for LEN+DEX diverge much, a position that the company highlighted during the 1st AC. But the extrapolation for LEN+DEX suggests an AUC for the ToT curve that is only 69% that of the PFS curve.

There is evidence that the ToT curve and the PFS curve for IXA+LEN+DEX diverge during the trial, with the AUC of the ToT curve falling to perhaps a little over 90% that of the PFS curve. But the extrapolation suggests an AUC for the ToT curve that is only 62% that of the PFS curve. The credibility of the extrapolated 62% for IXA+LEN+DEX has to be read alongside the 69% extrapolation for LEN+DEX for which there appears to be limited evidence. That said, it should be borne in mind that the ToT parameterised curves for IXA+LEN+DEX and LEN+DEX have been estimated as a single function with a treatment coefficient and so the shapes of the curves for each arm are to a degree bound together. The same applies for the PFS curves.

As reviewed in the section that applies Weibulls for OS, PFS and ToT, the divergence between the ToT parameterised curves and the PFS parameterised curves is in large part due to different functional forms being applied to them in the company base case. The gamma of the PFS has a somewhat longer tail than the exponential of the ToT, whereas they are roughly equalised if Weibulls are applied for both.

[c] Calculated as 1.599 years ToT to 2.323 years PFS. Note also that this is the ratio of the AUCs of the TOT curve to the PFS curve curtailed by the OS curve. The ratios of the uncurtailed curves would be lower than this.

*ToT and PFS events and censoring*

The construction of the PFS Kaplan Meier curves and the definition of events and censoring events is pre-specified. The construction of the ToT Kaplan Meier curves and the definition of events and censoring events is not pre-specified and has been undertaken by the company. The company has provided the patient numbers for the 2IA data cut by arm for patients split into whether patients discontinued treatment due to progression, adverse event, withdrawal from the study, the study term[d], protocol violation, other reason or remained on treatment at the time of the data cut. These patients are further split into whether

- they had been measured as having progressed prior to the 2IA data cut
- they had had at least one measure of being progression free and no subsequent measure of progression prior to the 2IA data cut
- they had not had their progression status measured between randomisation and the 2IA data cut.

The ERG assumes that within the construction of the PFS curve patients falling into the first category would be deemed to have had a PFS event, and that patients falling into the second and third categories would be treated as PFS censored[e].

Note that the degree of LOCF that is within the PFS status data was not asked for by the ERG and is not available. Also note that the arguments here are not particularly concerned with the differences between LEN+DEX and IXA+LEN+DEX but rather with how fast the ToT KM curves are modelled as falling below the PFS curves.

[d] The ERG does not know how this differs from remaining on treatment at the data cut.

[e] The company reports that patients who died were assigned a progression event at time of death.

**Table 24-** ***Events and censoring events for the ToT curves***

| | Prog. | AE | Withdr. | S. Term. | Pr. Viol. | Other | 2IA[f] |
|---|---|---|---|---|---|---|---|
| LEN+DEX | | | | | | | |
| Prog before 2IA | 57 | 4 | 1 | 0 | 0 | 0 | 4 |
| Prog free at 2IA | 0 | 20 | 8 | 1 | 0 | 1 | 42 |
| Prog status 2IA n.a. | 0 | 6 | 4 | 0 | 1 | 0 | 0 |
| Total | 57 | 30 | 13 | 1 | 1 | 1 | 46 |
| IXA+LEN+DEX | | | | | | | |
| Prog before 2IA | 46 | 3 | 0 | 0 | 0 | 0 | 1 |
| Prog free at 2IA | 0 | 19 | 9 | 1 | 0 | 3 | 59 |
| Prog status 2IA n.a. | 0 | 2 | 5 | 0 | 0 | 0 | 0 |
| Total | 46 | 24 | 14 | 1 | 0 | 3 | 60 |

The last column gives the number of patients within the category at the 2IA data cut. The ERG is confused that any progressing before the 2IA data cut should be within this column, but it may be that their progression was measured at the 2IA data cut or that they continued with treatment after their progression was measured.

The company model contains the facility to model patients who remain on treatment at the time of the data cut to be modelled as stopping treatment at that point; i.e. to be treated as an event rather than as a censoring event within ToT curves. The company describes this as "*ToT based on duration of treatment observed in the TMM1 trial*" (which is slightly misleading though literally correct), and labels it the DoT analysis within the model. By definition it causes the proportion remaining on treatment at the data cut to fall to zero at the end of the data cut. This example clearly illustrates that the company has exercised choice about which events should be defined as events and which as censoring events in its construction of the ToT curves.

[f] The company labels this as "censor" and notes that "The only event that causes a patient to be "censored" for this outcome is if the patients are still on treatment at time of cut-off."

The company base case treats those who remain on treatment at the time of the data cut as being censored in the ToT KM curve, which is as it should be. The company base case assumes that all the other events should be treated as events and not as censoring events. It is not as clear that this should be the case and it may drive an artificial wedge between the PFS curve and the ToT curve. The ERG assumes that the patients who withdraw from therapy and are progression free or of unknown progression status at the 2IA data cut, (of whom there is a reasonably substantial number), are treated as being censored in the PFS curve at the 2IA data cut. In other words they are events for the company ToT curves and cause the ToT curves to drop but are censoring events for the PFS curves and do not cause the PFS curves to drop.

A similar concern is that those stopping due to adverse events and not having had progression might be more likely to subsequently progress due to being off treatment than those remaining within the trial. Again, there may be an artificial wedge being driven between the ToT curves and the PFS curves. But this may be more problematic. It could be argued that events in the ToT curve are informative in terms of the likelihood of subsequent progression and that these patients should not be treated as censored in the PFS curve in the same manner as those in the PFS curve who are censored due to remaining progression free at the data cut.

What is clear is:

- The company and not the trial protocol defines how the ToT curves are constructed.
- The company has explored treating the end of the data cut as events. This causes the ToT curves to fall the fastest.
- The company base case treats all events other than the end of the data cut as events. Of the possible assumptions, this causes the ToT curves to fall the next fastest.

*BoR and assessment of number of prior therapies*

Section 1 above has highlighted that the 2+ prior therapies subgroup of 2IA data set can be defined in two ways: Investigator assessed and Blinded Medical Review assessed. The company used the BoR rates for Investigator assessed as outlined below.

**Table 25-** ***BoR patient numbers: Investigator assessed 2+ prior therapies patients***

| | Missing | PD | SD | PR | VGPR+ | N |
|---|---|---|---|---|---|---|
| IXAL | 11 | 7 | 11 | 39 | 80 | 148 |
| LEND | 16 | 8 | 26 | 45 | 54 | 149 |

*PD = progression; SD= stable disease; PR= partial response; VGPR+ =very good partial response and more*

The ERG clinical review has highlighted that BoR PR and VGPR+ patient numbers change when the number of therapies is defined by the Blinded Medical Review assessment. In order to provide estimates of the BoR SD and PD response categories the ERG has been forced to make a number of assumptions. The simplest that can be made is that the numbers of patients with missing data and the number of patients assessed with a BoR of PD does not change between Investigator assessed and Blinded Medical Review assessed. Note that these will not be correct as the number of 2+ prior therapies patients falls by more in the IXA+LEN+DEX arm than the LEN+DEX arm when assessed by Blinded Medical Review.

**Table 26-** ***BoR patient numbers: Blinded Medical Review assessed 2+ prior therapies patients***

| | Missing | PD | SD | PR | VGPR+ | N |
|---|---|---|---|---|---|---|
| IXAL | 11 | 7 | 36 | 12 | 70 | 136 |
| LEND | 16 | 8 | 33 | 34 | 54 | 145 |

*PD = progression; SD= stable disease; PR= partial response; VGPR+ =very good partial response and more*

The main effect of the Blinded Medical Review patient numbers, some of which are inferred, is to reduce the gain from IXA+LEN+DEX over LEN+DEX in the proportions

of patients with BoRs of PR and VGPR+ and to broadly equalise the proportion with BoRs of SD. The ERG will provide a scenario analysis that applies the Blinded Medical Review BoR rates, as estimated above. This is illustrative of what the effect is upon response rates, these determining the quality of life values that are applied within the model.

The possible impact upon the parameterised curves from applying the Blinded Medical Review assessment of 2+ prior treatments cannot be explored by the ERG. The ERG assumes that the parameterised curves are based upon the Investigator assessment of 2+ prior treatments. Given the changes to the VGPR+ and PR BoR rates that occur when the Blinded Medical Review assessment of 2+ prior treatments is applied, it is possible that there may be parallel effects upon the parameterised curves, which would be anticipated to worsen the cost effectiveness estimate for IXA+LEN+DEX. The degree of sensitivity of results to this cannot be determined by the ERG.

*Quality of life analyses*

The company has provided three quality of life functions, all based upon repeated measures analysis. The original submission regressed 1IA data cut quality of life data on patients' best overall response (BoR) provided that patients' BoR was stable disease or better, and assessed the effect of progressive disease by the subset of EQ-5D responses subsequent to progression being measured. The current submission regresses 2IA data cut quality of life data on patients' contemporaneous response state. To provide a bridge between these, at clarification the company provided the parallel analysis to the current submission that uses the 1IA data cut. Note that the original quality of life regression was on the log scale and that the values below have been transformed into natural units.

**Table 27-** ***Company quality of life regressions***

| | BoR | Contemporaneous response | |
|---|---|---|---|
| | 1IA | 1IA | 2IA |
| Intercept | 0.712* | 0.810* | 0.806* |
| VGPR+ | .. | reference | reference |
| PR | .. | -0.007 | 0.001 |

| | | | |
|---|---|---|---|
| SD | .. | -0.028* | -0.011 |
| BoR – VGPR+ | reference | .. | .. |
| BoR – PR | -0.037* | .. | .. |
| BoR – SD | -0.059* | .. | .. |
| PD | -0.058* | -0.046* | -0.038* |
| Grade 3/4 AE | -0.016 | -0.029* | -0.031* |
| Hospitalised | -0.071 | -0.091* | -0.091* |
| New primary malignancy | -0.300* | .. | .. |
| Death within 3 months | -0.132* | -0.130* | -0.106* |
| Age - years | .. | -0.001 | -0.001 |
| Male | .. | -0.061* | 0.055* |
| White race | .. | -0.051* | -0.059* |
| Cumulative patient char** | .. | -0.076 | -0.017 |
| * significant at 5%<br>**Based upon the 1st cycle of the model which applies a baseline reference age of 0 years, 56% male and 82% white race. This is an ERG summation and is not assessed for statistical significance. | | | |

The above estimates result in the following quality of life estimates for patients without a grade 3/4 adverse event, hospitalisation, new primary malignancy or death within 3 months. The first three columns are based upon ERG calculations while the company reported values that are "*based upon the mean of covariates*" on page 31 of **Error! Reference source not found.** of the current submission are in the final column. Note that the company estimates "*based upon the mean of covariates*" are only within the text of the submission and are not applied in the model.

**Table 28- Quality of life estimates by response category**

| | ERG | | | Company |
|---|---|---|---|---|
| | BoR QoL | Contemporaneous response QoL | | |
| | 1IA | 1IA | 2IA | 2IA |
| VGPR+ | 0.712 | 0.734 | 0.789 | 0.689 |
| PR | 0.674 | 0.727 | 0.790 | 0.690 |
| SD | 0.653 | 0.706 | 0.778 | 0.678 |
| PD | 0.654 | 0.688 | 0.751 | 0.650 |

Within the ERG calculated values it is immediately noticeable that the quality of life values for the 1IA BoR analysis are lower than those for the 1IA contemporaneous response analysis. This is much as would be expected since for; e.g. VGPR+ the BoR analysis will include SD, PR and VGPR+ responses while the contemporaneous response analysis will only include VGPR+ responses.

Another aspect worth noting is that the quality of life values for the 1IA contemporaneous response analysis are somewhat lower than those of the 2IA analysis. If these were BoR based estimates this might be anticipated, since the time prior to attaining the BoR would be a larger proportion of the follow up for the 1IA data cut than for the 2IA data cut. But within the contemporaneous analysis there is no obvious reason why this should occur. The company regressions suggest that among patients who retain e.g. a PR response, their quality of life continues to improve over time.

The ERG calculated values for the 2IA analysis are all virtually exactly 0.1 higher than the company "*mean of covariate*" values. The ERG reported values are however in line with the modelled quality of life estimates for PFS and PD, excluding the effects of grade 3/4 adverse event, hospitalisation, new primary malignancy or death within 3 months as outlined below.

**Table 29-** ***ERG quality of life estimates applying BoR rates to company coefficients***

| | BoR QoL | | | Contemporaneous response QoL | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1IA | | | | | | 2IA | | |
| | QoL | BoR rates | | QoL | BoR rates | | QoL | BoR rates | |
| | | LEND | IXAL | | LEND | IXAL | | LEND | IXAL |
| VGPR+ | 0.712 | 38% | 59% | 0.734 | 38% | 59% | 0.789 | 43% | 62% |
| PR | 0.674 | 41% | 31% | 0.727 | 41% | 31% | 0.790 | 36% | 30% |
| SD | 0.653 | 21% | 10% | 0.706 | 21% | 10% | 0.778 | 21% | 8% |
| PFS QoL | | 0.685 | 0.695 | | 0.725 | 0.729 | | 0.787 | 0.788 |

A key element of the above is the difference between the PFS QoL values derived from applying the 1IA BoR rates to the 1IA BoR analysis and the PFS QoL values derived

from applying the 1IA BoR rates to the 1IA contemporaneous response analysis. This is as would be expected due to the latter unfortunately applying BoR rates to a contemporaneous response analysis. This will bias the PFS QoL estimates to be too high. A similar bias will apply in when applying the 2IA BoR rates to the 2IA contemporaneous response analysis, as in the company base case.

The other aspect to note is that despite the 2IA and 1IA BoR rates being fairly similar the estimated PFS quality of life from the 2IA contemporaneous analysis is noticeably higher than that of the 1IA contemporaneous analysis, due to the higher quality of life values in the 2IA analysis.

During clarification the ERG asked the company to clarify what was the reference age. The company response was:

> "*No reference category for age is applicable in the statistical regression model, as age is included as a continuous predictor. The coefficient for age indicates how much the utility score is expected to decrease when age increases by one unit (i.e. one year) (interpretation is consistent with that from linear regression modelling adjusting for a continuous covariate).*"

The ERG interpretation of this is that the age coefficient relates to the number of years the data point is subsequent to patient trial entry. As a consequence the model should apply the age coefficient to the time since baseline and not to the patient age, but this remains unclear.

It can be noted that in the contemporaneous response analyses the 1IA data cut estimates progressive disease compared to a VGPR+response to cause a reduction of -0.046 in quality of life. The 2IA analysis with a longer duration of PD follow-up suggests a smaller reduction of -0.038, or 82% of the 1IA estimate. The confidence interval for the 1IA data cut is slightly wider than that of the 2IA data cut and there is considerable overlap between them, but there has been a general upward shift in the central estimate and confidence intervals in the move from the 1IA data cut to the 2IA data cut.

The company stresses that the difference between stable disease and progressive disease is larger for the contemporaneous 2IA analysis than the BoR 1IA analysis. This is correct, and is also correct when comparing contemporaneous 1IA analysis with the contemporaneous 2IA analysis which is the more appropriate comparison.

The above estimates do not take into account the number of prior treatments. The company has provided an additional analysis that does so for the 2IA data cut at clarification, the coefficient for which is -0.003 for the 2+ prior compared to the 1 prior which is not statistically significant and has a 95% confidence interval that is broadly symmetric about zero [-0.038, 0.033].

The key aspect of the above is that the company has chosen to apply BoR rates to the contemporaneous response coefficients. It would be anticipated that a patient with a contemporaneous VGPR+ would have on average have a higher quality of life than the average of patients with a BoR of VGPR+, but the proportion of time spent with a contemporaneous VGPR+ will be less than that of a BoR of VGPR+, since by definition the duration of a BoR of VGPR+ is either the duration of the patient's PFS or the duration of the patient's follow-up. In effect the company has assumed that patients with a BoR of VGPR+, instantaneously attain VGPR+ and remain in VGPR+ until the point of progression.

The intention of the ERG in suggesting that contemporaneous response might be better when analysing quality of life was that the BoR analysis in effect assumed that patients' mean response for a given BoR response would apply throughout their PFS. Analysing quality of life by contemporaneous response would avoid this, but would also require an explicit consideration of the time to best overall response, the duration of best overall response and how best overall response is lost as a patient worsens and moves towards progression. The ERG expectation was that this would probably benefit IXA+LEN+DEX, since the arm with the longer duration of PFS would probably be

modelled as having a greater proportion of PFS spent with a contemporaneous response equal to the BoR.

Since the ERG only has access to BoR data, the ERG will apply the 2IA BoR data to the 1IA BoR QoL estimates, as this uses the most up to date response estimates and the most up to date quality of life values that are of the same form as these response estimates[g]. When applying the BoR rates it would have been desirable to also have an 2IA updated regression of the 1IA BoR analysis, but unfortunately the ERG did not ask for this at clarification.

Given the company stress upon the difference in the SD and PD estimates for the 2IA contemporaneous response estimates, the ERG will provide a scenario analysis that applies this, -0.038 - -0.011 = -0.027, but it should be noted that this mixes BOR quality of life estimates with the contemporaneous response quality of life estimates.

The ERG will also provide a scenario analysis that applies the estimates of the revised company base case. Given the importance of the quality of life estimates to the cost effectiveness estimates, the ERG will provide multivariate analyses that apply the company quality of life estimates alongside other changes.

The values derived by the ERG from the company regressions can be compared with those of previous NICE assessments.

**Table 30-** ***Quality of life values in previous NICE assessments***

| | BoR | Contemporaneous resp. | | | |
|---|---|---|---|---|---|
| | 1IA | 1IA | 2IA | TA171 | TA338 |
| VGPR+ | 0.712 | 0.734 | 0.789 | 0.810 | 0.750 |
| PR | 0.674 | 0.727 | 0.790 | 0.810 | 0.750 |
| SD | 0.653 | 0.706 | 0.778 | 0.810 | 0.650 |

[g] Note that due to the revised company model structure this still applies the 2IA contemporaneous response age coefficient.

| | | | | | |
|---|---|---|---|---|---|
| PD | 0.654 | 0.688 | 0.751 | 0.640 | 0.610 |

The ERG will provide scenario analyses that apply the quality of life values of TA171[4], of TA338[5] and the company "*mean of covariates*" values.

None of the company analyses, the ERG analyses or the scenario analyses factor in the effect of the further worsening of patients' quality of life following progression after subsequent therapies, though the age coefficient is applied, as is the end of life coefficient.

*Subsequent treatment costs modelled as weekly costs [ACD Section 3.22]*

For the 1st submission using the 1IA data cut, the company estimated a treatment rate post progression of 24%. The ERG revised this to 41% and the company agreed that this revision was appropriate. These calculations have been revised by the company using the 2IA data cut as outlined below.

**Table 31-** ***Numbers of treatments post-progression***

| Data cut | 1IA | 2IA | | |
|---|---|---|---|---|
| Patient group | All | 2+ IXAL | 2+ LEND | 2+ |
| Sample size | 722 | 148 | 149 | 297 |
| Number of patients progressing by 2IA | 433 | [redacted] | [redacted] | 151 |
| Patient years of PPS follow-up | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean years follow-up per PPS patient | [redacted] | [redacted] | [redacted] | [redacted] |
| Number of patients receiving at least 1 PPS Tx | 176 | [redacted] | [redacted] | 99 |
| % PPS patients receiving at least 1 PPS Tx | 41% | [redacted] | [redacted] | 66% |
| Number of PPS treatments | | [redacted] | [redacted] | |
| Bendamustine + Prednisolone | 18 | [redacted] | [redacted] | 11 |
| Cyclophosphamide | 63 | [redacted] | [redacted] | 41 |
| Doxorubicin | 16 | [redacted] | [redacted] | 9 |
| Bortezomib | 99 | [redacted] | [redacted] | 53 |
| Carfilzomib | 13 | [redacted] | [redacted] | 6 |
| Lenalidomide | 27 | [redacted] | [redacted] | 21 |
| Melphalan | 24 | [redacted] | [redacted] | 18 |

| | | | | |
|---|---|---|---|---|
| Pomalidomide | 25 | [redacted] | [redacted] | 20 |
| Thalidomide | 28 | [redacted] | [redacted] | 12 |
| Total number of PPS treatments | 313 | [redacted] | [redacted] | 191 |
| Per PPS patient | [redacted] | [redacted] | [redacted] | [redacted] |
| Per PPS patient that received Tx | [redacted] | [redacted] | [redacted] | [redacted] |
| Per year of PPS follow-up | [redacted] | [redacted] | [redacted] | [redacted] |

The company states that:

> "*In response to comments in Section 3.22 of the ACD, the inclusion of weekly cycle costs has been considered in the economic analysis for costs relating to post-progression treatments*."

In the opinion of the ERG while this could be seen as being literally and arithmetically correct it is misleading of the company to present it in this way. For those receiving PPS anti-cancer therapy the company estimates a treatment initiation cost of £1,081 and a total one-off post progression treatment cost of £78,607 for the 2+ prior therapies subgroup[h]. The same £78,607 one off cost is applied in both arms regardless of the duration of PPS.

The reason that the company can claim to apply weekly post progression treatment costs is that the one-off total cost of £78,607 for the 2+ prior therapies subgroup is divided by the modelled duration of post progression survival: 111 weeks for IXA+LEN+DEX and 85 weeks for LEN+DEX. This yields weekly costs of £708 for IXA+LEN+DEX and £927 for LEN+DEX. When these are multiplied by the durations of post progression survival they result in undiscounted post progression treatment costs of £78,607 for both IXA+LEN+DEX and LEN+DEX. The exercise appears to be circular.

The ERG considers that it would have been more reasonable for the company to simply state that for the 2+ prior therapies subgroup, corresponding to 3rd and 4th line based on

[h] The company assumes that those receiving bortezomib + dexamethasone, carfilzomib + dexamethasone and pomalidomide + dexamethasone during PPS follow up during the trial, [redacted] of the total, would in the NHS receive panobinostat + bortezomib + dexamethasone.

the data from the trial, it applies a one off post progression treatment cost of £78,607. The unstated company assumption is that the number of treatments patients receive post progression and the length and the likelihood of these treatment course being curtailed are unaffected by the duration of their post progression survival. The revised company base cases estimate an additional 26 weeks post progression survival for IXA+LEN+DEX compared to LEN+DEX for the 2+ prior therapies subgroup.

ERG clinical opinion is that among patients progressing after 3rd or 4th line there is a limited number of further treatments that can be received. This will provide a maximum treatment cost that can be incurred per PPS patient that receives further treatment. But the actual number of further treatments and possibly also their duration will be limited by a patient's PPS duration.

The mean trial follow-up per PPS patient is slightly but not markedly less in the IXA+LEN+DEX arm compared to the LEN+DEX arm. Despite this, the mean number of treatments per PPS patient is slightly higher in the IXA+LEN+DEX, mainly due to the proportion receiving PPS treatment being higher at [redacted] compared to [redacted] for LEN+DEX. There is no obvious reason to anticipate this.

It might be anticipated that the proportion of PPS patients who receive therapy will tend to rise at subsequent data cuts due to a longer duration of PPS follow-up. Unfortunately, for the 1IA data cut the ERG only has data for all patients, while for the 2IA data cut, it only has data for the 2+ prior therapies subgroup. It cannot be unambiguously stated from the above data that the proportion of 2+ prior therapies PPS patients who received subsequent treatment was higher in the 2IA data cut than in the 1IA data cut, but it seems highly likely. This argues for a sensitivity analysis that increases the proportion of PPS patients who receive a PPS treatment and in the absence of other evidence the ERG will present a scenario analysis where 100% of PPS patients receive PPS treatment.

The above data also has a higher number of treatments per year of PPS follow-up in the IXA+LEN+DEX arm compared to the LEN+DEX arm. This is despite a shorter mean PPS follow-up in the IXA+LEN+DEX, which might tend to suggest that PPS treatments are front loaded with a cap to the total number that can be administered. But the differences are not large, particularly in the mean years of PPS follow-up which is also not specific to the subgroup of PPS patients who receive treatment. It is difficult to conclude much with confidence about these considerations from the above data.

In the light of the above, ERG opinion is that a longer PPS will typically increase

- the likelihood of a patient receiving PPS treatment;
- the likelihood of a PPS course of treatment being completed; and
- the number of PPS treatments that are received.

But it also seems likely that there will be an upper limit of the number of PPS treatments that can be received by patients progressing after 3rd or 4th line. Based on currently recommended treatments, panobistonat, pomalidomide and bendamustine, this suggests to the ERG an upper limit of three further treatments.

In the absence of other evidence, the above would seem to argue for applying a common probability of patients receiving a PPS treatment. At a minimum a sensitivity analysis that equalises the weekly PPS treatment cost between IXA+LEN+DEX and LEN+DEX is required. This might even form the base case if an appropriate cap to the number of weeks of PPS treatment could be arrived at and implemented within the model, but this is far from straightforward within the company model structure[i] and has not been undertaken by the ERG.

For the 34% of patients modelled as not receiving post progression treatment it is assumed that these receive monthly outpatient follow up with some additional blood tests.

[i] Among other things it requires the incidence of progression to be modelled which is not entirely straightforward within a partitioned survival analysis.

At an absolute minimum the model should also apply this cost for the periods spent off treatment among those receiving some treatment post progression. The ERG will apply this for its revised base case.

## 2.6 Exploratory ERG analyses

As previously noted, the company provides a PAS which is a simple [redacted] reduction in the list price, reducing the four weekly cost per pack of ixazomib from £6,336 to [redacted]. This reduces the annual cost of ongoing dosing with ixazomib from £82,651 to [redacted]. All cost effectiveness estimates in this chapter are inclusive of the [redacted] PAS.

*ERG analyses performed*

Whether the direct drug costs should be based upon the PFS curves or the TOT curves is central to the analysis. The reasonableness of the extrapolated TOT curves AUCs as a proportion of the PFS curves AUCs complicates this. As a consequence, the ERG presents two full sets of analyses. The first costs treatment based upon the TOT curves and the second based upon the PFS curves.

Other than permitting the drug costs to be based upon the PFS curves, the ERG has made minimal revisions to the company base case. It has:

- Applied the 2IA BoR rates to the BoR quality of life regression and
- Applied the weekly PPS costs for those not receiving treatment to PPS patients who are between treatments.

The change to the quality of life function that is applied for the base case is the main revision. Without it the ERG revised base case that uses the ToT curve for costing purposes is little different from the company base case.

For completeness, the ERG runs through the various functional forms that are possible for the parameterised OS, PFS and ToT curves.

For the base case for the 2+ prior therapies subgroup, the ERG has used the Gamma, the exponential, and the Weibull curves for PFS, TOT, and OS respectively. For the base case for the 2 prior therapies subgroup, the ERG has applied the Weibull curves for PFS, TOT, and OS.

The ERG also presents the following sensitivity analyses.

- SA01: Retaining the same functional forms of the base case but applying the unadjusted curves
- SA02: Restricting the treatment effect to the 2IA median follow up of 23 months[j], to the 2IA maximum follow up of 32 months, and introducing a waning of the treatment effect over 1, 2, 5 and 10 years subsequent to 32 months.
- SA03: Applying the 2IA curves that the company chose to apply in its original submission: log-normal curves for OS and PFS and the gamma curve for ToT
- SA04: Applying a 0.028 QoL decrement for SD to PD, the TA171[4] QoL values, the TA338 QoL values, the 2IA mean of covariates values and applying the 2IA BoR rates to the coefficients of the 2IA contemporaneous response QoL regression.
- Applying the 2IA BoR rates to the 2IA contemporaneous response QoL regression coupled with:
    - SA05: No treatment effect beyond 32 months.
    - SA06: The 2IA curves that the company chose to apply in its original submission.
    - SA07: Equalising the PPS weekly costs between IXA+LEN+DEX and LEN+DEX and assuming that all PPS patients receive further active treatment.

[j] Note that this does not bring the curves immediately together but rather equalises the hazards between the arms. As a consequence, the model still estimates that there are net survival gains from IXA+LEN+DEX compared to LEN+DEX after 23 months.

  - SA08: Setting the costs of LEN+DEX in the IXA+LEN+DEX and the LEN+DEX arm equal to zero.
  - SA09: Applying the ToT to PFS AUC ratio to the drug costs.
- SA10: Applying the Medical Review assessment of 2+ prior therapies and associated BoR rates.
- SA11: Applying the company DoT curves for costing purposes.
- SA12: Equalising hospitalisation rates between the arms.
- SA13: Equalising the weekly PPS cost among those receiving further active treatments between the arms.
- SA14: Assuming that all PPS patients receive further active treatment.
- SA15: SA13 and SA14 combined.
- SA16: Setting the costs of LEN+DEX in the IXA+LEN+DEX and the LEN+DEX arm equal to zero.
- SA17: Applying the ToT to PFS AUC ratio to the drug costs.

*Revised ERG base case*

The current PAS and the ERG revised base case analyses for the 2+ prior therapies subgroup are as follows.

**Table 32-** ***ERG base case analyses with PAS, ToT costing, 2+ prior therapies subgroup***

| | Undisc. LY | | | QALYs | | | Costs | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | PFS | PPS | OS | PFS | PPS | Total | Drug | ConMed | Ongoing | Total |
| LEND | 2.289 | 1.626 | 3.914 | 1.435 | 0.963 | 2.371 | £71,452 | £6,717 | £54,616 | £132,786 |
| IXAL | 3.350 | 2.127 | 5.477 | 2.073 | 1.204 | 3.251 | £193,619 | £9,093 | £53,584 | £256,296 |
| Net | 1.061 | 0.501 | 1.562 | 0.638 | 0.240 | 0.880 | £122,166 | £2,376 | -£1,032 | £123,510 |
| ICER | | | | | | | | | | £140k |

The probabilistic modelling run over 10,000 iterations suggest a net cost of £137k, a net gain of 0.875 QALYs and a cost effectiveness estimate of £145k per QALY.

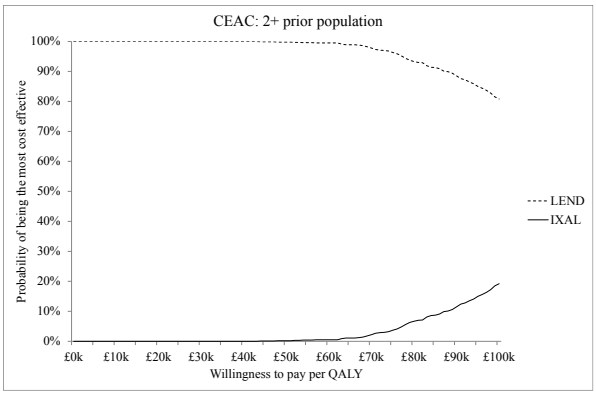



**Figure 16-** ***ERG base case analyses CEAC with PAS, ToT costing, 2+ prior therapies subgroup***

**Table 33-** ***ERG base case analyses with PAS, PFS costing, 2+ prior therapies subgroup***

| | Undisc. LY | | | QALYs | | | Costs | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | PFS | PPS | OS | PFS | PPS | Total | Drug | ConMed | Ongoing | Total |
| LEND | 2.289 | 1.626 | 3.914 | 1.435 | 0.963 | 2.369 | £74,909 | £6,717 | £55,233 | £136,858 |
| IXAL | 3.350 | 2.127 | 5.477 | 2.073 | 1.204 | 3.248 | £250,677 | £9,093 | £54,327 | £314,097 |
| Net | 1.061 | 0.501 | 1.562 | 0.638 | 0.240 | 0.879[k] | £175,768 | £2,376 | -£905 | £177,239 |
| ICER | | | | | | | | | | £202k |

The probabilistic modelling run over 10,000 iterations suggest a net cost of £177k, a net gain of 0.878 QALYs and a cost effectiveness estimate of £201k per QALY.

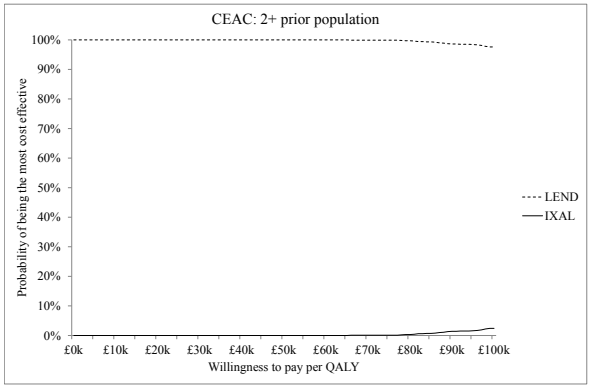



**Figure 17-** ***ERG base case analyses CEAC with PAS, PFS costing, 2+ prior therapies subgroup***

[k] Note that the gain of 0.879 QALYs is marginally different from the gain of 0.880 QALYs of the ToT costing analysis. The ERG has not been able to identify the reason for this.

*Revised ERG scenario analyses*

The ERG revised base case analyses for the 2+ prior therapies subgroup as follows.

**Table 34-** ***ERG OS scenario analysis with PAS, ToT costing, 2+ prior therapies subgroup***

| | Δ LY (%PFS) | Δ QALY | Δ Cost | ICER |
|---|---|---|---|---|
| Base case : OS Weibull | 1.562 (68%) | 0.880 | £124k | £140k |
| OS Exponential* | 2.522 (48%) | 1.238 | £124k | £100k |
| OS Gompertz* | 0.992 (85%) | 0.609 | £122k | £200k |
| OS Lognormal* | 2.231 (54%) | 1.074 | £125k | £116k |
| OS Log-Logistic* | 1.949 (62%) | 0.979 | £125k | £127k |
| OS Gamma* | 2.162 (56%) | 1.076 | £124k | £115k |

** PFS and TOT as in base case: Gamma and exponential curves respectively*

Applying the exponential for overall survival results in the largest survival gains of over 2.5 years. For the base case and the Weibull OS curves most survival gains, 68%, are experienced in PFS. With the exponential OS curves the minority of the gains, 48%, are in PFS. There is a clear pattern for the proportion of the gain in survival that is realised from increased progression free survival to fall as the modelled gain in survival increases.

The stability of the net costs illustrates how the company model applies a fixed treatment cost for PPS patients receiving subsequent treatment rather than a weekly cost.

**Table 35-** ***ERG PFS scenario analysis with PAS, ToT costing, 2+ prior therapies subgroup***

| | Δ LY | Δ QALY | Δ Cost | ICER |
|---|---|---|---|---|
| Base case : PFS gamma | 1.562 | 0.880 | £124k | £140k |
| PFS Exponential* | 1.562 | 0.874 | £121k | £139k |
| PFS Weibull* | 1.562 | 0.868 | £122k | £140k |
| PFS Gompertz* | 1.562 | 0.865 | £122k | £141k |
| PFS Lognormal* | 1.562 | 0.878 | £123k | £140k |
| PFS Log-Logistic* | 1.562 | 0.878 | £123k | £141k |

** OS and TOT as in base case: Weibull and exponential respectively*

When costing using the ToT curves, given the similarity of the PFS QoL value and the PPS QoL value the functional form for the PFS curve has little impact upon results.

**Table 36-** ***ERG TOT scenario analysis with PAS, ToT costing, 2+ prior therapies subgroup***

| | Δ LY | Δ QALY | Δ Cost | ICER |
|---|---|---|---|---|
| Base case : ToT Exponential | 1.562 | 0.880 | £124k | £140k |
| TOT Weibull* | 1.562 | 0.880 | £123k | £140k |
| TOT Gompertz* | 1.562 | 0.880 | £124k | £141k |
| TOT Lognormal* | 1.562 | 0.879 | £164k | £186k |
| TOT Log-Logistic* | 1.562 | 0.880 | £157k | £178k |
| TOT Gamma* | 1.562 | 0.880 | £127k | £145k |

** PFS and OS as in base case: Gamma and Weibull curves respectively*

The net costs are relatively insensitive to the choice of ToT curve, provided that the log-normal and log-logistic are discounted. Given their tails, the log-normal and log-logistic result in somewhat higher net costs and worsen the cost effectiveness estimate to £186k and £178k respectively.

**Table 37-** ***ERG scenario analyses with PAS, ToT costing, 2+ prior therapies subgroup***

| | Δ LY | Δ QALY | Δ Cost | ICER |
|---|---|---|---|---|
| Base case | 1.562 | 0.880 | £124k | £140k |
| SA01: Unadjusted Curves | 1.379 | 0.782 | £120k | £154k |
| SA02a: Tx Eff. 23 months | 0.432 | 0.295 | £110k | £374k |
| SA02b: Tx Eff. 32 months | 0.599 | 0.391 | £114k | £293k |
| SA02c: Tx Eff. 32 mths, 1yr waning | 0.706 | 0.450 | £116k | £258k |
| SA02d: Tx Eff. 32 mths, 2yrs waning | 0.803 | 0.503 | £118k | £234k |
| SA02e: Tx Eff. 32 mths, 5yrs waning | 1.028 | 0.620 | £120k | £194k |
| SA02f: Tx Eff. 32 mths, 10yrs waning | 1.242 | 0.727 | £122k | £167k |
| SA03: 1st Sub 2IA curves | 2.231 | 1.071 | £129k | £120k |
| SA04a: 2IA SD to PD QoL dec. | 1.562 | 0.869 | £124k | £142k |
| SA04b: TA171 QoL | 1.562 | 0.934 | £124k | £132k |
| SA04c: TA338 QoL | 1.562 | 0.888 | £124k | £139k |
| SA04d: 2IA QoL 2IA Mean of Covar | 1.562 | 0.854 | £124k | £145k |
| SA04e: 2IA contemp. response QoL | 1.562 | 0.981 | £124k | £126k |
| SA05: SA04e + SA02b | 0.599 | 0.422 | £114k | £271k |
| SA06: SA04e + SA03 | 2.231 | 1.202 | £129k | £107k |

| | | | | |
|---|---|---|---|---|
| SA07: SA04e + SA15 | 1.562 | 0.981 | £143k | £146k |
| SA08: SA04e + SA16 | 1.562 | 0.981 | £114k | £116k |
| SA09: SA04e + SA17 | 1.562 | 0.981 | £124k | £126k |
| SA10: Med Review 2+ prior for BoR | 1.562 | 0.865 | £124k | £143k |
| SA11: DoT drug costing | 1.562 | 0.880 | £81,430 | £92,485 |
| SA12: Equal Hospitalisation rates | 1.562 | 0.879 | £124k | £141k |
| SA13: Equal PPS weekly cost | 1.562 | 0.880 | £137k | £156k |
| SA14: All PPS treated | 1.562 | 0.880 | £122k | £139k |
| SA15: SA14 + SA15 | 1.562 | 0.880 | £143k | £162k |
| SA16: LEN and DEX zero cost | 1.562 | 0.880 | £114k | £130k |
| SA17: ToT to PFS AUC ratio applied | n.a. | n.a. | n.a. | n.a. |

The application of the unadjusted curves worsens the cost effectiveness estimate by around 10%. Limiting the duration of the treatment effect quite dramatically worsens the cost effectiveness estimate, even if the waning of effect is over the ten years subsequent to 32 months.

The parameterised curves that the company chose for the 2IA analysis of its original submission improve the cost effectiveness estimate by a reasonable amount.

Applying the mean of covariate quality of life values worsens the cost effectiveness by £5k per QALY. Applying the 2IA BoR rates to the 2IA contemporaneous response QoL analysis improves the cost effectiveness estimate by around 10%.

Using the company DoT curves dramatically improves the cost effectiveness estimate.

Equalising the weekly costs during post-progression survival between IXA+LEN+DEX and LEN+DEX somewhat worsens the cost effectiveness estimate, and if this is coupled with all PPS patients being treated the cost effectiveness estimate worsens by £22k per QALY or 16%.

If the costs of LEN+DEX are set to zero this improves the cost effectiveness estimate to £130k per QALY. The costs of LEN+DEX do make it harder for ixazomib to be cost effective when used in conjunction with LEN+DEX. But the costs of LEN+DEX are not in themselves the reason why the cost effectiveness estimate for IXA+LEN+DEX compared to LEN+DEX lies outside conventional NICE willingness to pay thresholds.

The sensitivity results when drug costs are estimated using the PFS curves is as follows.

**Table 38-** ***ERG OS scenario analysis with PAS, PFS costing, 2+ prior therapies subgroup***

| | Δ LY (%PFS) | Δ LY | Δ QALY | Δ Cost | ICER |
|---|---|---|---|---|---|
| Base case : OS Weibull | 1.562 (68%) | 1.562 | 0.879 | £177k | £202k |
| OS Exponential* | 2.522 (48%) | 2.522 | 1.237 | £189k | £153k |
| OS Gompertz* | 0.992 (85%) | 0.992 | 0.609 | £159k | £262k |
| OS Lognormal* | 2.231 (54%) | 2.231 | 1.073 | £190k | £177k |
| OS Log-Logistic* | 1.949 (62%) | 1.949 | 0.979 | £190k | £194k |
| OS Gamma* | 2.162 (56%) | 2.162 | 1.075 | £189k | £176k |

** PFS and TOT as in base case: Gamma and exponential curves respectively*

**Table 39-** ***ERG PFS scenario analysis with PAS, PFS costing, 2+ prior therapies subgroup***

| | Δ LY | Δ QALY | Δ Cost | ICER |
|---|---|---|---|---|
| Base case : PFS gamma | 1.562 | 0.879 | £177k | £202k |
| PFS Exponential* | 1.562 | 0.874 | £148k | £170k |
| PFS Weibull* | 1.562 | 0.868 | £136k | £157k |
| PFS Gompertz* | 1.562 | 0.865 | £132k | £153k |
| PFS Lognormal* | 1.562 | 0.878 | £170k | £194k |
| PFS Log-Logistic* | 1.562 | 0.878 | £170k | £194k |

** TOT and OS as in base case: Exponential and Weibull respectively*

**Table 40-** ***ERG scenario analyses with PAS, PFS costing, 2+ prior therapies subgroup***

| | Δ LY | Δ QALY | Δ Cost | ICER |
|---|---|---|---|---|
| Base case | 1.562 | 0.879 | £177k | £202k |
| SA01: Unadjusted Curves | 1.379 | 0.781 | £171k | £218k |
| SA02a: Tx Eff. 23 months | 0.432 | 0.294 | £158k | £537k |
| SA02b: Tx Eff. 32 months | 0.599 | 0.390 | £163k | £417k |

| | | | | |
|---|---|---|---|---|
| SA02c: Tx Eff. 32 mths, 1yr waning | 0.706 | 0.450 | £165k | £366k |
| SA02d: Tx Eff. 32 mths, 2yrs waning | 0.803 | 0.502 | £166k | £331k |
| SA02e: Tx Eff. 32 mths, 5yrs waning | 1.028 | 0.620 | £170k | £274k |
| SA02f: Tx Eff. 32 mths, 10yrs waning | 1.242 | 0.726 | £173k | £238k |
| SA03: 1st Sub 2IA curves | 2.231 | 1.071 | £180k | £168k |
| SA04a: 2IA SD to PD QoL dec. | 1.562 | 0.868 | £177k | £204k |
| SA04b: TA171 QoL | 1.562 | 0.934 | £177k | £190k |
| SA04c: TA338 QoL | 1.562 | 0.887 | £177k | £200k |
| SA04d: 2IA QoL 2IA Mean of Covar | 1.562 | 0.853 | £177k | £208k |
| SA04e: 2IA contemp. response QoL | 1.562 | 0.980 | £177k | £181k |
| SA05: SA04e + SA02b | 0.599 | 0.421 | £163k | £386k |
| SA06: SA04e + SA03 | 2.231 | 1.201 | £180k | £150k |
| SA07: SA04e + SA15 | 1.562 | 0.980 | £197k | £201k |
| SA08: SA04e + SA16 | 1.562 | 0.980 | £164k | £167k |
| SA09: SA04e + SA17 | 1.562 | 0.981 | £165k | £169k |
| SA10: Med Review 2+ prior for BoR | 1.562 | 0.864 | £177k | £205k |
| SA11: DoT drug costing | n.a. | n.a. | n.a. | n.a. |
| SA12: Equal Hospitalisation rates | 1.562 | 0.878 | £178k | £202k |
| SA13: Equal PPS weekly cost | 1.562 | 0.879 | £191k | £217k |
| SA14: All PPS treated | 1.562 | 0.879 | £176k | £200k |
| SA15: SA14 + SA15 | 1.562 | 0.879 | £197k | £224k |
| SA16: LEN and DEX zero cost | 1.562 | 0.879 | £164k | £187k |
| SA17: ToT to PFS AUC ratio applied | 1.562 | 0.879 | £165k | £188k |

The pattern of results is similar to that when using the ToT curves for drug costs, but as in the base case, the cost effectiveness estimates are somewhat worse.

# 3 END OF LIFE CONSIDERATIONS

In the original submission, the Company indicated that the currently available data for the Ixazomib regimen does not meet all of the NICE end-of-life criteria as further follow-up is warranted to determine the final benefit (CS, p152).

In the ACD response, the Company stated that they would like the AC to consider the IXA-LEN-DEX regimen under the revised EoL criteria for combination regimens.

The current end of life criteria are that:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.
- The estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review).
- The assumptions used in the reference case economic modelling are plausible, objective and robust.

The company appears to accept that the above end of life criteria 1 do not apply due to the patient life expectancy exceeding 24 months.

Regarding end-of-life criterion 2, using our preferred survival models, the mean life expectancy is 5.47 years for IXA-LEN-DEX and 3.91 years for LEN-DEX, this leads to an incremental 1.56 LYG (18.7 months gained). Overall, the ERG agree that Ixazomib fulfils criterion 2 for end-of-life treatment.

The NICE methods guide states that when the above end of life criteria are met the AC will consider the impact of giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age.

The ERG has amended the company model to permit this to be assessed. The quality of life values for a healthy individual of the same age are taken to be those reported in Table A of the CHE discussion paper 172 on UK population norms for EQ-5D, with the TMM-1 baseline age for the 2+ prior subgroup of 66 years being applied.

But it can be argued that while these are population norms they are not healthy individuals, particularly the older age groups. The 0.78 UK population norm for those aged 65-74 years is actually less than the company estimate of the mean baseline quality of life for PFS in the IXA+LEN+DEX arm of 0.787, and is not that much higher than the company estimate of the quality of life for PPS in the IXA+LEN+DEX arm of 0.749. As a consequence, this will also be assessed assuming that the additional survival is experienced at full quality of life; i.e. QoL =1, bearing in mind that this is an uppermost estimate and will be an over estimate[1].

*End of Life: Possible future criteria*

The company has asserted that NICE may permit the AC to judge that the end of life criteria apply if the following are met:

- The treatment is indicated for patients with a life expectancy normally more than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment; and,

[1] These are ERG additions to the company model and have not as yet been cross checked by the company.

- The new treatment is given in combination with an existing treatment and;
- Both treatments are licensed to be administered until disease progression

The above is relatively new and has not been formalised by NICE. The ERG is not aware of revised EoL criteria and is therefore unable to comment this. However, the ERG has noted that NICE has recently considered that Carfilzomib, which is another proteasome inhibitor used for people with multiple myeloma, does not meet the end-of-life criteria at first or second line since the modelled survival estimates were longer than 24 months. [6]

In the opinion of the ERG, the rationale for this may be a variant of the 'not cost effective at any price' argument. The DSU technical support document[7] that addressed treatments not being 'cost effective at any price' concluded that:

> "*Having considered the examples identified within the NICE TA programme and the methodological literature on this issue, we would argue that all costs which differ between the technology being appraised and the comparator technologies identified in the decision problem should be included within the ICER, provided they fall within the NHS and PSS perspective, as this provides an ICER which reflects the real opportunity cost of recommending the technology being appraised and is consistent with the objective of the NICE TA programme*."

The variation 'on the not cost effective at any price' argument appears likely to be that the costs of the other treatments in the combination therapy make it difficult for the new treatment to be cost effective when used in conjunction with them. It seems implicit within this that the costs of the other treatments in the combination therapy must be substantial. If the existing treatment was something cheap such as prednisolone and ixazomib had to be used in conjunction with it, in the opinion of the ERG it would be unlikely that the possible future end of life criteria would apply.

In the current context, ixazomib is used in conjunction with LEN+DEX. The longer PFS implies a longer duration of treatment with both ixazomib and LEN+DEX, and the

patient gains relative to the LEN+DEX arm need to be sufficient to justify the costs of both ixazomib and the additional LEN+DEX. Lenalidomide is quite costly, though there is a cycle cap to these costs. The additional LEN+DEX costs within the IXA+LEN+DEX triplet that arise from the longer PFS compared to the LEN+DEX arm consequently make it harder for IXA+LEN+DEX to be cost effective relative to LEN+DEX.

The company submission includes three options for the treatment of lenalidomide and dexamethasone costs, all with the proviso of the costs of lenalidomide being capped at a maximum of 26 treatment cycles:

- The base case of LEN+DEX costed in the IXA+LEN+DEX regimen as per standard methods using ToT and UK cost references.
- Exploratory scenario 2: Only additional LEN+DEX costed in the IXA+LEN+DEX regimen, over and above what is received in the LEN+DEX regimen. This scenario captures the additional cost of LEN+DEX required due to the increase in ToT associated with IXA+LEN+DEX
- Exploratory scenario 3: Additional LEN+DEX over and above what is received in the LEN+DEX regimen is not costed. This scenario only captures the cost of the LEN+DEX that would be received in current practice anyway.

Unfortunately, within the current submission the exploratory scenario analyses around the costs of LEN+DEX appear to have gone wrong, possibly due to the company inadvertently excising this facility from the electronic model.

It is difficult to reintroduce the original company scenario analyses to the revised company model with confidence. As a consequence, the ERG will present a scenario analysis that sets the costs of LEN+DEX to zero within both the IXA+LEN+DEX arm and the LEN+DEX arm. This is not presented as a realistic cost effectiveness estimate. It is an illustration of whether it is the costs of LEN+DEX that are driving the analysis and preventing ixazomib being cost effective at the conventional NICE willingness to pay thresholds of £20k/QALY and £30k/QALY. To the ERG, a necessary but not sufficient condition for the possible future end of life criteria to be considered is that

IXA+LEN+DEX is estimated to be cost effective relative to LEN+DEX at conventional willingness to pay thresholds if the LEN+DEX within both arms is costless.

Section 2 examined the impact of applying Weibulls for all the curves and of applying Weibulls for the PFS and the ToT curves with scenario analyses around the OS functional forms. The costs effectiveness estimates of these when the LEN+DEX costs are set to zero are as follows. These analyses are based upon PFS costing, but otherwise apply the company assumptions.

**Table 41-** ***Company base case with Weibulls: No LEN+DEX costs***

| Duration Tx effects | ΔQALYs | ΔCosts | ICER |
|---|---|---|---|
| Lifetime | 0.975 | £121,965 | £125,183 |
| 32 mths full, 10 year waning | 0.801 | £120,877 | £150,966 |
| 32 mths full, 5 year waning | 0.680 | £119,057 | £175,186 |
| 32 mths full, 2 year waning | 0.546 | £115,746 | £212,336 |
| 32 mths full, 1 year waning | 0.485 | £113,661 | £234,551 |
| 32 mths | 0.416 | £110,742 | £266,168 |

**Table 42-** ***Different OS forms with PFS and ToT Weibulls: No LEN+DEX costs***

| | LY | % PFS | QALY | Cost | ICER |
|---|---|---|---|---|---|
| OS Exponential | 2.522 | 33% | 1.382 | £122k | £90,016 |
| OS Weibull | 1.562 | 53% | 0.974 | £124k | £125k |
| OS Gompertz | 0.992 | 81% | 0.672 | £122k | £181k |
| OS Lognormal | 2.231 | 37% | 1.193 | £122k | £105k |
| OS Log-Logistic | 1.949 | 42% | 1.084 | £125k | £115k |
| OS Gamma | 2.162 | 38% | 1.195 | £124k | £104k |

The company estimate of the cost effectiveness of IXA+LEN+DEX compared to LEN+DEX with the currently agreed PAS is £125k per QALY.

- Setting the costs of LEN+DEX to zero improves the cost effectiveness estimate to £116k per QALY.

- Applying the population norm quality of life values to the additional survival gains has little impact and the cost effectiveness estimate remains at £125k per QALY.
- Applying a quality of life value of 1 to the additional survival gains improves the cost effectiveness estimate to £96,120 per QALY.

The ERG estimate of the cost effectiveness of IXA+LEN+DEX compared to LEN+DEX when costing drugs using the ToT curves with the currently agreed PAS is £140k per QALY.

- Setting the costs of LEN+DEX to zero improves the cost effectiveness estimate to £130k per QALY.
- Applying the population norm quality of life values to the additional survival gains improves the cost effectiveness estimate to £123k per QALY.
- Applying a quality of life value of 1 to the additional survival gains improves the cost effectiveness estimate to £95,239 per QALY.

Setting the costs of LEN+DEX to zero and running the model probabilistically over 10,000 iterations yields central estimates of a net cost of £114k, net gains of 0.870 and a cost effectiveness of £130k per QALY.

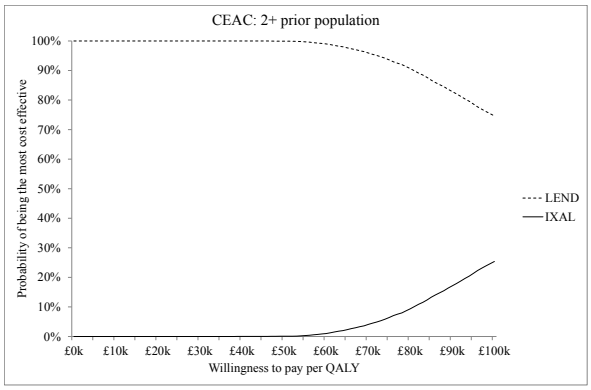



**Figure 18-** ***ERG CEACs with PAS, ToT costing, no cost LEN+DEX, 2+ prior***

The ERG estimate of the cost effectiveness of IXA+LEN+DEX compared to LEN+DEX when costing drugs using the PFS curves with the currently agreed PAS is £202k per QALY.

- Setting the costs of LEN+DEX to zero improves the cost effectiveness estimate to £187k per QALY.
- Applying the population norm quality of life values to the additional survival gains improves the cost effectiveness estimate to £177k per QALY.
- Applying a quality of life value of 1 to the additional survival gains improves the cost effectiveness estimate to £137k per QALY.

Setting the costs of LEN+DEX to zero and running the model probabilistically over 10,000 iterations yields central estimates of a net cost of £164k, net gains of 0.877 QALY, and a cost effectiveness of £187k per QALY.

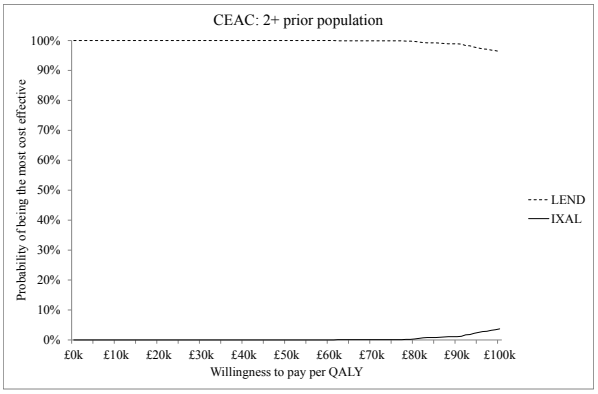



**Figure 19-** ***ERG CEACs with PAS, PFS costing, no cost LEN+DEX, 2+ prior therapies***

Setting the costs of LEN+DEX to zero throughout results in the following ERG scenario analyses when costing drugs using the ToT curves.

**Table 43-** ***ERG SAs with PAS, ToT costing, no cost LEN+DEX, 2+ prior therapies subgroup***

| | Δ LY | Δ QALY | Δ Cost | ICER |
|---|---|---|---|---|
| No LEN+DEX Costs | 1.562 | 0.880 | £114k | £130k |
| SA01: Unadjusted Curves | 1.379 | 0.782 | £112k | £143k |
| SA02a: Tx Eff. 23 months | 0.432 | 0.295 | £101k | £341k |
| SA02b: Tx Eff. 32 months | 0.599 | 0.391 | £105k | £268k |
| SA02c: Tx Eff. 32 mths, 1yr waning | 0.706 | 0.450 | £107k | £237k |
| SA02d: Tx Eff. 32 mths, 2yrs waning | 0.803 | 0.503 | £108k | £215k |
| SA02e: Tx Eff. 32 mths, 5yrs waning | 1.028 | 0.620 | £111k | £178k |
| SA02f: Tx Eff. 32 mths, 10yrs waning | 1.242 | 0.727 | £112k | £154k |
| SA03: 1st Sub 2IA curves | 2.231 | 1.071 | £119k | £111k |
| SA04a: 2IA SD to PD QoL dec. | 1.562 | 0.869 | £114k | £131k |
| SA04b: TA171 QoL | 1.562 | 0.934 | £114k | £122k |
| SA04c: TA338 QoL | 1.562 | 0.888 | £114k | £128k |
| SA04d: 2IA QoL 2IA Mean of Covar | 1.562 | 0.854 | £114k | £133k |
| SA04e: 2IA contemp. response QoL | 1.562 | 0.981 | £114k | £116k |
| SA05: SA04e + SA02b | 0.599 | 0.422 | £105k | £248k |
| SA06: SA04e + SA03 | 2.231 | 1.202 | £119k | £99,119 |
| SA07: SA04e + SA15 | 1.562 | 0.981 | £130k | £132k |
| SA08: SA04e + SA16 | 1.562 | 0.981 | £114k | £116k |
| SA09: SA04e + SA17 | 1.562 | 0.981 | £114k | £116k |
| SA10: Med Review 2+ prior for BoR | 1.562 | 0.865 | £114k | £132k |
| SA11: DoT drug costing | 1.562 | 0.880 | £73,081 | £83,003 |
| SA12: Equal Hospitalisation rates | 1.562 | 0.879 | £114k | £130k |
| SA13: Equal PPS weekly cost | 1.562 | 0.880 | £125k | £142k |
| SA14: All PPS treated | 1.562 | 0.880 | £113k | £129k |
| SA15: SA14 + SA15 | 1.562 | 0.880 | £130k | £148k |
| SA17: ToT to PFS AUC ratio applied | n.a. | n.a. | n.a. | n.a. |

Setting the costs of LEN+DEX to zero throughout results in the following ERG scenario analyses when costing drugs using the PFS curves.

**Table 44-** ***ERG SAs with PAS, PFS costing, no cost LEN+DEX, 2+ prior therapies subgroup***

| | Δ LY | Δ QALY | Δ Cost | ICER |
|---|---|---|---|---|
| No LEN+DEX Costs | 1.562 | 0.879 | £164k | £187k |
| SA01: Unadjusted Curves | 1.379 | 0.781 | £157k | £201k |
| SA02a: Tx Eff. 23 months | 0.432 | 0.294 | £145k | £493k |
| SA02b: Tx Eff. 32 months | 0.599 | 0.390 | £150k | £383k |
| SA02c: Tx Eff. 32 mths, 1yr waning | 0.706 | 0.450 | £152k | £337k |
| SA02d: Tx Eff. 32 mths, 2yrs waning | 0.803 | 0.502 | £153k | £305k |
| SA02e: Tx Eff. 32 mths, 5yrs waning | 1.028 | 0.620 | £157k | £253k |
| SA02f: Tx Eff. 32 mths, 10yrs waning | 1.242 | 0.726 | £160k | £220k |
| SA03: 1st Sub 2IA curves | 2.231 | 1.071 | £166k | £155k |
| SA04a: 2IA SD to PD QoL dec. | 1.562 | 0.868 | £164k | £189k |
| SA04b: TA171 QoL | 1.562 | 0.934 | £164k | £176k |
| SA04c: TA338 QoL | 1.562 | 0.887 | £164k | £185k |
| SA04d: 2IA QoL 2IA Mean of Covar | 1.562 | 0.853 | £164k | £192k |
| SA04e: 2IA contemp. response QoL | 1.562 | 0.980 | £164k | £167k |
| SA05: SA04d + SA02b | 0.599 | 0.421 | £150k | £355k |
| SA06: SA04d + SA03 | 2.231 | 1.201 | £166k | £138k |
| SA07: SA04d + SA15 | 1.562 | 0.980 | £180k | £184k |
| SA08: SA04d + SA16 | 1.562 | 0.980 | £164k | £167k |
| SA09: SA04d + SA17 | 1.562 | 0.981 | £154k | £157k |
| SA10: Med Review 2+ prior for BoR | 1.562 | 0.864 | £164k | £190k |
| SA11: DoT drug costing | n.a. | n.a. | n.a. | n.a. |
| SA12: Equal Hospitalisation rates | 1.562 | 0.878 | £165k | £187k |
| SA13: Equal PPS weekly cost | 1.562 | 0.879 | £175k | £199k |
| SA14: All PPS treated | 1.562 | 0.879 | £163k | £186k |
| SA15: SA14 + SA15 | 1.562 | 0.879 | £180k | £205k |
| SA17: ToT to PFS AUC ratio applied | 1.562 | 0.879 | £154k | £175k |

When the costs of LEN+DEX are set equal to zero neither the company base case, the ERG base case or any of the ERG scenario analyses have cost effectiveness estimates that fall within the conventional NICE willingness to pay thresholds. It is not the costs of LEN+DEX that cause ixazomib to fall outside conventional willingness to pay thresholds.

# 4 ELIGIBILITY FOR CANCER DRUG FUND

In the original submission, the Company considered that Ixazomib could be a potential candidate for use within the CDF for two years. This could offer the opportunity to collect clinical data such as more mature survival data.

In the ACD, it was concluded that Ixazomib does not meet the criteria to be included in the CDF.

In the response to ACD, the Company has asked the Committee to reconsider ixazomib for inclusion in the CDF.

As indicated in the original report, the ERG agree there is some uncertainty regarding the clinical effectiveness of Ixazomib since more mature data are needed to determine the benefit on survival in both people with 1 prior or 2+ prior therapies. However, as previously indicated in the original report, the ERG believes that mature overall survival data should be obtained from the TMM-1 trial once it becomes available.

Indeed, a two-year period of data collection within the CDF is likely to be irrelevant with the scope of MM even at the stage of relapsed or refractory disease since the median overall survival has not been reached for any of the included population (1 prior line and 2-3 prior lines) in either the IXA-LEN-DEX or LEN-DEX arms after a median follow-up of 23 months (second interim analysis) from the TMM-1 RCT. Therefore, there is no a priori reason why data two years of data collection within the CDF would enable acquisition of more mature data, if this has not already been possible within the two first years of data collection in the TMM-1 trial.

# 5 OVERALL CONCLUSIONS

## 5.1 Clinical effectiveness

1] It is uncertain which Tourmaline patients belong to the 2+ prior population.

2] Because of 1] it is uncertain which covariates should be used if OS and PFS models are to be adjusted

3] Takeda data indicates that number of priors could be an important covariate, but this may not have been fully accommodated in the adjustments included in the Takeda models.

4] Takeda's IXA LEN DEX model for PFS appears implausible because in extrapolation it generates more live non-progressed patients than total patients alive. Correcting for this by making the PFS curve the same as the OS curve is not reasonable because some patients would need to die instantaneously at the time of progression. The reason this difficulty arises is because during extrapolation, Takeda's g gamma PFS model predicts ever decreasing probability of progression, while the Takeda OS model predicts continuously increasing probability for death.

5] For IXA LEN DEX PFS Takeda's adjusted Weibull provides a better fit and a more plausible extrapolation than the generalised gamma model that the company selected.

6] Takeda's OS model for IXA LEN DEX may be over-optimistic in the context of the observed data.

7] For the Weibull IXA LEN DEX OS model Takeda used a treatment effect estimated using data to ~ 30 months and applied this without diminishment for the full 22 years of extrapolation beyond the observed data. It seems more reasonable to expect the treatment effect to gradually diminish during the extrapolation phase.

8] Takeda applied covariate adjustments based on analyses up to ~30 months to the whole of the 22 years of the extrapolation period; this seems a significant assumption in view of the uncertainty about the population and the fact that the number of priors received was not directly used for adjustments.

9] The Company provided an exploratory analysis on the 2 prior therapies subgroup. Considering the imbalance regarding several prognostic factors within the 2 prior therapies and 3 prior therapies subgroups, the ERG no longer believes on a presumed greater clinical effectiveness of IXA-LEN-DEX at fourth line compared to third line.

10] In the new submission, the Company did not provide an exploratory analysis on the clinical and cost-effectiveness of IXA-LEN-DEX relative to the Panobinostat regimen in the fourth line. However, results from a NMA in the 2+ prior therapies subgroup presented in the original submission by the Company suggests a reduced effectiveness for IXA-LEN-DEX relative to PANO-BORT-DEX compared to that of IXA-LEN-DEX relative to LEN-DEX.

## 5.2 Cost-effectiveness

The revised company base case:

- Estimates the parameterised curves, the quality of life function, the BoR rates, the proportion of post-progression patients who receive active treatment, the post – progression treatment costs and other more minor elements from the 2IA data cut.
- Adjusts the parameterised curves for the 2 prior therapies subgroup and the 2+ prior therapies subgroup for baseline characteristics.
- Applies the Weibull for OS, the gamma for PFS and the exponential for ToT for the 2+ prior therapies subgroup.
- Applies the Weibull throughout for the OS, PFS and ToT for the 2 prior therapies subgroup.
- Retains drug costing based upon the ToT curve.

- Does not present any analyses for the 3 prior therapies subgroup.
- Does not present any analyses for a comparison with PAN+BOR+DEX.

The revised company quality of life analysis suggests quality of life values for progression free survival similar to, or greater than, the UK norms for those of a similar age. It also estimates a drop of 0.028 from stable disease to progressive disease. There are no subsequent drops applied for later progressions. The prior treatments coefficient is small, far from statistical significance and not included in the final functional form. The age coefficient is small and suggests a slower decline than UK population norms.

The proportions of time in PFS that incur treatment costs are 62% for IXA+LEN+DEX and 69% for LEN+DEX.

The company model structure is very similar to that submitted alongside the first submission. The main structural change is in the handling of the post-progression active treatment costs. But this is rather circular and as far as the ERG can ascertain applies the same one-off cost[m] of £78,607 in both arms. There is an argument that there will be a maximum number of possible post progression treatments and costs associated with this, but the ERG thinks that the post-progression costs incurred will still be linked to the durations of patients' post-progression survival.

The revised company estimates for the 2+ prior therapies subgroup is a mean survival of 3.9 years for LEN+DEX and 5.5 years for IXA+LEN+DEX, resulting in a net gain of 1.6

[m] There will be very minor differences between the arms due to discounting.

years overall survival. This survival gain accrues mainly pre-progression, but around a third is modelled as accruing post-progression, which may raise questions. The survival gain translates into a gain of 0.981 QALYs[n] but at a net cost of £123k resulting in a cost effectiveness estimate of £125k per QALY. The probabilistic estimates are in line with this.

These results are sensitivity to the OS curve using the exponential, which increases the post-progression survival gains and so improves the cost effectiveness estimate to £88,453 per QALY. If ixazomib is costless the cost effectiveness estimate improves to £11,988 per QALY.

The revised company estimates for the 2 prior therapies subgroup is a mean survival of 5.6 years for LEN+DEX and 8.5 years for IXA+LEN+DEX, resulting in a net gain of 2.9 years overall survival. Of the 2.9 years overall survival gain only 0.5 years is due to increased progression free survival. The vast majority, 2.4 years, is modelled as accruing post-progression. When coupled with what these estimates imply for the 3 prior therapies subgroup the ERG thinks that the company estimates for the 2 prior subgroup are not credible.

What follows only considers the 2+ prior therapies subgroup.

[n] Life years have not been discounted. QALYs and costs have been discounted at an annual 3.5%.

The company has chosen a different set of curves for its current submission than it chose for the 2IA analysis it presented within its original submission. The reasons for the change are unclear.

Of the 1.6 years gain in overall survival, 88% is modelled as occurring after 32 months and so is pure extrapolation. This is an inevitable consequence of the immaturity of the OS data within multiple myeloma trials. But it highlights the uncertainty associated with this assessment and that the trial was primarily based upon the PFS. The modelled OS gains need to be sense checked against gains in PFS, and whether large gains in post-progression survival are anticipated.

Given the degree of extrapolation it may be optimistic to assume that the treatment effect continues indefinitely. The NICE methods guide suggests exploring the effect of the treatment effect waning. No such analyses are presented by the company and it is left to the ERG to explore this.

The ACD specified that any modelling of the 2 prior therapies subgroup should adjust for baseline covariates. The company also adjusts the curves of the 2+ prior therapies subgroup. This is not obviously justified for the PFS and the ToT curves based upon the information criteria. There may be stronger grounds for the OS curves based upon the information criteria, but the ERG has some concerns about adjusting the OS curves for age over 65 at baseline, but not for age over 75 at baseline. Being over 75 might be anticipated to have a stronger effect on all-cause mortality than being over 65. There was a larger discrepancy between the arms of 4% for the proportion being over 75, with this being to the detriment of LEN+DEX, compared to the discrepancy between the arms of 2% for the proportion being over 65, which was to the detriment of IXA+LEN+DEX.

There is some evidence that the IXA+LEN+DEX ToT KM curve diverges from the PFS KM curve, the ratio of the areas under the curves being around 92%. There is little evidence that the LEN+DEX ToT KM curve diverges from the PFS KM curve, the ratio of the areas under the curves being around 92%. The model suggests ratios of 62% for IXA+LEN+DEX and 69% for LEN+DEX. It seems questionable to apply the ToT curves and resulting model ratios for costing purposes.

The company explored different classifications of what should be treated as a censoring event and what as a discontinuation event within its construction of the ToT curves. It is unclear to the ERG whether quite as many events should be classified as discontinuation events, and there may be the possibility that this drives an artificial wedge between the ToT KM curves and the PFS KM curves.

It may be questionable to apply the PFS gamma, or to apply it indefinitely as it suggests an ever-falling hazard. The divergence between the ToT curve and the PFS curve is also in part a function of the PFS gamma being applied alongside the exponential for the ToT curve. There is an argument that it might be better to apply Weibulls for both the PFS and the ToT curves, or exponentials for both the PFS and ToT curves. This needs to be viewed with some caution since within the partitioned survival model it does not affect the overall survival that is extrapolated. Any change to the PFS curve requires that a sense check be performed on what it implies for the balance between those survival gains realised pre- and post-progression. Sections 2 and 3 present some exploratory scenarios around this, but retain the company choice of curves for the ERG revised base case.

The company does not present any analyses based upon costing using the PFS curves. The ERG presents a full set of analyses based upon costing using the ToT curves and upon costing using the PFS curves.

As explored in depth in the clinical review the classification of patients as being within the 2+ prior subgroup can be investigator assessed or by blinded medical review. Which is chosen has a reasonable effect on the best overall response rates. The ERG explores this as a sensitivity analysis, though the effects are limited. The main uncertainty around this is in terms of how the KM curves might be affected by this classification, with implications for the parameterised curves. This cannot be explored by the ERG.

The quality of life repeated measures analysis is based upon contemporaneous response status rather than best overall response status. But the company applies best overall response rates to these coefficients. This does not appear legitimate. Since the ERG only has estimates for best overall response rates, it applies these to the best overall response quality of life repeated measures analysis of the first submission. This is unsatisfactory but is addressed through extensive sensitivity analyses.

The only major differences between the company and ERG base cases are the ERG applying BoR rates to a BoR quality of life analysis and the ERG exploring both the ToT curve and the PFS curve for costing purposes. As a consequence, the net survival gain is the same at 1.6 years. But the patient gain falls to 0.880 QALYs. Costing using the ToT curves suggest net costs of £123k and a cost effectiveness estimate of £140k per QALY, while the PFS curves suggest a net cost of £176k and a cost effectiveness estimate of £202k per QALY.

The probabilistic estimates are in line with the above deterministic estimates.

Results are not particularly sensitive to the functional forms chosen for the ToT parameterised curves unless the log-normal or log-logistic is chosen and the analysis is based upon costing using the ToT curve.

If costings are based upon the PFS curve the gamma of the base case has the worst cost effectiveness estimate. A Weibull PFS curve improves the cost effectiveness estimate to £157k per QALY, but it should be borne in mind that since there is no functional relationship in the model between progression and survival this increases the proportion of the survival gain experienced post-progression, from 32% to 47%.

Results are sensitive to the functional form chosen for the OS curve, this underlines the degree of extrapolation and uncertainty around the modelled OS gains. The exponential OS curve increases the survival gains to 2.5 years, the majority of which is modelling as accruing post-progression. This improves the cost effectiveness to £100k per QALY based upon ToT costing and £153k per QALY based upon PFS costing.

Results show some sensitivity to:

- Applying the unadjusted curves, these worsening the cost effectiveness estimates to £154k per QALY for the ToT costing and £218k per QALY for the PFS costing.
- Applying a waning treatment effect. If it is slowly reduced to zero over the five years subsequent to the 32-month trial period, this worsens the cost effectiveness estimates to £194k per QALY for the ToT costing and £274k per QALY for the PFS costing. If it is slowly reduced to zero over two years subsequent to the trial period, this worsens the cost effectiveness estimates to £234k per QALY for the ToT costing and £331k per QALY for the PFS costing.
- Applying the curves the company chose for the 2IA analysis in its first submission, improves the cost effectiveness estimates to £120k per QALY for the ToT costing and £168k per QALY for the PFS costing.

- Applying the BoR rates to the contemporaneous response quality of life coefficients, improves the cost effectiveness estimates to £126k per QALY for the ToT costing and £181k per QALY for the PFS costing.
- Applying the company ToT curves which treat all events including end of follow-up as discontinuation events and none as censoring events, improves the cost effectiveness estimate to £92,485 per QALY for the ToT costing.
- Equalising the weekly post progression cost between the arms, worsens the cost effectiveness estimates to £156k per QALY for the ToT costing and £217k per QALY for the PFS costing. These worsen further if it is assumed that all patients rather than 66% of patients will receive an active treatment after progression.

The company appears to accept that the current end of life criteria do not apply. But it argues that revised end of life criteria may apply since the current treatment, LEN+DEX, is licensed for use until progression and ixazomib has to be used in conjunction with it. To the ERG this argues for exploring whether it is the costs of LEN+DEX that cause ixazomib to be estimated to not be cost effective at the NICE thresholds of £20k per QALY and £30k per QALY.

The company submission tables scenarios around the costs of LEN+DEX, but something appears to have gone wrong with them. The ERG explores this by setting the costs of LEN+DEX in both the IXA+LEN+DEX arm and the LEN+DEX arm to zero. This does not bring the cost effectiveness estimate to below £30k per QALY. It is not the costs of LEN+DEX that cause the cost effectiveness estimate for ixazomib to be above £30k per QALY.

# 6 REFERENCES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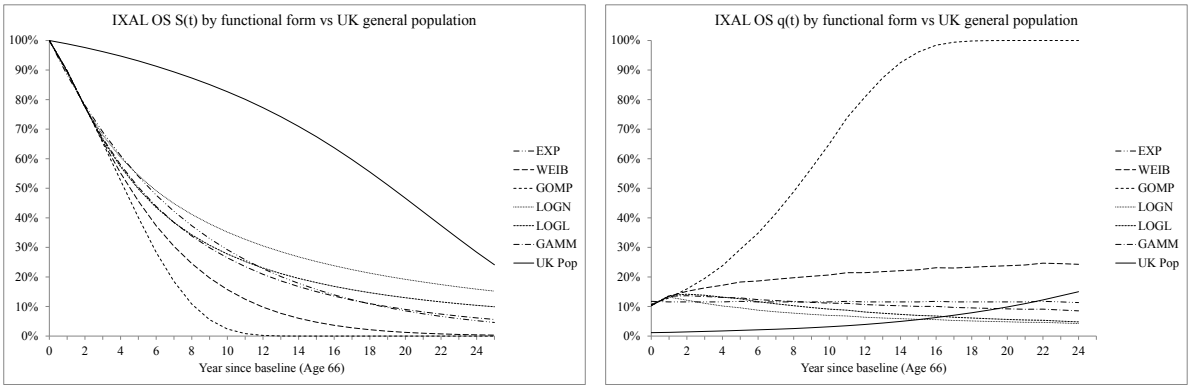
**ID807 Ixazomib Addendum: Modelled survival and UK population norms**

The 2+ prior OS survival curves are presented alongside that of the UK general population with a baseline age of 66 years and 57% male, the baseline median age and male proportion of the TMM-1 trial. The proportion of those alive who die during the subsequent year, q(t), can also be plotted.

*Figure 01: Modelled survival vs UK pop: IXA+LEN+DEX: 2+ prior patients*




The goodness of fit statistics for the OS parameterised curves are as follows.

*Table 01: AIC and BIC: OS Parameterised adjusted curves: 2+ prior patients*

| | EXP | WEIB | GOMP | LOGN | LOGL | GAMM |
|---|---|---|---|---|---|---|
| AIC | 821 | 819 | 822 | 819 | 819 | 820 |
| BIC | 836 | 838 | 840 | 838 | 837 | 843 |

The main points seem to be:

- The median time since diagnosis for those enrolled to TMM-1 was 43 months or around 3½ years. The patient population under consideration had already failed on 2+ prior treatments.
- The log-logistic has the best combined AIC and BIC. The company appears to reject this due to infeasible numbers being modelled as surviving in the longer term. The modelled proportion dying in the later years of the model also falls below that of the UK general population.
- On the basis of the combined information criteria there is little to choose between the exponential, the Weibull, the log-normal and the log-logistic.
- The measures of goodness of fit of the parametric curves only tell us how well they fit the KM curves of the trial. They tell us little about the feasibility of their extrapolated values over the subsequent 22 years.
- There is little difference between the parametric curves over the period of the KM curve. They only diverge during extrapolation, diverging quite dramatically after the 32 months maximum follow up of the 2IA data cut.
- All OS models other than the Gompertz and the Weibull eventually predict a lower probability of death than that of the UK general population.
- The exponential predicts a constant probability of death over the entire extrapolated period up to the end of the time horizon at age 91 years.

*Age at baseline*

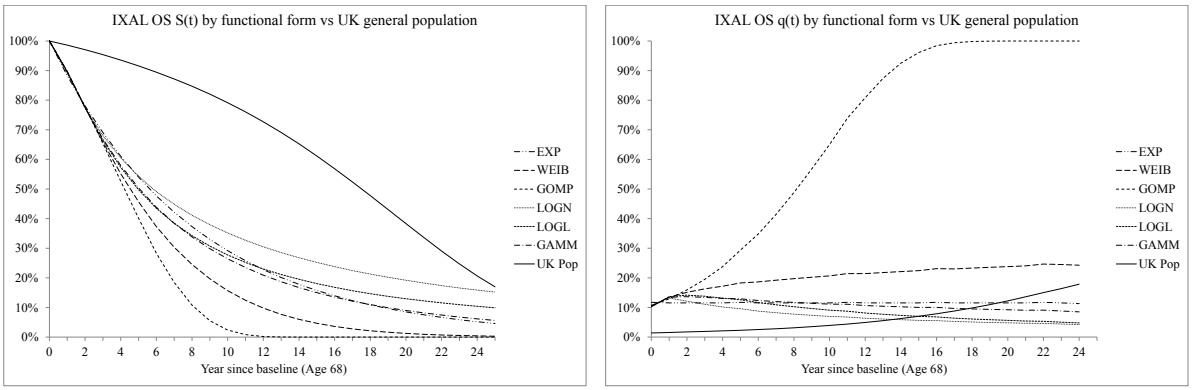
The submission and clinical study report give a median baseline age of 66 years. The ERG has not been able to identify the mean baseline age, or anything specific to the 2+ prior subgroup other than the proportions within the age bands as reported below[1].

*Table 02: Baseline proportions of patients in age bands by number of prior treatments*

| | All | 2 prior | 2+ prior | 3 prior |
|---|---|---|---|---|
| ≤ 65 years | 48% | 49% | 48% | 44% |
| > 65 yrs, ≤ 75 years | 37% | 35% | 35% | 36% |
| > 75 years | 15% | 16% | 17% | 21% |

As would be anticipated the distribution between the age bands for the 2+ prior population implies an older mean baseline age than that for all patients. All-cause mortality increases quite rapidly at the end of the time horizon, the UK population S(t) and the q(t) diagrams changing as below.

*Figure 02: S(t) and q(t) for a baseline age of 68*




If the average patient age at baseline is 68 years instead of 66 years, as would be expected the point on the exponential at which the proportion modelled as dying falls to below that of the UK population all-cause mortality is between 19 and 20 years from baseline rather than between 21 and 22 years. But it should be borne in mind that the above only considers the median age at baseline across all patients and the age banding.

Varying the baseline age also underlines how the extrapolated curves are invariant to all-cause mortality and so how during the extrapolation period they may not fully reflect it. All-cause mortality for the UK population during the 32 months from baseline is relatively low compared to mortality during the TMM-1 trial and compared to subsequent all-cause mortality.

[1] Based upon patient proportions and numbers in Table 2 of 19th May company response to ACD

**ID807: Additional ERG analyses at the request of NICE**

NICE has requested the equivalent to tables 23 and 42 of the ERG report that apply the ERG revisions to the company base case of section 5.4 of the ERG report. This results in the following when costing is based on PFS.

*Table 01: Equivalent of table 23 with ERG assumptions of section 5.4 and PFS costing*

| | LY | % PFS | QALY | Cost | ICER |
|---|---|---|---|---|---|
| OS Exponential | 2.522 | 33% | 1.221 | £139,348 | £114,088 |
| OS Weibull | 1.562 | 53% | 0.867 | £136,043 | £156,864 |
| OS Gompertz | 0.992 | 81% | 0.604 | £135,721 | £224,696 |
| OS Lognormal | 2.231 | 37% | 1.057 | £139,547 | £132,026 |
| OS Log-Logistic | 1.949 | 42% | 0.963 | £138,923 | £144,316 |
| OS Gamma | 2.162 | 38% | 1.059 | £138,898 | £131,128 |

*Table 02: Equivalent of table 42 with ERG assumptions of section 5.4 and PFS costing*

| | LY | % PFS | QALY | Cost | ICER |
|---|---|---|---|---|---|
| OS Exponential | 2.522 | 33% | 1.221 | £125,988 | £103,150 |
| OS Weibull | 1.562 | 53% | 0.867 | £122,833 | £141,633 |
| OS Gompertz | 0.992 | 81% | 0.604 | £122,105 | £202,153 |
| OS Lognormal | 2.231 | 37% | 1.057 | £125,909 | £119,123 |
| OS Log-Logistic | 1.949 | 42% | 0.963 | £125,295 | £130,159 |
| OS Gamma | 2.162 | 38% | 1.059 | £125,410 | £118,394 |

If costing is based upon ToT it results in the following.

*Table 03: Equivalent of table 23 with ERG assumptions of section 5.4 and TOT costing*

| | LY | % PFS | QALY | Cost | ICER |
|---|---|---|---|---|---|
| OS Exponential | 2.522 | 33% | 1.222 | £124,417 | £101,819 |
| OS Weibull | 1.562 | 53% | 0.868 | £121,062 | £139,505 |
| OS Gompertz | 0.992 | 81% | 0.605 | £120,422 | £199,189 |
| OS Lognormal | 2.231 | 37% | 1.057 | £124,616 | £117,840 |
| OS Log-Logistic | 1.949 | 42% | 0.963 | £123,991 | £128,734 |
| OS Gamma | 2.162 | 38% | 1.060 | £123,967 | £116,974 |

*Table 04: Equivalent of table 42 with ERG assumptions of section 5.4 and TOT costing*

| | LY | % PFS | QALY | Cost | ICER |
|---|---|---|---|---|---|
| OS Exponential | 2.522 | 33% | 1.222 | £115,154 | £94,238 |
| OS Weibull | 1.562 | 53% | 0.868 | £111,950 | £129,005 |
| OS Gompertz | 0.992 | 81% | 0.605 | £110,907 | £183,450 |
| OS Lognormal | 2.231 | 37% | 1.057 | £115,075 | £108,818 |
| OS Log-Logistic | 1.949 | 42% | 0.963 | £114,460 | £118,839 |
| OS Gamma | 2.162 | 38% | 1.060 | £114,575 | £108,112 |

-----Original Message-----
From: Ramasamy Karthik (RTH) OUH [mailto:[redacted]]
Sent: 21 July 2017 22:48
To: TA Comm D <TACommD@nice.org.uk>
Subject: Re: Important query: ixazomib citrate for treating relapsed or refractory multiple myeloma [ID807]

* Although the survival data from the trial of ixazomib are immature, consultees have suggested that ixazomib is likely to improve overall survival compared with lenalidomide.

* Question 1a: Is it likely that the survival benefit would be maintained after the patient has stopped treatment with ixazomib? Yes, the trial results ( improved PFS) support the scientific hypothesis that the combination of ixazomib, Lenalidomide and dexamethasone is able to over come multiple genetic subclones present in relapsed myeloma. And that this benefit would continue for the rest of the patient's life? The benefit is likely to be maintained for atleast 1-2 further relapses, due to the combinatorial effect on myeloma and the marrow microenvironment.

* Question 1b: Alternatively, is it more likely that the survival benefit of ixazomib would reduce over time after the patient stops treatment? Yes over about 2 years . Over what time period might the benefit reduce (eg 1, 2, 5, 10 years from stopping treatment)?

* Question 2: Is the probability of needing subsequent lines of treatments likely to be influenced by how long a patient lives (after they have stopped ixazomib)? Yes Is the number of subsequent lines of treatment started (and completed) by the patient likely to be influence by how long they live? Yes

thanks

Karthik Ramasamy

On 21 Jul 2017, at 18:58, National Institute for Health and Care Excellence <TACommD@nice.org.uk<mailto:TACommD@nice.org.uk>> wrote:

21/07/2017

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Single Technology Appraisal

Ixazomib citrate for treating relapsed or refractory multiple myeloma [ID807]

Dear Dr Ramasamy,

Thank you again for your contribution to the NICE Appraisal Committee meeting on ixazomib in multiple myeloma in March. The Committee are meeting again on 26 July to discuss the consultation comments, and we have a couple of clinical issues we would appreciate your input on.

* Although the survival data from the trial of ixazomib are immature, consultees have suggested that ixazomib is likely to improve overall survival compared with lenalidomide.

* Question 1a: Is it likely that the survival benefit would be maintained after the patient has stopped treatment with ixazomib? And that this benefit would continue for the rest of the patient's life?

* Question 1b: Alternatively, is it more likely that the survival benefit of ixazomib would reduce over time after the patient stops treatment? Over what time period might the benefit reduce (eg 1, 2, 5, 10 years from stopping treatment)?

* Question 2: Is the probability of needing subsequent lines of treatments likely to be influenced by how long a patient lives (after they have stopped ixazomib)? Is the number of subsequent lines of treatment started (and completed) by the patient likely to be influence by how long they live?

We would be very grateful of a response by end of day Tuesday 25 July.

Thank you in advance.

Kind regards,

Kate Moore

Technology Appraisals Project Manager - Committee D

National Institute for Health and Care Excellence

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**From:** Yong, Kwee [mailto:[redacted]]
**Sent:** 23 July 2017 22:25
**To:** TA Comm D <TACommD@nice.org.uk>
**Subject:** Re: Important query: ixazomib citrate for treating relapsed or refractory multiple myeloma [ID807]

Please see below my answers, hope this helps
Kwee

**From:** National Institute for Health and Care Excellence <TACommD@nice.org.uk>
**Reply-To:** National Institute for Health and Care Excellence <TACommD@nice.org.uk>
**Date:** Friday, 21 July 2017 at 19:01
**To:** Kwee Yong <[redacted]>
**Subject:** Important query: ixazomib citrate for treating relapsed or refractory multiple myeloma [ID807]

21/07/2017
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## Single Technology Appraisal
## Ixazomib citrate for treating relapsed or refractory multiple myeloma [ID807]

Dear Prof Yong,
Thank you again for your contribution to the NICE Appraisal Committee meeting on ixazomib in multiple myeloma in March. The Committee are meeting again on 26 July to discuss the consultation comments, and we have a couple of clinical issues we would appreciate your input on.

- Although the survival data from the trial of ixazomib are immature, consultees have suggested that ixazomib is likely to improve overall survival compared with lenalidomide.
    - **Question 1a:** Is it likely that the survival benefit would be maintained after the patient has **stopped treatment** with ixazomib**? - yes, for a period of time** And that this benefit would continue for the rest of the patient's life? **Not sure what this question is referring to**
    - **Question 1b**: Alternatively, is it more likely that the survival benefit of ixazomib would reduce over time after the patient stops treatment? **Possibly** Over what time period might the benefit reduce (eg 1, 2, 5, 10 years from stopping treatment)? **1-2 years**
- **Question 2:** Is the probability of needing subsequent lines of treatments likely to be influenced by how long a patient lives (after they have stopped ixazomib)? **Yes, this sounds likely.** Is the number of subsequent lines of treatment started (and completed) by the patient likely to be influence by how long they live? **This again sounds plausible**

We would be very grateful of a response by end of day **Tuesday 25 July**.

Thank you in advance.

Kind regards,
Kate Moore
Technology Appraisals Project Manager - Committee D
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