NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (CDF review of TA505) [ID1635]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (CDF review of TA505) [ID1635]

Contents:

The following documents are made available to consultees and commentators:

Access the TA505 guidance on the NICE website.
Access the final scope and final stakeholder list on the NICE website.

1. **Company submission** from Takeda

2. **Clarification questions and company responses:**
   a. Main response
   b. Additional response

3. **Patient group, professional group, and NHS organisation submission** from:
   a. Myeloma UK:
      i. Submission
      ii. Patient treatment survey report

4. **Evidence Review Group report** prepared by Warwick Evidence:
   a. Main report
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   c. Erratum

5. **Evidence Review Group report – factual accuracy check**

6. **Public Health England Study Report**

7. **Technical engagement response from company**

8. **Technical engagement responses and expert statements from:**
   a. Professor Gordon Cook, Professor of Haematology – clinical expert, nominated by Takeda
   b. Professor Graham Jackson, Professor of Clinical Haematology – clinical expert, nominated by Takeda

9. **Technical engagement responses from consultees and commentators:**
   a. Myeloma UK

10. **Evidence Review Group critique of company response to technical engagement** prepared by Warwick Evidence

11. Evidence Review Group appendix post-pre-meeting briefing (PMB)

12. Response to commercial briefing note from the company, Takeda

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review of TA505

Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [ID1635]

Company evidence submission for committee

October 2021

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ID1635_Ixazomib_Company-Submission_[redacted]_v3.0	3.0	No	08/10/2021

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Cancer Drugs Fund review submission

A.1 Background

On 21st November 2016, the European Commission granted conditional marketing authorisation for Ninlaro® (ixazomib) in combination with lenalidomide and dexamethasone (IXA+LEN+DEX) for the treatment of adult patients with multiple myeloma (MM) who have received at least one prior therapy – marketing authorisation was renewed in this indication on 20th November 2020.[1] In December 2017, the National Institute for Health and Care Excellence (NICE) recommended IXA+LEN+DEX within the Cancer Drugs Fund (CDF) as an option for treating adults with MM if they had 2 or 3 lines of therapy and the conditions in the managed access agreement for ixazomib were followed.[2] Although IXA+LEN+DEX is indicated for adult patients with MM who have received at least one prior therapy, the NICE Committee concluded that in England it would be used in patients that had received 2 or 3 lines of therapy, for whom current treatment at that time was LEN+DEX. Therefore, the initial appraisal focused on the 2 or 3 prior lines population, and LEN+DEX as the comparator.[2]

To make its decision, the Committee used data from the second interim analysis (IA2) of the TOURMALINE-MM1 (TMM1) study – with a median follow-up of 23-months – to assess the cost-effectiveness of IXA+LEN+DEX.[2,3] At IA2, progression-free survival (PFS) data were mature, and demonstrated a significant 9-month median PFS advantage for IXA+LEN+DEX vs. LEN+DEX (hazard ratio [HR] = 0.617, 95% confidence interval [CI] 0.445–0.855; p=0.033) in patients who have had 2 or 3 prior lines of therapy.[4] While overall survival (OS) data were immature at IA2, there was a trend towards a survival benefit for IXA+LEN+DEX compared with LEN+DEX (HR: 0.645, 95% CI, 0.409–1.017; p=0.0569).[5] However, as the median OS had not been reached in either arm, uncertainty remained around the magnitude of OS benefit for IXA+LEN+DEX.[2,6] The Committee also highlighted residual uncertainty regarding:[2]

- duration of treatment
- quality of life impact, and
- the continued treatment effect of ixazomib after discontinuation.

Based on the submitted economic model, the Committee's preferred base case resulted in an ICER of £31,691 per QALY gained.[2] This ICER reflected a commercial access agreement (CAA) of [redacted] discount applied to the list price of ixazomib in addition to [redacted]. On a per cycle basis, the net acquisition cost of ixazomib within the CAA was [redacted]. This CAA made ixazomib [redacted] of all novel therapies for MM in the UK at the time and demonstrated Takeda's commitment to ensuring this medicine is available for patients.

There was plausible potential for ixazomib to be cost-effective pending final results on OS from TMM1, and the NICE Committee therefore recommended the regimen to the CDF for further data collection.[2] The CDF data collection agreement (DCA) for ixazomib specified the final analysis of TMM1 trial as the primary data source for the reappraisal.[7] Secondary data sources were listed in the DCA as real-world evidence from the Systemic Anti-Cancer Therapy (SACT) database – collected during the CDF period– and the ixazomib Named Patient Programme.[7]

The final OS results are now available from TMM1 (final data cut-off, September 2020, with a median follow-up time of 85-months), and this submission presents the updated cost-effectiveness analysis of IXA+LEN+DEX vs. LEN+DEX for patients who have received 2 or 3 prior lines of therapy using the final TMM1 data.

During the CDF data collection period, IXA+LEN+DEX has been proven a well-tolerated, effective and easy to use all-oral regimen that is appropriate for a broad range of patients. The Committee previously heard evidence from patient and clinical experts who emphasised the importance of oral treatment regimens for patients with MM, a benefit of IXA+LEN+DEX that has become even more important during the COVID-19 pandemic. This has been evidenced in real-world clinical practice by the strong uptake of IXA+LEN+DEX on the CDF. According to the Public Health England (PHE) report for ixazomib, over 2,500 patients received IXA+LEN+DEX during its first 30-months on the CDF (~80–90 new patients per month),[8] demonstrating the ongoing clinical need for this regimen and its importance to patients and clinicians in England.

Feedback from 12 UK clinicians that specialise in MM during a Takeda advisory board conducted in March 2021 highlighted the benefits of this all-oral triplet regimen for patients and the NHS.[9] Clinicians stated that they particularly valued the IXA+LEN+DEX tolerability profile which enabled use in up to 90% of all patients with 2 or 3 prior lines of therapy that they see in clinic.[9] All advisors were unanimous regarding the ongoing clinical need for IXA+LEN+DEX in this place in therapy.[9] In addition, since April 2020, IXA+LEN+DEX has been offered to clinicians in England and Wales at an earlier stage in the pathway as an interim treatment option during COVID-19. This has enabled [redacted] patients with MM (during the period from May 2020 to end May 2021) to shield at home while continuing to receive an effective all-oral MM therapy and has alleviated pressure on the NHS during this challenging time.

During the original appraisal and COVID-19 pandemic, Takeda demonstrated a commitment to working collaboratively and transparently with NICE, NHS England and other stakeholders to allow patient access to IXA+LEN+DEX. Takeda reaffirms this commitment to working with all stakeholders to allow patients and the NHS to continue to benefit from having access to this effective and important all-oral triplet MM regimen.

A.2 Key Committee assumptions

Area	Committee preferred assumption(s)	Assumption(s) in the company submission	Rationale if different from Committee's preferred assumption(s)
Population	Adults with relapsed or refractory multiple myeloma who have had 2 or 3 lines of therapy.	As per Committee preferred assumption	Not applicable
Comparators	Lenalidomide plus dexamethasone (LEN+DEX).	As per Committee preferred assumption	Not applicable
Time on treatment	Updated time on treatment (ToT) data should be derived from the TOURMALINE MM-1 trial and the generalisability of this assumption should be validated using the data collected within the SACT dataset. Unless the company justifies an alternative extrapolation choice a Weibull curve should be fitted to these data.	ToT data have been updated using the final analysis from TMM1. Data have been extrapolated using a Weibull curve.	Not applicable
Survival data	The company should use updated survival data from the TOURMALINE MM-1 trial. Unless the company justifies an alternative extrapolation choice a Weibull curve should be fitted to these data.	OS data have been updated using the final analysis from TMM1 and adjusted to reflect the UK clinical pathway. Data have been extrapolated using a generalised gamma curve in line with clinical feedback.	Not applicable
Utilities	The company should use any updated EQ-5D data from the TOURMALINE MM-1 trial.	Regression analyses have been performed using the final analysis from TMM1.	Not applicable
Continued treatment effect	The company should present evidence that the proportional hazard assumption is applicable with the more mature survival data.	No treatment waning is applied in the base case.	The TMM1 final analysis captures the impact of discontinuing therapy on the treatment effect for ~96% and ~99% of patients who have stopped treatment during follow-up in the IXA+LEN+DEX and LEN+DEX arms, respectively. Therefore, no treatment waning is included in the base case. A scenario analysis applies treatment

Area	Committee preferred assumption(s)	Assumption(s) in the company submission	Rationale if different from Committee's preferred assumption(s)
			waning to the ~4% and ~1% of patients still receiving treatment.
Subsequent therapies	The company should explore the most appropriate subsequent treatments costs to be included in the model for both arms based on the more mature TOURMALINE MM-1 trial data.	Costed based on subsequent therapy use from the final analysis for TMM1 and adjusted for the impact of subsequent therapies which would not be received in UK clinical practice.	The base case adjusts the OS to adjust for the impact of subsequent therapies which are not routinely funded in the UK (i.e. not available or only funded via the CDF). The costing of subsequent therapies in the base case reflects this.
End of life	Ixazomib does not meet the end-of-life criteria.	As per Committee preferred assumption	Not applicable

A.3 Other agreed changes

In the response to the Terms of Engagement (ToE), Takeda highlighted that in the TMM1 trial there are *"notable differences between the two arms in terms of the subsequent therapies received, specifically in relation to novel therapies which are unavailable in current UK clinical practice (or are funded only via the CDF), and this has confounded the OS analysis"*. Specifically, more patients in the LEN+DEX arm than in the IXA+LEN+DEX arm received subsequent therapies which are known to have prognostic importance, for example: daratumumab (31/149=21% in LEN+DEX vs. 19/148=13% in IXA+LEN+DEX), elotuzumab (7/149=5% vs. 3/148=2%) and autologous stem-cell transplant (9/149=6% vs. 1/148=0.7%). Takeda also highlighted that the TMM1 trial had a double-blind design and that this too has potentially confounded the OS results as the majority of clinicians were not unblinded to study drug treatment allocation. As a consequence, patients in the IXA+LEN+DEX arm whose disease progressed after receiving a proteasome inhibitor (PI), ixazomib, were able to receive a PI containing regimen as next-line therapy, despite being PI refractory in their previous treatment line. Clinical experts noted that these factors may impact OS and advised Takeda to conduct further analyses on these issues;[9] these analyses are shown in detail in Sections A.6.1 and A.7 .

To adjust for the potential confounding effects of these factors on the OS results, Takeda clarified in the response to the ToE that it *"plans to undertake extensive treatment switching analyses, in accordance with the methods outlined in the NICE Technical Support Document (TSD) 16. This will include removing the effect of treatments that are only available through the CDF, as per NICE guidance regarding the status of CDF medicines".* This approach is consistent with NICE's Position Statement that medicines available only via the CDF and not via routine commissioning should not be included as a comparator or subsequent therapy.[10] The approach was also discussed and agreed with NICE during the kick-off meeting for this reappraisal that was held on 5th March 2021, and a subsequent call with the ERG on 29th March 2021.

A.4 The technology

Table 1 Technology being reviewed

UK approved name and brand name	Brand name: Ninlaro® Approved name: ixazomib (formulated as ixazomib citrate)
Mechanism of action[11]	Ixazomib is a small-molecule PI that reversibly inhibits the 20S proteasome core of the 26S proteasome complex. The ubiquitin-proteasome system (UPS) is the major regulatory system through which protein homeostasis occurs and represents the primary mechanism by which cells degrade proteins, including those involved in growth control, cell cycle regulation, and apoptosis. When protein homeostasis is disrupted by a PI, the MM cells undergo apoptosis more readily than normal cells,[12] thus conferring selectivity to these agents.
Marketing authorisation/CE mark status[1]	On 21st November 2016, the European Commission granted a Conditional Marketing Authorisation for Ninlaro® (ixazomib). On 20th November 2020, the European Commission adopted the decision to renew the conditional Marketing Authorisation for Ninlaro® (ixazomib).
Indications and any restriction(s) as described in the summary of product characteristics	The indication for ixazomib is: "*Ninlaro in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.*"[1] This submission focuses on a subgroup of patients within the indication, namely adults with MM who have received 2 or 3 prior lines of therapy as this was the NICE recommended use in the CDF.
Method of administration and dosage[1]	Ixazomib is administered orally, at a recommended starting dose of 4mg (one capsule) once a week on days 1, 8 and 15 of each 28-day treatment cycle. Treatment should be continued until disease progression or unacceptable toxicity.
Additional tests or investigations[1]	Treatment with IXA+LEN+DEX must be initiated and monitored under the supervision of a physician experienced in the management of MM. No additional tests or investigations are required when ixazomib is used in combination with LEN+DEX, other than those that are already required for the LEN+DEX regimen.

<table>
<tr><td>List price and average cost of a course of treatment</td><td>
<table>
<tr><th></th><th>Administration and Cost</th><th>Source</th></tr>
<tr><td>Acquisition cost (excluding VAT) *</td><td>Basic NHS List Prices
4mg capsules; pack of 3 capsules = £6,336
3mg capsules; pack of 3 capsules = £6,336
2.3mg capsules; pack of 3 capsules = £6,336
Ixazomib is indicated in combination with LEN+DEX. The acquisition costs of lenalidomide and dexamethasone are:
lenalidomide: £4,368 per 21-tablet (25mg) pack (£208 per tablet)
dexamethasone: £2.77 per 50-tablet (2mg) pack (£0.06 per tablet)
Please note that LEN currently has a confidential simple PAS in the form of a straight discount which is unknown to Takeda. LEN loss of exclusivity (LOE) is expected in [redacted]</td><td>BNF

eMIT
eMIT</td></tr>
<tr><td>Average cost of a course of treatment (i.e. cycle)</td><td>In combination with lenalidomide and dexamethasone:
Ixazomib: £6,336 per cycle
Lenalidomide: £4,368 per cycle
Dexamethasone: £4.43 per cycle
Total: £10,708 per cycle
Excluding adjustments relating to dose intensity and wastage.</td><td>Takeda</td></tr>
</table>
</td></tr>
</table>

Commercial arrangement (if applicable)	In the CDF, ixazomib is subject to a CAA which offers a net price of [redacted] per capsule (a discount of [redacted] off the NHS list price) or [redacted] per cycle [redacted]. The CAA consists of the following elements: [redacted] Takeda is currently in discussions with NHS England regarding potential future commercial arrangements if ixazomib were recommended by NICE for baseline commissioning. Following guidance from NICE's project team, all analyses in the main body of this submission have been presented using the list price of ixazomib. Arising from the initial discussions with NHS England, Takeda applied to reinstate a [redacted] discount off the NHS list price (a net price of [redacted] per capsule). NHS England & NHS Improvement has agreed that this PAS proposal may be considered by NICE as part of this appraisal of ixazomib. Appendix F shows the cost-effectiveness results including the proposed [redacted] PAS for ixazomib. Once commercial discussions are concluded with NHS England, Takeda will if necessary, submit an updated appendix that shows the cost-effectiveness results incorporating the final commercial agreement.
Date technology was recommended for use in the CDF	December 19, 2017
Data collection end date	June 18, 2020

*Ixazomib is indicated in combination with lenalidomide and dexamethasone. The recommended starting dose of lenalidomide is 25 mg administered daily on Days 1 to 21 of a 28-day treatment cycle. The recommended starting dose of dexamethasone is 40 mg administered on Days 1, 8, 15, and 22 of a 28-day treatment cycle.
[1]

A.5 Clinical effectiveness evidence

Consistent with the NICE ToE and the CDF DCA, the primary data source for clinical effectiveness evidence is the final analysis of TMM1 (data cut-off 28 September 2020), at a median follow-up of 85-months (Table 2). This provides mature OS, time on treatment (ToT) and EQ-5D data, and addresses the key areas of uncertainty raised by the Committee during the original appraisal of ixazomib. Please note that as specified in the T-MM1 Statistical Analysis Plan (SAP), data on PFS were not collected beyond the second interim analysis (IA2) of TMM1. Therefore, there are no updates to PFS and the same data and extrapolations will be used as in the original appraisal.

Supporting evidence from the SACT/CDF data cohort and the ixazomib Named Patient Program (UVEA-IXA [Use Via Early Access to ixazomib]), listed as secondary data sources in the DCA, are presented in summary below, and in detail in Appendices C and D, respectively (Table 3).

Table 2 Primary source of clinical effectiveness evidence

Study title	NCT01564537 (TOURMALINE-MM1 [C16010])
Study design	Phase III, randomised, double-blind, placebo-controlled multicentre clinical trial
Population	Adult (≥18 years) patients with RRMM who had received 1 to 3 prior therapies
Intervention(s)	IXA+LEN+DEX
Comparator(s)	Placebo+LEN+DEX
Outcomes collected that address Committee's key uncertainties	**OS, measured as the time from the date of randomisation to the date of death** **ToT** **Assess health utility values per the EQ-5D questionnaire** Health care utilisation
Reference to section in appendix	Appendix A.3, A.4 and A.5

Abbreviations: IXA+LEN+DEX, ixazomib-lenalidomide-dexamethasone; LEN+DEX, lenalidomide-dexamethasone; OS, overall survival; RRMM, relapsed and/or refractory multiple myeloma; ToT, time on treatment

BOLD black = data collected in TMM1 used in the updated base-case model for IXA+LEN+DEX vs. LEN+DEX

Table 3 Secondary source of clinical effectiveness evidence

Study title	SACT/CDF data cohort	UVEA-IXA (Use Via Early Access to Ixazomib) study
Study design	Observational data collection from the SACT dataset during the CDF period	European, multicentre, observational, longitudinal cohort study
Population	Adult (≥18 years) patients with RRMM who had received 2 or 3 prior therapies treated in England via the CDF	Adult patients with RRMM who have received 1–3 prior therapies as a part of the Takeda early access Named Patient Programme (NPP)
Intervention(s)	IXA+LEN+DEX	IXA+LEN+DEX
Comparator(s)	Not applicable	Not applicable
Outcomes collected that address Committee's key uncertainties	Treatment duration, calculated from the start of a patient's treatment to their last known treatment date in SACT. OS, calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis.	Primary outcomes: CR, VGPR, ORR, TTP and PFS. Secondary outcomes: patient and disease characteristics, prior therapy and clinical outcomes
Reference to section in appendix	Appendix C	Appendix D

Abbreviations: Cr, complete response; IXA+LEN+DEX, ixazomib-lenalidomide-dexamethasone; LEN+DEX, lenalidomide-dexamethasone; ORR, overall response rate; PFS, progression-free survival; RRMM, relapsed and/or refractory multiple myeloma; TTP, time to progression; VGPR, very good partial response.

A.6 Key results of the data collection

During the initial appraisal, the efficacy and cost-effectiveness of IXA+LEN+DEX was informed by the IA2 data from TMM1.[2] Table 4 summarises the TMM1 data used for the initial and current IXA+LEN+DEX appraisals. No further data on PFS were available at final analysis, as these data were mature and not collected beyond IA2 in line with the T-MM1 SAP, agreed with the regulators.[6] The Committee has already concluded that IXA+LEN+DEX offers a significant 9-month median PFS advantage over LEN+DEX.[2] Therefore, PFS was not included in the DCA as an area of uncertainty requiring further evidence collection. The main remaining uncertainties deemed by the Committee were OS, ToT and health-related quality of life (HRQoL).

Table 4: TMM1 data used for the initial and current IXA+LEN+DEX appraisals

<table>
<tr><th rowspan="2">2 or 3 prior therapies subgroup</th><th colspan="2">Analysis timepoint</th></tr>
<tr><th>Initial appraisal</th><th>Current appraisal</th></tr>
<tr><td>Progression-free survival</td><td rowspan="4">IA2 (median follow-up of 23-months)</td><td>IA2</td></tr>
<tr><td>Overall survival</td><td rowspan="3">Final analysis (median follow-up of 85-months)</td></tr>
<tr><td>Treatment duration</td></tr>
<tr><td>Health-related quality of life</td></tr>
</table>

Abbreviations: IA2, second interim analysis; IXA+LEN+DEX, ixazomib-lenalidomide-dexamethasone.

A.6.1 *Primary data source | TOURMALINE-MM1*

Overall survival

At a median follow-up of 85-months, the median OS for patients with 2 or 3 prior therapies was 53.0 months and 43.0 months for patients receiving IXA+LEN+DEX and LEN+DEX, respectively (Table 5, Figure 1).[13] While the 2 or 3 prior therapies subgroup was not statistically powered, this is a clinically meaningful 10-month survival benefit for IXA+LEN+DEX compared with LEN+DEX (HR, 0.845; 95% CI, 0.642–1.114, p=0.232).[14,15]

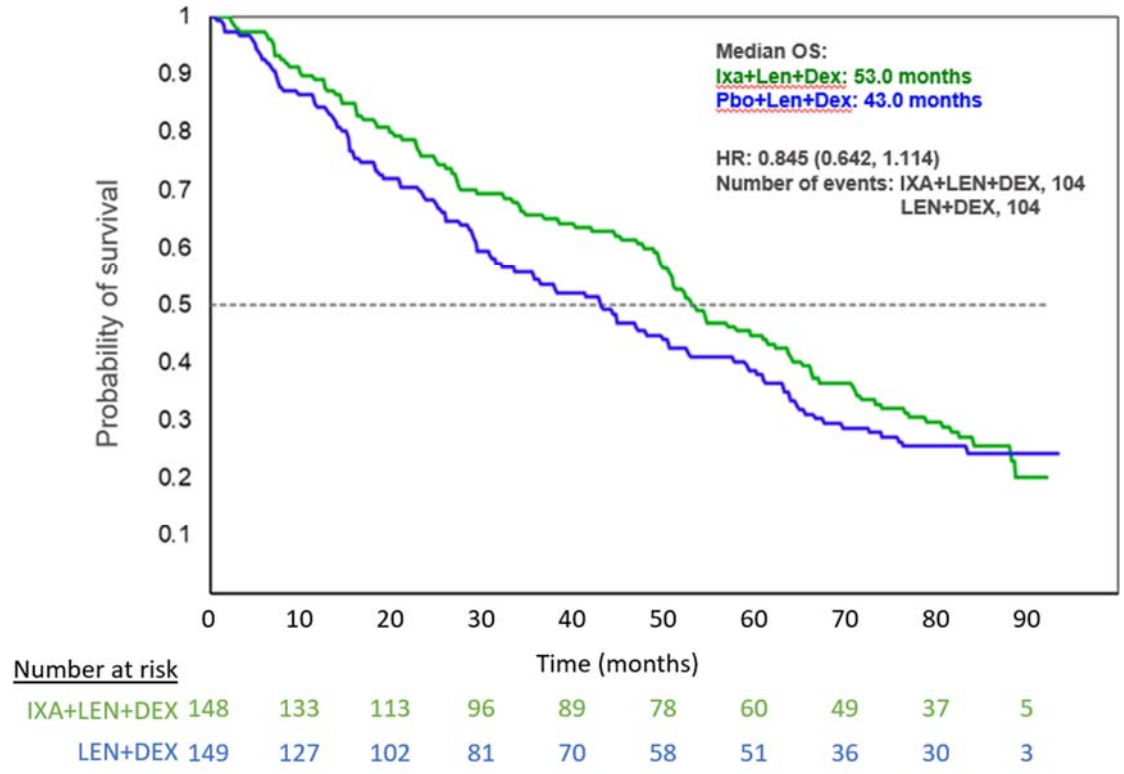
In T-MM1, more patients in the LEN+DEX arm than in the IXA+LEN+DEX arm received subsequent therapies which are known to have prognostic importance, for example: daratumumab, elotuzumab and autologous stem-cell transplant. Differences in the proportions of patients receiving subsequent therapies between treatment arms in T-MM1 is likely to have confounded the OS, an effect that is explored in detail in the following section. As a consequence of confounding due to subsequent therapies received, the magnitude of the OS benefit, as reflected by the hazard ratio, has declined from IA2 to the final analysis (Table 5). The Kaplan–Meier plot for the 2 or 3 prior therapies subgroup at IA2 is shown in Appendix A.3.

Table 5: Median OS for patients with 2 or 3 prior lines of therapy in TMM1 at second interim analysis and final analysis[5,14,15]

	IA2		Final Analysis	
	IXA+LEN+DEX (N=148)	LEN+DEX (N=149)	IXA+LEN+DEX (N=148)	LEN+DEX (N=149)
Median OS, months	NE	NE	53.0	43.0
Hazard Ratio (95% CI)	0.645 (0.409–1.017)		0.845 (0.642–1.114)	
p-value	0.0569		0.232	

Abbreviations: IXA+LEN+DEX, ixazomib-lenalidomide-dexamethasone; LEN+DEX, lenalidomide-dexamethasone; NE, not estimable; OS, overall survival

Figure 1: Kaplan–Meier plot for overall survival for patients with 2 or 3 prior therapies in TMM1 at final analysis[14,15]



Abbreviations: HR, hazard ratio; IXA+LEN+DEX, ixazomib-lenalidomide-dexamethasone; LEN+DEX, lenalidomide-dexamethasone; OS, overall survival.

Confounding of OS by subsequent therapies in TMM1

In MM clinical trials with long follow-up, effective subsequent therapies can confound OS analysis and make it difficult to demonstrate the true OS benefit of a specific treatment regimen used in an earlier treatment line.[16] In TMM1, 70% (105/149 patients) and 63% (93/148 patients) of patients in the 2 or 3 prior therapies subgroup went on to receive at least one subsequent therapy after completing treatment with IXA+LEN+DEX or LEN+DEX, respectively. Tables 11 and 12 in Appendix B show the subsequent therapies which were received in each treatment arm of the TMM1 study for the 2 or 3 prior therapies subgroup. Importantly, the subsequent therapies were not reflective of the UK clinical pathway and the extent of this divergence differed across treatment arms with more patients in the LEN+DEX arm receiving novel treatments not routinely funded in the UK.

Firstly, TMM1 was a double-blind, placebo-controlled multi-country study in which treating clinicians were not automatically unblinded to study drug treatment allocation when selecting subsequent therapies after patients had progressed. Unblinding only occurred in TMM1 if requested by the investigator and, as a result, only a minority (7.6%) of patients with 2 or 3 prior therapies in the trial were actually unblinded at the point of disease progression. This is relevant because in clinical practice, patients who have progressed on (and are refractory to) a particular class of therapy – a PI, for example – would not receive therapy with the same mode of action at the next line of therapy.[9] Standard clinical practice is to use a next-line regimen with a different mode of action that a patient is not refractory to.[9] As shown in Table 6, the blinding influenced clinicians' choice of next treatment in TMM1. Blinded clinicians (the majority) used the same proportion of PI vs. non-PI containing regimens as the next line of therapy for patients, irrespective of whether patients progressed from the IXA+LEN+DEX arm (40% PI vs. 60% non-PI) or the LEN+DEX arm (39% PI vs. 61% non-PI). On the other hand, unblinded clinicians were much less likely to choose a PI as next-line therapy if the patient had just progressed on IXA+LEN+DEX (14% PI vs. 86% non-PI) in comparison to LEN+DEX (88% PI vs. 12% non-PI). In the March 2021 advisory board, all 12 UK clinical experts unanimously informed Takeda that they would not use a PI-containing regimen as next-line therapy for a PI-refractory patient. The advisors also thought that this had very likely confounded the OS analysis in the TMM1 trial.[9]

Secondly, the subsequent therapies included several agents that are not available or funded in the UK or are only available via the CDF. With respect to these therapies, there are important differences between the two treatment arms. Specifically, more patients in the LEN+DEX arm than in the IXA+LEN+DEX arm received subsequent therapies which are known to have prognostic importance, for example: daratumumab (31/149=21% in LEN+DEX

vs. 19/148=13% in IXA+LEN+DEX), elotuzumab (7/149=5% vs. 3/148=2%) and autologous stem-cell transplant (9/149=6% vs. 1/148=0.7%). These treatments are either not available in the UK or are only funded by the CDF. The imbalance in these therapies confounds the interpretation of the survival benefit, as more patients in the LEN+DEX arm received therapies that extend survival for patients with MM.

Takeda was advised by the clinical experts to explore the impact of subsequent therapies on OS for patients with 2 or 3 prior lines of therapy. Treatment switching analyses were conducted following the methods outlined in NICE Technical Support Document (TSD) 16,[17] which attempted to adjust for the effect of subsequent therapies which are either unavailable or would not be used in UK clinical practice.[9] For a full description of the treatment switching methods and the adjusted OS – including Kaplan–Meier plots – please refer to Section A.7.1 and A.7.2.

Table 6: Influence of blinding versus unblinding of study drug allocation on clinician choice of next-line therapy in TMM1 for all patients who received at least one subsequent therapy[14]

Treatment Arm	Next line of therapy	Unblinded n (%)	Blinded n (%)	Total receiving next-line therapy, n (%)
IXA+LEN+DEX	PI-based	1 (14)	39 (40)	40 (38)
	Non-PI-based	6 (86)	59 (60)	65 (62)
	Total	7 (100)	98 (100)	105 (100)
LEN+DEX	PI-based	7 (88)	33 (39)	40 (43)
	Non-PI-based	1 (12)	52 (61)	53 (57)
	Total	8 (100)	85 (100)	93 (100)

Abbreviations: IXA+LEN+DEX, ixazomib-lenalidomide-dexamethasone; LEN+DEX, lenalidomide-dexamethasone; PI, proteasome inhibitor.

Time on treatment

Median ToT for patients with 2 or 3 prior therapies was 18.2 months and 13.4 months for patients receiving IXA+LEN+DEX and LEN+DEX in TMM1, respectively (Table 7).[14] ToT from the final analysis of TMM-1 was similar to that reported at IA2.[5,14] Kaplan–Meier plots for ToT at the final analysis and IA2 are shown in Appendix A.3.

Table 7. Median ToT for patients with 2 or 3 prior lines of therapy in TMM-1 at final analysis and second interim analysis[5,14]

	IA2		Final Analysis	
	IXA+LEN+DEX (N=148)	**LEN+DEX (N=149)**	**IXA+LEN+DEX (N=148)**	**LEN+DEX (N=149)**
Median ToT (95% CI)	17.7 (14.0–20.6)	12.6 (11.1–16.8)	18.2 (16.1–22.4)	13.4 (11.2–17.3)
Range (min – max)	0.23–31.38	0.07–31.47	0.26–88.34	0.07–89.17
Median follow-up (months)	23		85	
Hazard Ratio	0.75 (0.56–0.99)		0.76 (0.60–0.96)	
p-value	0.045		0.0242	

Abbreviations: CI, confidence interval; IA2, second interim analysis; IXA+LEN+DEX, ixazomib-lenalidomide-dexamethasone; LEN+DEX, lenalidomide-dexamethasone.

Health-related quality of life

HRQoL data were collected in the trial using the EQ-5D-3L. The updated regression-based analyses using the final analysis from TMM1 is shown in Section A.7.5. Utility values and coefficients are shown in Appendix A.4.

Safety and tolerability

Safety data are available from the final analysis after a median follow-up of 85-months, which involved a safety population of 720 patients (IXA+LEN+DEX, n=361; LEN+DEX, n=359). At the time of this analysis, 96% of patients had discontinued treatment in both arms, predominantly due to disease progression.[14]

The safety profile of IXA+LEN+DEX was consistent with that seen at the 23-month follow-up analysis (IA2), and no new safety signals were observed (Table 8). Safety outcomes over the longer-follow-up period confirmed the minimal additional toxicity added by ixazomib to the LEN+DEX backbone. Appendix A.5 provides further details on the safety and tolerability of IXA+LEN+DEX at the final analysis.

Table 8 Overall safety profile at the second interim analysis and the final analysis[5,14,15,18]

	IA2		Final analysis			
	2 or 3 prior lines		2 or 3 prior lines		Safety population[c]	
AEs, n (%)	**IXA+LEN+DEX N=148**	**LEN+DEX N=149**	**IXA+LEN+DEX N=148**	**LEN+DEX N=149**	**IXA+LEN+DEX N=361**	**LEN+DEX N=359**
Any AE	147 (99)	148 (99)	148 (100)	148 (99)	359 (99)	357 (99)
Any grade ≥3 AE	114 (77)	113 (76)	122 (82)	120 (81)	289 (80)	266 (74)
Any serious AE	69 (47)	83 (56)	88 (59)	90 (61)	205 (57)	201 (56)
AE resulting in dose reduction of any drug	113 (76)	101 (68)	89 (60)	72 (49)	218 (60)	195 (54)
AE resulting in discontinuation of any drug[a]	38 (26)	38 (26)	59 (40)	57 (39)	140 (39)	116 (32)
AE resulting in discontinuation of regimen[b]	24 (16)	30 (20)	37 (25)	44 (30)	91 (25)	78 (22)
On-study death	5 (3)	13 (9)	7 (5)	14 (9)	21 (6)	30 (8)

Abbreviations: AE, adverse event; IA2, second interim analysis; IXA+LEN+DEX, ixazomib-lenalidomide-dexamethasone; LEN+DEX, lenalidomide-dexamethasone; NR, not reported

Adverse events were graded per National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.

[a] Discontinuation of one or more of the three agents in the study drug regimen.

[b] Discontinuation of the full study drug regimen including discontinuation for disease progression.

[c] Safety population was defined any patient in the intention-to-treat population that received at least one cycle of their allocated regimen

A.6.2 *Secondary Data Source | SACT/CDF data*

Real-world OS data were collected and reported by PHE for patients who received IXA+LEN+DEX in the CDF between December 2017 and June 2020.8 Over 2,500 patients received IXA+LEN+DEX during its first 30-months on the CDF (~80–90 new patients per month),[8] demonstrating the ongoing clinical need for this regimen and its importance to patients and clinicians in England and Wales.

At a median follow-up of 15-months (data censored on 25th November 2020), median OS for the 2,460 evaluable patients with a treatment record in SACT was 30.0 months [95% CI: not estimable] (Table 9). OS at 6 months was 84% [95% CI: 82–85%], OS at 12 months was 73% [95% CI: 71–74%].The Kaplan–Meier curve for OS from SACT, is shown in Appendix C.4.

At a median follow-up of 8.3-months, the median treatment duration for all patients in the SACT/CDF dataset – including patients receiving ongoing treatment with IXA+LEN+DEX – was 11.5-months [95% CI: 10.5–12.2] (Table 9).8 At 12-months, 48% of patients were still receiving treatment [95% CI: 46–50%] and 38% of patients were still receiving treatment at 18-months [95% CI: 36–40%]. The Kaplan–Meier curve for treatment duration is shown in Appendix C.4.

Note: the median follow-up time in SACT was only 8.3-months for ToT and 15-months for OS, compared with 85-months for both endpoints in the TMM1 final analysis.

Table 9: OS and treatment duration for all patients with a treatment record in SACT, and patients with 2 or 3 prior lines of therapy in TMM1 at final analysis[8,14]

	SACT/CDF Data	TMM1 Final Analysis	
	IXA+LEN+DEX (N=2,460)	IXA+LEN+DEX (N=148)	LEN+DEX (N=149)
Overall survival			
Median follow-up	15 months	85 months	
Median OS, months	30.0	53.0	43.0
Treatment duration			
Median follow-up	8.3 months	85 months	
Median treatment duration, months	11.5	18.2	13.4

Abbreviations: CDF, Cancer Drugs Fund; IXA+LEN+DEX, ixazomib-lenalidomide-dexamethasone; LEN+DEX, lenalidomide-dexamethasone; OS, overall survival; SACT, Systemic Anti-Cancer Therapy; TMM1, TOURMALINE-MM1

Comparison of primary (TMM1) and secondary (SACT/CDF) data sources

While the data from SACT/CDF demonstrate the clear clinical need for IXA+LEN+DEX in real-world practice, care should be taken in any direct comparisons with TMM1 as there are important differences between the SACT and TMM1 datasets.

Firstly, the lack of a LEN+DEX comparator arm means that comparative efficacy of IXA+LEN+DEX vs. LEN+DEX cannot be derived directly from SACT.

Secondly, the duration of follow-up in SACT is significantly shorter than in the final analysis of the TMM1 trial (15 and 8.3 months for OS and duration of treatment in SACT, vs. 85 months for both endpoints in TMM1). Consequently, TMM1 is a more mature and robust data source than SACT, due to the longer follow-up period.

Thirdly, differences in patient characteristics across the two populations are highly likely to influence OS and ToT. At the March 2021 advisory board, UK MM experts highlighted that age and co-morbidities are key factors that would influence time-dependent outcomes (e.g. OS and ToT).[9] Table 10 highlights key differences between the SACT and TMM1 patient populations. As is common for real-world datasets when compared to clinical trials, the patients from SACT are generally older, less fit and had a poorer prognosis than patients in TMM1. The patient population in SACT was heavily skewed towards more elderly individuals (median age, 72-years; 18% of patients aged >80 years) compared with the IXA+LEN+DEX arm of TMM1 (median age in the 2 or 3 prior subgroup was 67-years). Fewer patients in SACT had received prior stem-cell transplant, again indicating a less fit patient population than in TMM1. Hence, it is not surprising that OS and ToT were shorter in SACT than in TMM1.

Notwithstanding the challenges in interpreting the real-world outcomes for IXA+LEN+DEX from SACT/CDF, the data nevertheless highlight the successful extension of IXA+LEN+DEX from clinical trial to real-world clinical practice. SACT data demonstrate that UK clinicians have been able to use IXA+LEN+DEX across a broad range of patients, particularly in relation to age (60% of patients in SACT were aged ≥70 years, an age group that is typically under-represented in clinical trials). Table 10 also shows that 95% of patients in SACT received IXA+LEN+DEX at third line, indicating that clinicians used the regimen as soon as possible in the treatment pathway, further demonstrating the clinical need for IXA+LEN+DEX.

Table 10. Comparison of patient characteristics for the SACT/CDF data and TMM1 2 or 3 prior therapy populations[4,8]

Patient characteristic		SACT/CDF data	TMM1 (2 or 3 prior therapies)		
		IXA+LEN+DEX (N=2,460)		IXA+LEN+DEX N=148	LEN+DEX N=149
Sex	**Male**	1,425 (58)	**Male**	81 (55)	86 (58)
	Female	1,035 (42)	**Female**	67 (45)	63 (42)
Age	**<40**	10 (<1)	**≤65 yrs**	68 (46)	72 (48)
	40-49	77 (3)			
	50-59	311 (13)			
	60-69	603 (25)	**>65 and ≤75 yrs**	58 (39)	49 (33)
	70-79	1,026 (42)	**>75 yrs**	22 (15)	28 (19)
	80+	433 (18)			
Median age, years		72.0	**Mean age, years (SD)**	65.9 (9.46)	66.1 (10.09)
Performance status (ECOG)	**0**	590	**0**		
	1	953 (24)	**1**	59 (40)	58 (39)
	2	318 (13)	**2**	77 (52)	74 (50)
	3	29 (1)	**3**	10 (7)	15 (10)
	4	6 (<1)	**4**	0	0
	Missing	564 (23)	**Missing**	2	2
Prior therapies	**1**	0 (0)	**1**	18 (12)	14 (9)
	2	2,340 (95)	**2**	91 (61)	102 (68)
	3	120 (5)	**3**	39 (26)	33 (22)
Previous treatment outcome	**Not refractory to all prior therapies**	2,057 (84)	**Relapsed***	93 (63)	90 (60)
	Refractory to at least one line of therapy	403 (16)	**Refractory****	15 (10)	19 (13)
			Relapsed and Refractory***	40 (27)	40 (27)
			Primary Refractory******	11 (7)	10 (7)
Prior SCT	**Yes, n (%)**	947 (38)	**Prior autologous SCT**	86 (58.1)	81 (54.4)
Prior IMiD***	**Received 1L**	46 (2)	**Exposed**	100 (68)	102 (68)
	Received 2L	26 (1)	**Naïve**	48 (32)	47 (32)
	Treatment naïve	822 (33)	**Refractory**	24 (16)	35 (23)
	Not captured	1,566 (64)			

*Relapsed (progressive disease > 60 days after last dose of any previous treatment) but not refractory. **Refractory (progressive disease on or within 60 days after last dose of any previous treatment). *** Relapsed from at least one previous treatment AND refractory to at least one previous treatment. ****Refractory to all lines of previous therapy defined as best response to prior therapy stable disease or disease progression on all lines of therapy. *****In TMM1, 12% of patients in both arms were exposed to lenalidomide.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IXA+LEN+DEX, ixazomib-lenalidomide-dexamethasone; LEN+DEX, lenalidomide-dexamethasone; NR, not reported; SACT, Systemic Anti-Cancer Therapy; SCT, stem-cell transplant; TMM1, TOURMALINE-MM1.

Red highlights indicate important differences between the two patient populations.

A.6.3 *Secondary Data Source | UVEA-IXA*

The "Use Via Early Access to Ixazomib" (UVEA-IXA) study is a European, multicentre, observational, longitudinal cohort study of patients with relapsed/refractory MM (RRMM) receiving ixazomib-based therapy at specialist centres via an Early Access Program (EAP). The EAP was commonly referred to as the Named Patient Programme (NPP) in the UK and enabled UK patients to access ixazomib free of charge prior to the CDF recommendation.

At the data cut-off of 30th September 2019, 358 patients had been enrolled; the largest proportion of patients were treated in the UK [redacted].[19,20] In total, [redacted] patients from [redacted] UK centres were enrolled in UVEA-IXA, of whom [redacted] were evaluable at the data cut-off.[19] The analysis presented here will focus on the cohort of UK treated patients who had a median observation period of [redacted]-months [redacted];[19] all UK patients in UVEA-IXA received the IXA+LEN+DEX regimen.

Median duration of IXA+LEN+DEX treatment [redacted] was [redacted]-months (range,[redacted], and the mean number of cycles of IXA+LEN+DEX treatment received was [redacted] cycles (SD, [redacted].[19] Median OS during the whole observation period was [redacted]-months (95% CI: [redacted].[19]

A.7 Incorporating collected data into the model

The economic model used for decision making in the original NICE submission (TA505), including integration of the ERG scenarios [file name: ID807 ixazomib ERG revised model 16102017KM (ACIC) _CORRECTED], has been updated using the final analysis from TMM1 with the updated and correct treatment switching analyses. The results and scenarios from the original submission can be achieved in the economic model through drop-down options on the 'Main Settings' sheet. The updates in this dossier describe: OS (with and without subsequent therapy adjustments), subsequent therapies, ToT, HRQoL, adverse events, hospitalisations, concomitant medications and costs.

A.7.1 *Treatment switching analyses*

While extending the follow-up time for OS addresses the uncertainty associated with long-term extrapolation, it also introduces confounding stemming from subsequent therapies. The confounding introduced into the treatment effect is defined as the difference (error) between the estimated treatment effect and the effect that would have been observed if the treatment pathway had reflected UK clinical practice or if the distribution of subsequent therapies were balanced between treatment arms. This confounding is particularly important to address when the subsequent therapy profile differs between treatment arms, as observed in TMM1.

As discussed in Section A.6.1, there are two key aspects when considering the subsequent therapy pathway observed in TMM1 compared to current UK clinical practice: (1) the use of novel therapies in the TMM1 trial which are neither reimbursed nor routinely available for use in clinical practice in the UK and (2) the use of a PI-containing regimen as the next line of therapy for patients who have progressed while receiving a PI-containing regimen. (i.e. IXA+LEN+DEX). As per the NICE Position Statement,[10] medicines available only via the CDF and not via routine commissioning should not be included as a comparator or subsequent therapy. This section presents the extensive statistical analyses and clinical validation undertaken to derive the OS data that would have been expected had the subsequent therapy profile in TMM1 aligned with UK clinical practice (termed the "adjusted OS" data).

Firstly, we describe the treatment pathway which would be expected in UK clinical practice and identify the patients who deviate from this within the TMM1 data. Secondly, we describe the methodologies applied to adjust for the effect of these subsequent therapies from the OS data. Finally, we present the results of the treatment switching analyses compared with the unadjusted data and detail the feedback from our clinical validation.

In the following sections, the term “switchers” refers to patients who have received a subsequent therapy that requires adjustment and the term “switch date” refers to the date at which they received the subsequent therapy of interest.

Identifying the “switchers”

Switchers were identified based on receipt of novel agents which are either not reimbursed or not routinely available in UK clinical practice (i.e. medicines that are only available through the CDF). Such therapies were received in the TMM1 clinical trial as patients were enrolled across multiple countries where these novel agents were available. The following regimens were identified as novel: carfilzomib (CARF)-based, elotuzumab (ELOT)-based, BORT+LEN+DEX, pomalidomide (POM)+BORT+DEX, re-treatment with IXA or LEN, stem-cell transplants (SCT), plitidepsin, cetuximab, pembrolizumab and nivolumab. In addition, daratumumab (DARA)-based and isatuximab (ISA)-based regimens were adjusted for as they are only funded via the CDF. This resulted in: N=59 patients and N=52 patients requiring adjustment for receipt of agents not routinely available in the UK in the IXA+LEN+DEX and LEN+DEX treatment arms, respectively.

In MM clinical practice, the type of prior therapy received is important in informing treatment decisions at the next stage of the pathway. For the majority of treating physicians in TMM1, informed decisions regarding the choice of next line of therapy for their patients were limited by the double-blind nature of the trial. The implications of this were that many patients who had received and progressed on a PI at third or fourth line, in the ixazomib arm, and were thus PI refractory were re-exposed to a PI as their next line of therapy. from UK-based MM specialists were unanimous during the March 2021 advisory board that this does not reflect UK clinical practice.[9]

In total 42 patients in the IXA+LEN+DEX arm received a PI as their immediate next line of therapy; 25 of these patients were also identified as switchers as they received therapies unavailable in routine UK practice either at the next line (i.e. carfilzomib which is both a PI and a therapy not routinely available in UK clinical practice) or at later lines. Therefore, there was significant overlap between the group of switchers identified as receiving a next-line PI and the group of switchers identified as receiving a treatment not routinely funded in UK clinical practice. It was not possible to disentangle the effects on OS of the next-line PI from the subsequent therapies unavailable in routine UK clinical practice due to the considerable overlap between patients who were identified as switchers. For these reasons, patients who received a next-line PI in the IXA+LEN+DEX arm were not included as switchers in the analyses.

For clarity, consistent with the NICE Position Statement,[10] switchers were defined as patients who received a subsequent treatment which is not routinely available in UK clinical practice.

Table 11 presents the number of patients who were adjusted for by treatment arm based on type of subsequent therapy received – data are presented for all lines of subsequent therapy and for the next line only. **Note:** some patients received multiple lines of novel therapies, Table 11 reflects the first of the novel therapies received which was used as the switch date.

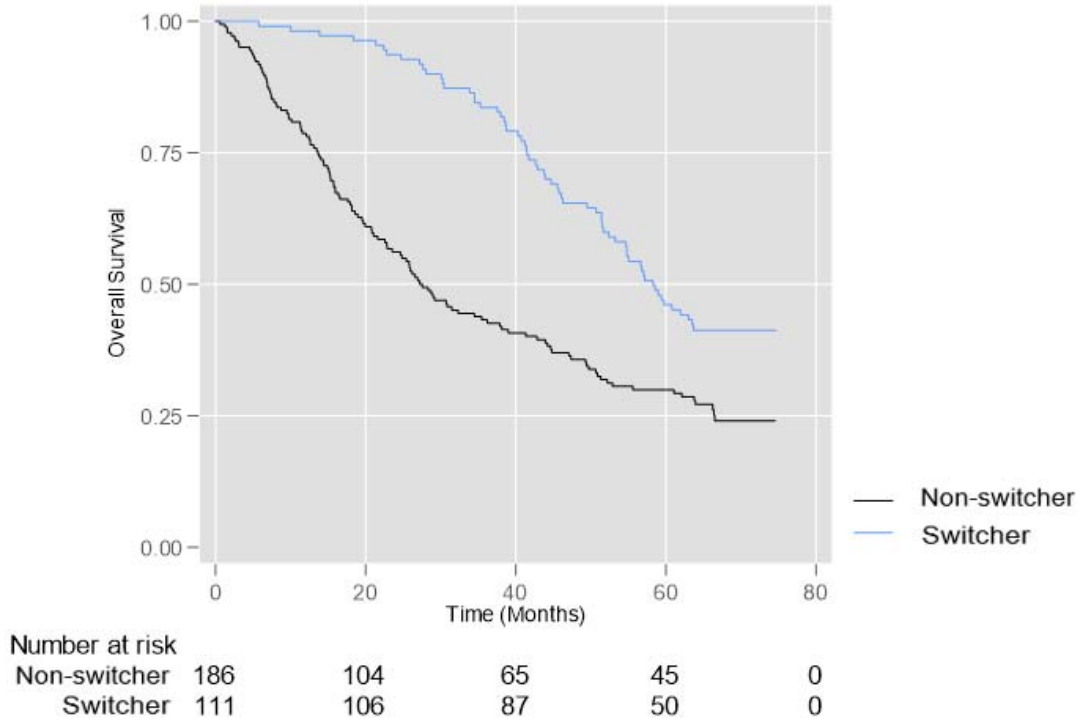
Table 11: Patients adjusted for in the treatment switching analyses

	All subsequent lines		Next line		Later line	
	IXA+LEN+DEX	LEN+DEX	IXA+LEN+DEX	LEN+DEX	IXA+LEN+DEX	LEN+DEX
Therapies not available or routinely funded in the UK						
DARA-based	11	10	6	5	5	5
DARA+LEN-based	1	0	1	0	0	0
CARF-based	18	13	4	4	14	9
ELOT-based	2	4	1	2	1	2
ISA-based	1	0	1	0	0	0
LEN-based	14	8	6	5	8	3
IXA-based	3	5	1	4	2	1
PLIT-based	2	1	1	1	1	0
CETUX-based	1	0	1	0	0	0
PEMBRO-based	2	1	2	0	0	1
SCT	0	5	0	3	0	2
BORT+LEN+DEX	2	1	0	0	2	1
POM+BORT+DEX	2	3	0	2	2	1
NIVO-based	0	1	0	1	0	0

Abbreviations: PI, proteasome inhibitor; DARA, daratumumab; LEN, lenalidomide; CARF, carfilzomib; ELOT, elotuzumab; ISA, isatuximab; IXA, ixazomib; PLIT, plitidepsin; CETUX, cetuximab; PEMBRO, pembrolizumab; SCT, stem-cell transplant; BORT, bortezomib; DEX, dexamethasone; POM, pomalidomide; NIVO, nivolumab.

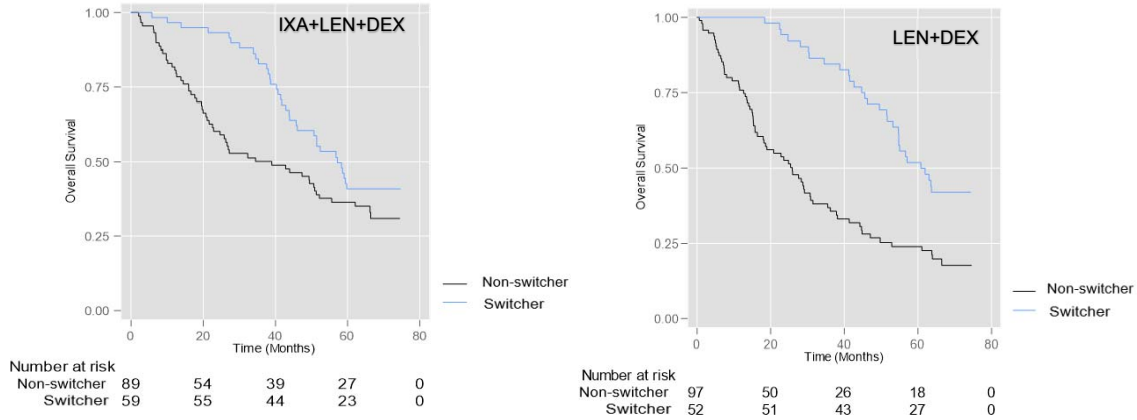
Figure 2 presents the Kaplan–Meier curves comparing the unadjusted OS for patients identified as switchers vs. non-switchers (Figure 3 presents these analyses separately for the IXA+LEN+DEX and LEN+DEX treatment arms). Note: these are naïve analyses which break randomisation and do not adjust for differences in prognostic factors or treatment-effect modifiers between the switching subgroups. Despite this, it is important to note that a trend is observed towards improved OS for patients that switch compared with those that do not.

Figure 2: OS unadjusted Kaplan–Meier curves for patients identified as switchers vs. non-switchers (all patients)



Abbreviations: OS, overall survival

Figure 3: OS unadjusted Kaplan–Meier curves for patients identified as switchers vs. non-switchers (separated by treatment arms)



Abbreviations: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; OS, overall survival

Adjusting for the "switchers"

The treatment switching analysis framework, as outlined in the NICE TSD 16,[17] was followed for the analyses. The following methods were considered:

- Naive analyses (i.e., censoring patients at switch and excluding patients who switch)
- Inverse probability of censoring weights (IPCW)
- Two-stage methods
- Rank preserving survival failure time models (RPSFTM)

The naïve analysis in which patients are censored from the switch date or excluded from the analysis completely was explored as a reference point; this methods likely introduce selection bias through informative censoring as the chances of switching are likely dependent on prognostic patient characteristics. Therefore, the results of this analysis were not implemented in the economic model.

Similar to the naïve analysis, the IPCW method censors patients at the switch date. The remaining observations are then weighted based upon covariate values and a model of the probability of being censored (i.e. probability of switch). This allows patients who have not been censored (i.e. not switched) to be weighted to reflect their similarities to patients who have been censored (i.e. switched), in an attempt to remove the selection bias caused by the censoring. This method requires the assumption of no unmeasured confounders (i.e. data must be available, and accounted for, on baseline and time-dependent variables that predict both treatment switching and prognosis). The list of variables considered in these analyses includes the following: gender, age, region (North America vs. other), race (white vs. non-white vs. unknown), prior PI (yes vs. no), corrected calcium (continuous), serum protein (continuous), urine M-protein (continuous), platelets (continuous), ISS stage (I vs. II vs. III), time since diagnosis and time to next treatment. To ensure that the most important prognostic factors for switching and survival are captured, this list was informed and validated through feedback from the clinical advisory board and follow-up communication with clinicians.

The two-stage estimator (TSE) methodology was explored using date of receipt of subsequent antineoplastic therapy as a secondary baseline. This method estimates a treatment effect specific to patients who switch and then the survival times of these patients are adjusted to reflect what would have been expected had they not switched, subsequently allowing the treatment effect specific to a population without switching to be estimated for the whole population. This method also requires the no unmeasured confounders assumption. These confounders only need to be accounted for at the secondary baseline – the same list of

covariates as considered in the IPCW analyses was considered for the TSE. This method also requires a secondary baseline to proxy the point of switch to be identifiable. For the purposes of this analysis, the date of receipt of subsequent antineoplastic therapy is assumed to be the secondary baseline. This was preferred to the use of progression because PFS was not collected as part of the final data cut from TMM1. Using PFS data from an earlier data cut would be inconsistent with the OS data from the final data cut and would result in missing secondary baseline dates for some patients (of the 111 patients identified as switchers, only 53 had a recorded progression event based on the second interim analysis from TMM1).

The construction of counterfactual survival times was then performed as:

$$T_i^{a=0} = T_{i,xot} + T_{i,pxo}\exp(\psi_2)$$

Where $T_i^{a=0}$ is the counterfactual survival time for the ith individual, $T_{i,xot}$ is the time from baseline to 'switch', and $T_{i,pxo}$ is the time between 'switch' and death (or censoring). The process of adjusting survival times introduces an informative censoring bias. As described by Latimer et al,[21] for TSE, informative censoring is induced because the counterfactual survival model involves adjusting survival times for those who 'switched', but not for those who did not. For some patients who 'switched', the time of death may not be observed, and censoring occurs. For such patients, the TSE adjusts censoring times. This will result in informative censoring if there is an association between switching and prognosis – which is very likely to be the case in this context where the treatments defining a switcher are novel therapies with efficacious profiles. Additionally, naïve comparisons of the OS outcomes between switchers and non-switchers indicate a trend towards superior outcomes for those patients that switch – see Figure 2 and Figure 3. For this reason and following NICE TSD 16 recommendation, re-censoring has been applied in adjustment analyses.[22] In the context of TSE, the process of re-censoring is summarised by Latimer et al.[23] Counterfactual survival times are re-censored for all patients in the respective study arm at the minimum of the administrative censoring time of the study C_i and $C_i\exp(\psi_2)$, representing the earliest possible censoring time over all possible treatment trajectories.

The RPSFTM methods were also considered. However, in MM, the common treatment effect assumption has been shown to be invalid across multiple trials. This was confirmed by UK clinical experts who noted the relative efficacy of different treatment regimens varies depending on the line of therapy. Therefore, these methods were discounted from further analysis.

Results of the treatment switching analyses

Table 12 presents the results from the treatment switching analyses. The OS hazard ratios for IXA+LEN+DEX vs. LEN+DEX are shown to improve in all treatment switching adjusted analyses, relative to the unadjusted data. However, when looking at the effect of the treatment switching adjustments on absolute survival outcomes, the IPCW does not align with clinical expectations. The IPCW method improves OS in both treatment arms, resulting in adjusted Kaplan–Meier curves which are clinically implausible; clinical experts considered that OS should reduce when adjusting for the effects of efficacious subsequent therapies. Additionally, the predicted survival was considered to be too optimistic compared to real-world expectations. For these reasons, the IPCW does not appear to have appropriately adjusted for the confounding introduced by subsequent therapies. Furthermore, clinical experts noted that the survival estimate predicted by IPCW over-estimate survival for MM patients and are clinically implausible.

The results from the two-stage methodology align with clinical expectations for both the relative and absolute effects on the OS curves; the outcomes of this analysis most closely align with what would be expected in UK clinical practice where, for the purposes of a NICE appraisal, agents that are not routinely funded have been excluded from the treatment sequence. The unadjusted, IPCW and two-stage analyses are built into the economic model and can be selected on the 'Model Settings' sheet. See Section 7.2 for the survival analysis on the adjusted data.

Table 12: Unadjusted and adjusted OS hazard ratios

	Hazard ratio (95% CI), p-value IXA+LEN+DEX vs. LEN+DEX
Unadjusted	0.845 (0.642 - 1.114; p=0.2316)
Naïve – censor at switch	0.712 (0.507 - 0.999; p=0.0484)
Naïve – 'per protocol'‡	0.699 (0.493 - 0.990; p=0.0428)
TSE (no re-censoring + adjust for baseline characteristics†)	0.785 (0.596 - 1.035; p=0.0857)
TSE (re-censored* + adjust for baseline characteristics†)	0.713 (0.535 - 0.952; p=0.0216)
IPCW (stabilised weights + adjust for baseline characteristics†)	0.674 (0.465 – 0.979; p=0.0383)

Abbreviations: CI, confidence interval; IPCW, inverse probability of censoring weighting; IXA+LEN+DEX, ixazomib-lenalidomide-dexamethasone; LEN+DEX, lenalidomide-dexamethasone; OS, overall survival; TSE, two-stage estimator.
Note: p-values from stratified log-rank tests for analyses which do not adjust for baseline characteristics. For analyses which adjust for baseline characteristics, p-values are those associated with the coefficient from a Cox regression model including treatment arm and baseline characteristics as covariates.
† Adjusts for high risk, age>65, ISS stage at screening, and history of bone lesions.
‡ Excludes all patients who switched from the analysis.

* Counterfactual survival times are re-censored for all patients at the minimum of the administrative censoring time of the study (28th September 2020; C_i) and $C_i\psi_2$, where $\psi_2$is the adjustment factor associated with group 2 membership. This represents the earliest possible censoring time.

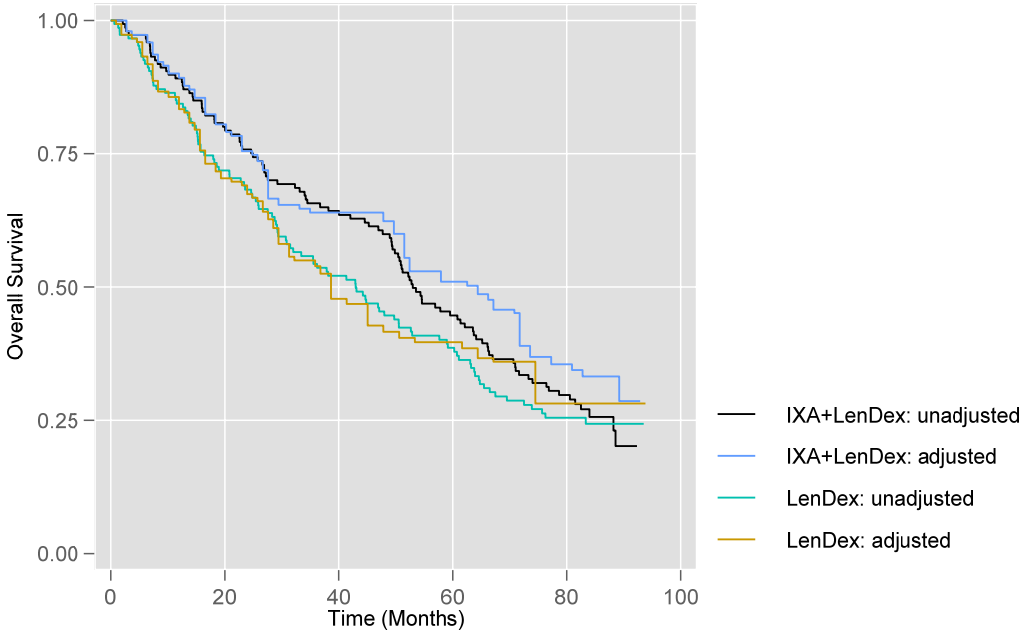
Naïve analyses

Naïve approaches led to improvements in the estimates of OS for IXA+LEN+DEX vs LEN+DEX when compared to the unadjusted analysis. As 'switching' was associated with improved clinical outcomes (Figure 3), and more patients were adjusted in the IXA+LEN+DEX arm, this result is expected but is subject to selection bias.

IPCW

Figure 4 presents the adjusted Kaplan–Meier curves following IPCW adjustment relative to the unadjusted data. The results appear counterintuitive as the OS was shown to improve in both treatment arms following adjustment – which is not aligned with clinical expectations after adjusting for the effect of efficacious subsequent therapies.

Figure 4: IPCW analysis

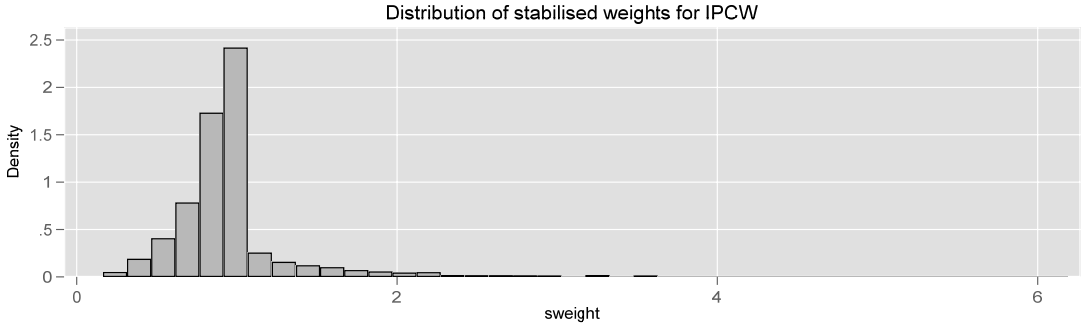


Abbreviations: DEX, dexamethasone; IPCW, inverse probability of censoring weights; IXA, ixazomib; LEN, lenalidomide

The IPCW method requires the correct specification of model 'switching' (i.e. a model of 'why' a patient 'switched') and survival. The model predicting switching had poor explanatory power

(pseudo R^2=0.05). Unstabilised weights were highly clustered around 1. However, a small number of observations had extreme weights; even following stabilisation (max 91), see Figure 5. For these reasons and because the outcomes of the IPCW adjustment are not clinically plausible, the IPCW method is explored in the economic model only as a scenario analysis.

Figure 5: Distribution of weights in IPCW



Abbreviations: IPCW, inverse probability of censoring weights

Two-stage estimator

Figure 6 and Figure 7 present the adjusted Kaplan-Meier curves following two-stage adjustment (without and with re-censoring, respectively) relative to the unadjusted data. The results align with clinical expectations (i.e. OS reduces in both treatment arms following adjustment for efficacious subsequent therapies).

Figure 6: Two-stage adjustment without re-censoring

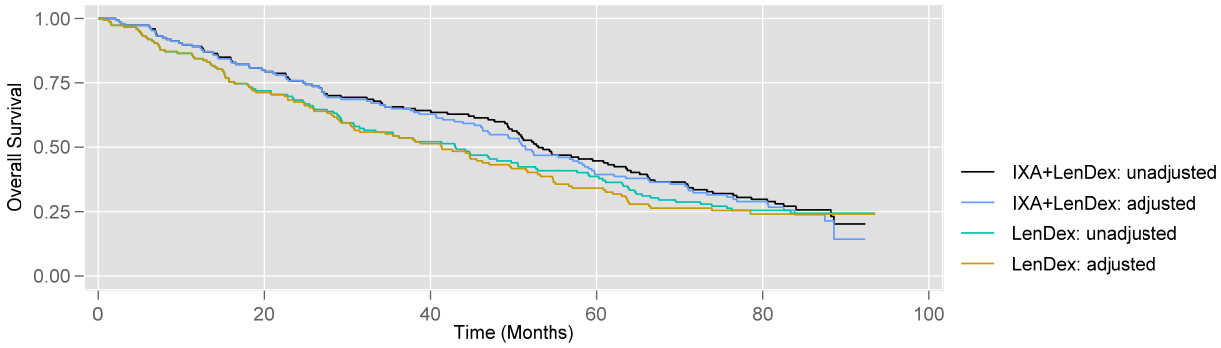
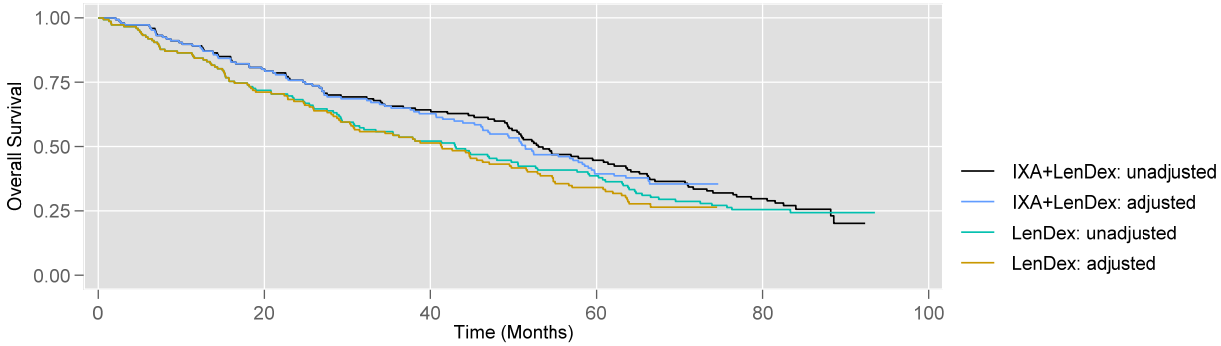


Figure 7: Two-stage adjustment with re-censoring



A total of 198 patients began next-line anti-cancer therapy and were eligible for inclusion in the model of survival from the new secondary baseline.

It is important to recognise that at the point of the secondary baseline, subjects are not randomised to 'switch' or not; the TSE analysis aims to control for confounders which may bias such comparisons to provide unbiased estimates of the consequence of being a patient who switched vs. a patient who did not. The TSE analysis makes the assumption that there are no unmeasured confounders. Final covariates included in the model of survival post-secondary-baseline were restricted to those which achieved statistical significance and included: high risk status, sex, age > 65, history of bone lesions, baseline serum M protein, time from initial diagnosis to first dose, and baseline platelet count.

The two-stage adjustment aligned with clinical expectations following the adjustment for subsequent therapies unavailable in UK routine clinical practice. Therefore, in line with the NICE Position Statement and the NICE TSD,[10,17] this method was applied with re-censoring as the base case in the economic analysis.

A.7.2 *Overall survival*

The original NICE submission extrapolated OS data from the IA2 of TMM1, with a median follow-up of 23-months. The NICE Committee concluded that, although the results from the IA2 data cut were promising, the data were too immature to allow a reliable conclusion to be drawn about the magnitude of the OS benefit. As specified in the ToE, these data have been updated with the final analysis from the TMM1 trial – in line with Section A.6.1 – with a median follow-up of 85-months. While extending the follow-up time for OS addresses the uncertainty associated with long-term extrapolation, it also introduces confounding stemming from the subsequent therapies received within the trial.

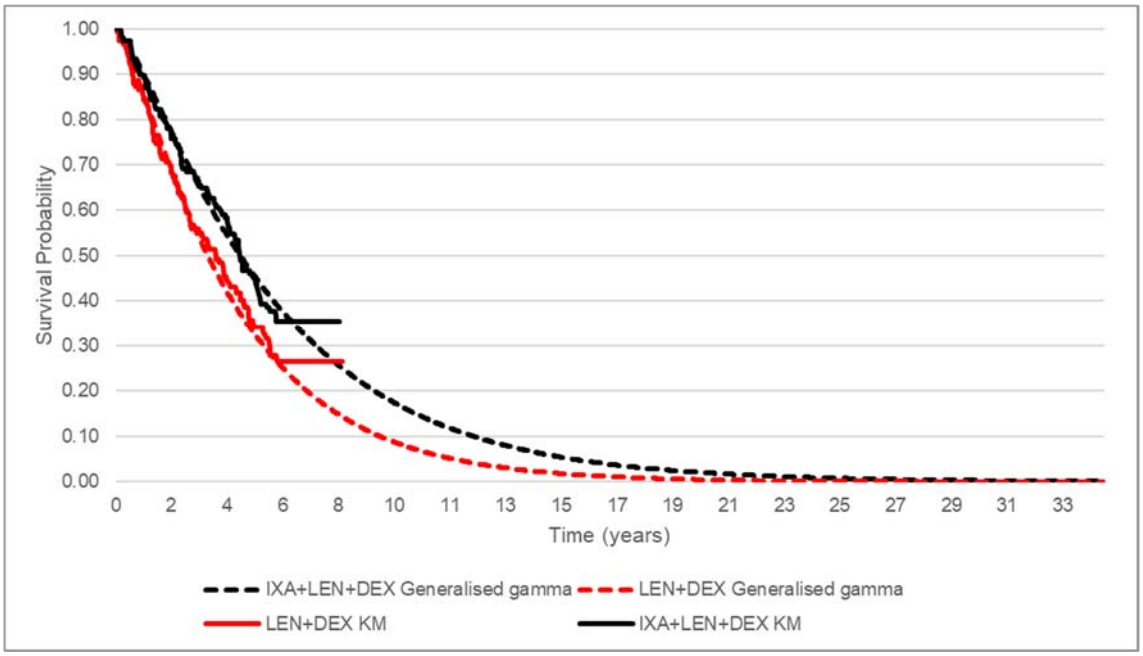
Extensive statistical analyses and clinical validation have been undertaken to estimate the OS had the subsequent therapy profile aligned with routine UK clinical practice, termed the "adjusted OS" data. The base case applies the two-stage methodology with re-censoring to account for the confounding introduced through subsequent therapies as detailed in Section A.7.1. The adjusted OS data are used to extrapolate survival within the base case of the economic model. The generalised gamma curve is applied in the base case based on the validity of long-term survival predictions. Scenario analyses explore the impact of using the unadjusted OS data, adjusted OS data using the two-stage analysis without re-censoring and adjusted OS data using the IPCW analysis – see Section A.11. All options are included in the economic model and can be selected on the 'Main Settings' sheet.

In line with the original submission, univariate and multivariate approaches were undertaken in the OS analyses. The univariate approach only accounts for the treatment arm as a covariate. The multivariate approach aims to address any imbalances in key prognostic factors and/or treatment effect modifiers between the treatment arms in the 2 or 3 prior lines subgroup of the TMM1 population. The original NICE submission presents the methodology underpinning the selection of covariates in detail. In line with the original submission, the multivariate approach is assumed in the base case to ensure a balance in all key characteristics between treatment arms in the subgroup. Both options are included in the economic model and can be selected on the 'Main Settings' sheet.

Figure 8 presents the generalised gamma fit to the two-stage adjusted OS data with re-censoring, accounting for background mortality. The generalised gamma curve was considered to provide an estimation of predicted outcomes which most closely aligned with current outcomes observed in the UK by clinical experts. **Note:** background mortality was not included in the original NICE submission. However, it has been added to ensure the mortality rate of the model population is greater than or equal to the general population in England and Wales. The multivariate approach applied in the base case accounts for: treatment arm, high-

risk cytogenetics, ISS stage, history of bone lesions and age (>65 years). Table 13 presents the landmark analyses for the proportion of patients surviving at 10-, 15-, 20- and 25-years.

Figure 8: Comparison of fitted (generalised gamma) 2-stage with re-censoring for adjusted OS curves with adjusted Kaplan–Meier curves



Abbreviations: IXA+LEN+DEX, ixazomib-lenalidomide-dexamethasone; LEN+DEX, lenalidomide-dexamethasone; OS, overall survival.

Table 13: Landmark analyses TSE adjusted OS with re-censoring (Generalised gamma)

	10-years	**15-years**	**20-years**	**25-years**
IXA+LEN+DEX	16.07%	5.81%	2.10%	0.77%
LEN+DEX	7.84%	1.98%	0.51%	0.13%

Abbreviations: IXA+LEN+DEX, ixazomib, lenalidomide and dexamethasone; LEN, lenalidomide; LEN+DEX, lenalidomide and dexamethasone; OS, overall survival.

The FAD from the original NICE appraisal stated that the continued treatment effect of IXA+LEN+DEX beyond discontinuation was unclear.[2] A number of scenarios were presented by the Company and the ERG to explore the impact of waning the treatment effect from different start points and over different durations. However, the base case did not include any treatment effect waning. The updated OS data from TMM1 reflects survival outcomes for >96% of patients who have discontinued treatment with IXA+LEN+DEX and for >99% of patients who have discontinued treatment with LEN+DEX. Therefore, any treatment effect waning is already reflected within these updated OS data. For illustrative purposes, a scenario analysis is presented which explores waning the treatment effect for both the IXA+LEN+DEX and LEN+DEX treatment arms from the end of the trial follow-up over a 5-year time period for

the 4% and 1% of patients still on treatment in the trial. **Note:** based on feedback from clinical experts during the original NICE appraisal, this is a conservative assumption as advice indicated the treatment benefit could be maintained for one or two further relapses.

A.7.3 *Subsequent therapies*

The model maintains the ERG's preferred methodology for TA505, which is that subsequent therapy costs are split into a one-off cost applied upon progression, on-active treatment costs and off-active treatment costs.

On-active-treatment

As discussed in Section A.6.1, statistical analyses were conducted to adjust for the impact of subsequent therapies on OS that are not routinely funded in UK clinical practice. The two-stage adjusted OS data with re-censoring are applied in the base case to align with the NICE reference case and UK clinical practice. Table 14 presents the resulting subsequent therapy distribution and compares this with the unadjusted OS data and the original NICE submission dossier for TA505 (2016).

Table 14: Subsequent therapy distribution for costs

	Adjusted OS		Unadjusted OS		Original submission	
	IXA+LEN +DEX	LEN +DEX	IXA+LEN +DEX	LEN +DEX	IXA+LEN + DEX	LEN +DEX
BEN+PRED[a]	10.34%	14.32%	6.67%	8.60%	11.11%	11.11%
CYC[b]	22.16%	30.43%	14.29%	18.28%	41.41%	41.41%
BORT+DOX[c]	8.86%	10.74%	5.71%	6.45%	9.09%	9.09%
BORT+DEX[d]	54.66%	62.64%	35.24%	37.63%	0.00%	0.00%
CARF+DEX[e]	0.00%	0.00%	22.86%	21.51%	0.00%	0.00%
LEN+DEX[f]	0.00%	0.00%	27.62%	23.66%	21.21%	21.21%
MELPH+PRED[g]	23.64%	39.38%	15.24%	23.66%	18.18%	18.18%
POM+DEX[h]	63.53%	69.80%	40.95%	41.94%	0.00%	0.00%
THAL+DEX[i]	23.64%	14.32%	15.24%	8.60%	12.12%	12.12%
PANO+BORT+DEX[j]	7.39%	8.95%	4.76%	5.38%	79.80%	79.80%
BORT+BEN+DEX[k]	10.34%	21.48%	6.67%	12.90%	0.00%	0.00%
CARF+LEN+DEX[l]	0.00%	0.00%	1.90%	3.23%	0.00%	0.00%
DARA[m]	0.00%	0.00%	13.33%	29.03%	0.00%	0.00%
DARA+LEN+DEX[n]	0.00%	0.00%	4.76%	7.53%	0.00%	0.00%
DEX[o]	5.91%	5.37%	3.81%	3.23%	0.00%	0.00%
ELOT+THAL+DEX[p]	0.00%	0.00%	0.00%	2.15%	0.00%	0.00%
ELOT+POM+DEX[q]	0.00%	0.00%	2.86%	5.38%	0.00%	0.00%
ISA+POM+DEX[r]	0.00%	0.00%	0.95%	1.08%	0.00%	0.00%

IXA+DEX[s]	0.00%	0.00%	1.90%	3.23%	0.00%	0.00%
IXA+LEN+DEX[t]	0.00%	0.00%	2.86%	2.15%	0.00%	0.00%
POM+CARF+DEX[u]	0.00%	0.00%	1.90%	1.08%	0.00%	0.00%
SCT	0.00%	0.00%	0.95%	10.75%	0.00%	0.00%

[a]Includes the following treatments: BEN, BEN+BETAMETHASONE, BEN+DEX, BEN+methylPRED, BEN+PRED, BEN+PRED+DEX and BEN+THAL+DEX; [b]Includes the following treatments: CYC, CYC/MELPH+DEX, CYC+DEX, CYC+DEX+CIS+ETOP+DOX+SCT, CYC+DEX+PRED, CYC+DOX+VIN+DEX, CYC+MELPH+DEX, CYC+methylPRED, CYC+PRED, CYC+PRED+DOX, CYC+VIN+DOX and CYC+VIN+MELPH+LOMUSTINE+methylPRED; [c]Includes the following treatments: BORT+DOX, BORT+DOX/THAL+DEX, BORT+DOX+DEX and BORT+DOX+MELPH+DEX; [d]Includes the following treatments: BORT, BORT+CYC, BORT+CYC/DEX, BORT+CYC+DEX, BORT+CYC+DEX+CIS+ETOP, BORT+CYC+methylPRED, BORT+CYC+THAL+PRED, BORT+CYTARA+METHO+DEX, BORT+DEX, BORT+DEX+ETOP, BORT+MELPH+DEX, BORT+MELPH+PRED, BORT+MELPH+PRED+DEX, BORT+THAL+DEX, BORT+THAL+DEX+CIS+DOX+CYC+ETOP and BORT+THAL+ETOP+CYC+CIS+DOX+DEX; [e]Includes the following treatments: CARF+THAL+DEX, CARF+DEX, CARF+CYC, CARF+CYC+DEX and CARF; [f]Includes the following: LEN+BEN+DEX/PRED, LEN, LEN+BETAMETHASONE, LEN+BORT+BETAMETHASONE, LEN+BORT+CYC+DEX, LEN+CYC+DEX, LEN+CYC+PRED, LEN+DEX, LEN+IDARUBICIN+DEX, BORT+LEN+DEX, BORT+LEN+DEX+DOX and LEN+PRED; [g]Includes the following treatments: CAPECITABINE- OXALIPLATIN, CYTARA + HYDROCORTISONE + METHO, DCEP (DEXAMETHASONE+CYCLOPHOSPHAMIDE+ETOPOSIDE+CISPLASTIN), ETOP+DEX+CYTARA+CIS, MELPH, MELPH+DEX, MELPH+methylPRED, MELPH+PRED, MELPH+THAL+PRED, methylPRED, PRED, PREDNISONE, ETOPOSIDE, PROCARBAZINE AND CYCLOPHOSPHAMIDE (PEP-C), PROCARBAZINE+PRED+CYC+ETOP+MELPH, RANIMUSTINE+methylPRED/PRED and VINCRISTINE-ADRIAMYCINE-DEX; [h]Includes the following: POM+methylPRED, POM+MELPH, POM+DEX, POM+CYC+DEX, POM+CYC+CLARITROMICIN+DEX, POM+BORT+DEX, POM+BORT+CYC+DEX and POM; [i]Includes the following: THAL, THAL+CYC, THAL+CYC+CIS+DOX+ETOP+DEX, THAL+CYC+DEX, THAL+DEX, BEN+THAL+DEX, THAL+MELPH+PRED and THAL+PRED+DEX; [j]Includes the following: PANO+BORT+DEX and PANO+LEN+DEX; [k]Includes the following treatments: BEN+BORT+DEX, BEN+BORT+PRED, BORT+BEN, BORT+BEN+BETAMETHASONE, BORT+BEN+CYC+DEX, BORT+BEN+DEX and BORT+BEN+THAL+DEX; [l]Includes the following treatments: CARF+LEN+DEX and CARF+POM+DEX; [m]Includes the following treatments: DARA, DARA+BORT, DARA+BORT+DEX, DARA+DEX, DARA+MELPH, DARA+THAL+CYC+DEX and DARA+THAL+DEX; [n]Includes the following treatments: DARA+CARF+DEX, DARA+POM+DEX, DARA+POM+PRED/DEX and DARA+LEN+DEX; [o]Includes the following treatments: DEX; [p]Includes the following treatments: ELOT+THAL+CYC+DEX and ELOT+THAL+PRED; [q]Includes the following treatments: ELOT+LEN+DEX, ELOT+POM+BETAMETHASONE, and ELOT+POM+DEX; [r]Includes the following treatments: ISA+POM+DEX; [s]Includes the following treatments: IXA+CYC+DEX, IXA+CYC+DOX+PRED, and IXA+DEX; [t]Includes the following treatments: IXA+LEN, and IXA+LEN+DEX; [u]Includes the following treatments: POM+CARF+CLARITHROMYCIN+DEX, and POM+CARF+DEX.

The total cost of active subsequent therapies includes: therapy costs, administration costs for IV therapies, adverse event costs and routine management costs. It is assumed that routine management includes an outpatient oncology visit, a complete blood count and a blood testing-chemistry panel each treatment cycle. All costs from the original NICE submission dossier were updated to reflect 2018/2019 prices. All additional costs, required through the introduction of new subsequent therapies, were sourced from the British National Formulary, the electronic marketing information tool (eMIT), the NHS Reference Costs (2018/19) or the PSSRU (2020).

Please note all costs reflect list prices only and do not include any confidential discounts or PAS.

Dosing information and duration of therapy were obtained from relevant clinical trials. Table 15 presents the weekly costs relating to therapy, administration, adverse events and routine management for each subsequent therapy. These are summed and multiplied by the duration of therapy as a ratio of time spent in the post-progression health state, before being weighted by the proportion of patients receiving the respective therapy in the IXA+LEN+DEX and

LEN+DEX treatment arms – see Table 14. This results in weekly costs of £576.01 and £797.33 for IXA+LEN+DEX and LEN+DEX in the 2-stage adjusted (with re-censoring) base case, respectively. This is compared with £456.33 and £628.46, respectively, from the original NICE submission. **Note:** when the unadjusted OS data are used within the model the weekly costs are £752.88 and £981.11, respectively, which reflects the increased use of expensive subsequent therapies in the LEN+DEX arm.

Table 15: Weekly costs relating to subsequent therapies

	Duration of treatment in weeks	Weekly treatment cost	Weekly AE cost	Weekly routine management costs	Total weekly costs
BEN+PRED	15.91	£198.55	£40.86	£48.78	£288.19
CYC	82.55	£394.47	£16.99	£48.78	£460.24
DOX	15.00	£556.19	£98.62	£65.04	£719.86
BORT+DEX	26.52	£851.35	£32.83	£65.04	£949.22
CARF+DEX	24.00	£3,718.37	£28.20	£66.93	£3,813.49
LEN+DEX	82.55	£299.48	£16.99	£48.78	£365.25
MELPH+PRED	48.00	£104.94	£31.66	£39.03	£175.63
POM+DEX	43.48	£2,222.11	£23.87	£48.78	£2,294.76
THAL+DEX	17.39	£301.81	£42.59	£48.78	£393.18
PANO+BORT+DEX	21.74	£1,912.43	£65.30	£65.04	£2,042.77
BORT+BEN+DEX	24.00	£468.05	£36.70	£48.78	£553.53
CARF+LEN+DEX	88.00	£2,196.46	£14.03	£66.93	£2,277.41
DARA	14.78	£3,613.78	£29.09	£48.78	£3,691.66
DARA+LEN+DEX	148.71	£1,789.86	£7.72	£48.78	£1,846.36
DEX	43.48	£3.33	£22.13	£48.78	£74.24
ELOT+THAL+DEX	43.48	£2,446.76	£19.35	£48.78	£2,514.90
ELOT+POM+DEX	36.00	£4,639.24	£14.26	£48.78	£4,702.28
ISA+POM+DEX	41.03	£4,652.28	£31.47	£48.78	£4,732.54
IXA+DEX	107.95	£1,585.11	£11.99	£48.78	£1,645.88
IXA+LEN+DEX	107.95	£1,883.42	£11.99	£48.78	£1,944.19
POM+CARF+DEX	28.00	£4,254.06	£29.86	£48.78	£4,332.70
SCT	1.00	£10,324.82	£0.00	£0.00	£10,324.82

Off-active-treatment

The off-treatment costs relating to the post-progression health state reflect one outpatient visit to the oncologist, one complete blood count and one blood testing-chemistry panel every 4-weeks. This sums to £27.99 and £10.61 every 4-weeks in the IXA+LEN+DEX and LEN+DEX arms, respectively – comparable inputs were £24.70 and £18.67 from the original NICE submission.

One-off cost

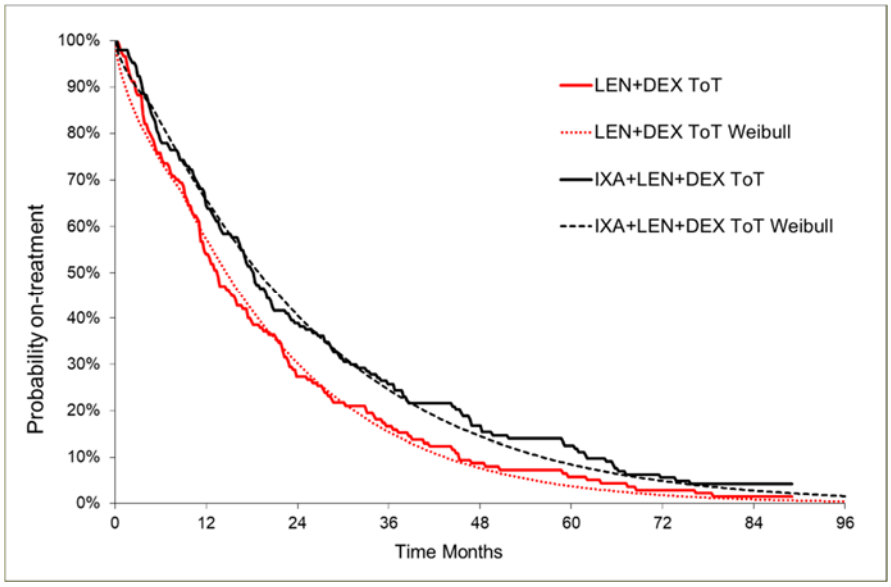
A one-off cost was also applied upon progression – in line with the ERG's feedback from the original NICE submission. This cost included: three outpatient consultations and laboratory tests. Updating the costs applies a one-off cost of £1,233.80 compared with the £1,081.29 applied in the original NICE submission.

A.7.4 *Time on Treatment*

The original NICE submission extrapolated ToT data from the IA2 of TMM1 (median follow-up of 23-months). These data have been updated with the final analysis from the clinical trial – in line with Section A.6.1 – with a median follow-up of approximately 85-months.

Aligned with the original NICE submission, the base case continues to assume a Weibull distribution. Figure 9 presents the Weibull curves fit to the ToT data; Weibull provided the best fit of the distributions tested. **Note:** the multivariate approach accounts for: treatment arm, ISS stage, prior immunomodulation agent, renal dysfunction and age (>65 years).

Figure 9: Comparison of fitted (Weibull) ToT curves with Kaplan–Meier curves



Abbreviations: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; ToT, time on treatment.

A.7.5 *Health-related quality of life*

The final analysis from the TMM1 trial also offers extended HRQoL follow-up – as measured by the EQ-5D-3L. HRQoL was measured at baseline, every 4-weeks until progression and every 12-weeks post-progression until study close. The HRQoL data have been analysed in line with the methods presented in the original NICE submission (i.e. a regression model has been fit to the data which accounts for multiple observations per patient). The potential list of covariates to include in the regression analysis were informed by the original NICE submission and clinical feedback; these included:

- EQ-5D-3L utility score at baseline (continuous)
- Age (continuous)
- Response assessment (based on overall response assessment from the time that the EQ-5D-3L was assessed in the trial – in line with the NICE Committee's and ERG's preferred approach in the original NICE submission; VGPR+ vs. PR vs. SD vs. PD)
- Death within 3-months of EQ-5D-3L assessment (no vs. yes)
- Death within 3-6 months of EQ-5D-3L assessment (no vs. yes)
- Grade 3/4 adverse event (no vs. yes)
- Hospitalisations (no vs. yes)
- Race (white vs. non-white)
- Sex (male vs. female)

Backward stepwise elimination identified the variables which were not significant drivers of HRQoL. The final regression model retained significant drivers and included: EQ-5D-3L utility score at baseline, age, response assessment, death within 3-months of EQ-5D-3L assessment and hospitalisations. Experiencing grade 3/4 adverse events was not found to be a significant predictor of HRQoL using the longer follow-up. This is likely due to the correlation between adverse events and hospitalisations. However, as a conservative approach the same utility decrement applied to adverse events in the original NICE submission is applied, in addition to the decrement for hospitalisations (-0.03106). **Note:** the analysis presented was conducted using the data from the 2 or 3 prior lines population – this is included in the economic model. Exploratory analyses considered number of prior lines as a predictor using the ITT data. However, this was shown to be non-significant in predicting HRQoL. Nevertheless, this scenario is available if required.

The resulting utility values and their comparison to the original NICE submission are presented in Appendix A.4 **Note:** an error was identified in the original NICE submission where the decrement applied to age did not account for the baseline age in the model. Therefore, a

toggle is included in the model to apply this correction on the 'Main Settings' sheet – this is always applied in the updated analyses. The relative differences between each of the health states are similar when using the data from the final analysis compared with IA2. However, the absolute utility values are lower when using the final analysis. This is largely driven by the inclusion of baseline EQ-5D-3L (0.658) as a covariate; further exploration of the data and feedback from clinicians indicated that this should be adjusted for. A comment from the original NICE submission was that the utility values were higher than expected and higher than those seen in other relevant MM NICE appraisals – thus the utilities estimated using from the final analysis better align with the literature and better reflect patients' HRQoL with RRMM.

A.7.6 *Adverse events*

The final analysis provides updated follow-up on the adverse events (AE) observed in the IXA+LEN+DEX and LEN+DEX arms – the number of adverse events and the duration of AE have been updated within the economic model.

The AEs were accounted for using the same methodology as in the original NICE submission; the numbers were converted into rates and then probabilities per model cycle (one-week) using the patient population size and the duration of treatment exposure. These were then multiplied by the cost of the relevant adverse event and the utility decrement to obtain cost and HRQoL impacts, respectively. The costs of adverse events have been updated to reflect the latest cost year (2018/2019) using the NHS Reference Costs and the PSSRU 2020. This resulted in a cost per cycle of £11.99 and £16.99 for IXA+LEN+DEX and LEN+DEX, respectively – compared with £15.27 and £20.69 from the original NICE submission. This resulted in a utility decrement per cycle of -0.00568 and -0.00537 for IXA+LEN+DEX and LEN+DEX, respectively – compared with -0.00236 and -0.00262 from the original NICE submission.

A.7.7 *Hospitalisations*

The final analysis provides updated follow-up on the hospitalisations required in the IXA+LEN+DEX and LEN+DEX arms in the pre-progression vs. post-progression health states – the number of hospitalisations and the length of stay have been updated within the economic model. Hospitalisations include: acute care unit, palliative care unit, intensive care unit and hospice admissions. Appendix A.6 compares the number of hospitalisations from the final analysis with those applied in the original NICE submission from IA2.

The hospitalisations were accounted for using the same methodology as in the original NICE submission; the numbers were converted into rates and then probabilities per cycle. These

were then multiplied by the cost of the relevant hospitalisation and the utility decrement to obtain cost and HRQoL impacts, respectively. The costs of hospitalisations have been updated to the latest cost year (2018/2019) using the NHS Reference Costs. This resulted in a cost per cycle of £5.45 vs. £4.79 (IXA+LEN+DEX; pre-progression vs. post-progression) and £7.49 vs. £6.09 (LEN+DEX; pre-progression vs. post-progression) – compared with £10.44 vs. £12.69 (IXA+LEN+DEX; pre-progression vs. post-progression) and £12.61 vs. £15.24 (LEN+DEX; pre-progression vs. post-progression) from the original NICE submission. This resulted in a utility decrement per cycle of -0.00021 vs. -0.00020 (IXA+LEN+DEX; pre-progression vs. post-progression) and -0.00031 vs. -0.00026 (LEN+DEX; pre-progression vs. post-progression) – compared with -0.00090 vs. -0.00137 (IXA+LEN+DEX; pre-progression vs. post-progression) and -0.00112 vs. -0.00153 (LEN+DEX; pre-progression vs. post-progression) from the original NICE submission. **Note:** the probability per cycle of hospitalisations has decreased in the final analysis vs. IA2 indicating the reducing rates of hospitalisation across the longer follow-up.

A.7.8 *Concomitant medications*

The final analysis provides updated follow-up on the number of concomitant medications required while on treatment with IXA+LEN+DEX or LEN+DEX – these have been updated in the economic model for patients receiving treatment. The costs of concomitant medications have also been updated to reflect the latest cost year (2018/2019) using the British National Formulary and eMIT. The resulting cost per cycle is £13.51 – compared with £35.92 in the original NICE submission.

A.7.9 *Costs*

All costs within the economic model were updated to reflect the 2018/2019 cost year – the original NICE submission was based on the 2014/2015 cost year. The impact of this change is minimal and the cost year can be toggled between 2014/2015 and 2018/2019 using the drop-down option on the ‘Model Settings’ sheet.

Takeda is currently in discussions with NHS England regarding potential future commercial arrangements if ixazomib were recommended by NICE for baseline commissioning. Following guidance from NICE’s project team, all analyses in the main body of this submission have been presented using the list price of ixazomib. Arising from the initial discussions with NHS England, Takeda have already applied to reinstate a PAS which [redacted] offered through the CAA in the CDF, thus offering a [redacted] straight discount off the NHS list price (a net price of £[redacted] per capsule). NHS England & NHS

Improvement has agreed that this PAS proposal may be considered by NICE as part of this appraisal of ixazomib. Appendix F shows the cost-effectiveness results including the proposed PAS for ixazomib. Once commercial discussions are concluded with NHS England, Takeda will, if necessary, submit an updated Appendix that shows the cost-effectiveness results incorporating the final commercial agreement.

It is assumed that lenalidomide will be available as a generic medicine from [redacted]. To reflect this, the cost of lenalidomide is based on the list price of the branded product (Revlimid®) for [redacted] (assuming a FAD for this CDF review is published in [redacted] before then being replaced by an estimated generic cost. Therefore, the model assumes [redacted] of branded lenalidomide (Revlimid®) costs before applying an assumed generic price for lenalidomide. The generic lenalidomide cost has been estimated by assuming [redacted] (i.e. one cycle of generic lenalidomide is assumed [redacted] equivalent to a [redacted] discount from the list price of branded lenalidomide). Scenarios are also included that assume a generic lenalidomide cost equivalent to discounts of [redacted] and [redacted] on the list price of branded lenalidomide (Revlimid®); such discounts are not unexpected for an oral, small-molecule generic medicine.

Note: although the list price of branded lenalidomide is applied, there is a confidential simple PAS discount on lenalidomide available to the NHS. NICE and the ERG will need to apply this confidential discount to lenalidomide when calculating the relevant decision-making ICERs for ixazomib, including all commercial arrangements for all relevant medicines.

A.8 Key model assumptions and inputs

The economic model used for decision making in the original NICE appraisal (TA505), including integration of the ERG scenarios [file name: ID807 ixazomib ERG revised model 16102017KM (ACIC) _CORRECTED], has been updated using the final analysis from TMM1 and the updated and correct treatment switching analyses. The results and scenarios from the original submission can be achieved in the economic model through drop-down options on the 'Main Settings' sheet. The updates in this dossier describe: OS (with and without subsequent therapy adjustments), subsequent therapies, ToT, HRQoL, adverse events, hospitalisations, concomitant medications and costs.

Table 16 presents details of all assumptions and inputs changed in the base case economic model following the CDF data collection period.

Table 16 Updates to key model assumptions and inputs

Model input and cross reference	Original parameter /assumption (Committee preferred)	Updated parameter /assumption	Source/Justification
Overall survival [Section A.7.2]	TMM1 IA2 (median follow-up 23-months). Unadjusted for subsequent therapies and extrapolated using a Weibull. No treatment waning was applied in the base case. Scenario analyses explored waning the treatment effect in both treatment arms from 42.5 months in the IXA+LEN+DEX arm and 35.5 months in the LEN+DEX arm across 5-years.	TMM1 final analysis (median follow-up 85-months). Adjusted for subsequent therapies which are not routinely funded or available in UK clinical practice using the 2-stage methodology with re-censoring and extrapolated using a generalised gamma. No treatment waning is applied in the base case. Scenario analyses explore waning the treatment effect in both treatment arms from the end of trial follow-up for the proportion of patients who are still on treatment.	The longer follow-up from the TMM1 final analysis has been incorporated into the economic model. This longer follow-up introduced confounding through imbalances in subsequent therapies received across the IXA+LEN+DEX and LEN+DEX treatment arms and through subsequent therapies that are not routinely funded or available in UK clinical practice. Therefore, statistical adjustments were made to the OS data to adjust for the impact of these subsequent therapies. The impact of these subsequent therapies was also adjusted for in the cost component of the economic model. Following updates to the treatment switching analyses, clinician feedback was sought to validate the parametric curves and survival predictions based on the corrected adjusted Kaplan-Meier data (adjusted based on the TSE with re-censoring). The feedback concluded that the generalised gamma provided a reasonable estimation of long-term outcomes with LEN+DEX and IXA+LEN+DEX. Therefore, this was applied in the base case. The TMM1 final analysis captures the impact of discontinuing therapy on the treatment effect for ~96% and ~99% of patients who have stopped treatment during follow-up in the IXA+LEN+DEX and LEN+DEX arms, respectively. Therefore, no treatment waning is included in the base case. A scenario analysis applies treatment waning to the ~4% and ~1% of patients still receiving treatment.
Subsequent therapies [Section A.7.3]	Costed based on pooled subsequent therapy use from TMM1 IA2	Costed based on subsequent therapy use from the final analysis for TMM1 and	The base case adjusts the OS to adjust for the impact of subsequent therapies which would not be received in UK clinical practice. The costing of subsequent therapies in the base case reflects this.

Model input and cross reference	Original parameter /assumption (Committee preferred)	Updated parameter /assumption	Source/Justification
		adjusted for the impact of subsequent therapies which would not be received in UK clinical practice.	
Time on treatment [Section A.7.4]	TMM1 IA2 Extrapolated using a Weibull	TMM1 final analysis Extrapolated using a Weibull.	The TMM1 final analysis final analysis was incorporated into the economic model. Limited differences were observed between parametric curves. The Weibull was considered plausible and aligned with the original NICE submission as per ToE.
HRQoL [Section A.7.5]	TMM1 IA2 Utility regression included: response assessment, grade 3/4 adverse events, age, gender, race, hospitalisations and death within 3 months.	TMM1 final analysis Utility regression included: response assessment, age, hospitalisations and death within 3 months.	The TMM1 final analysis was incorporated into the economic model. **Note**: grade 3/4 adverse events, gender and race were shown not to be significant drivers of HRQL in the backwards stepwise selection process with the updated data. Therefore these were not included in the final regression model. However, to ensure no HRQL impact is being missed in relation to adverse events, the decrement assumed in the original NICE submission is applied in the base case.
Adverse events [Section A.7.6]	TMM1 IA2 Costed using 2014/2015 inputs.	TMM1 final analysis Costed using 2018/2019 inputs.	The TMM1 final analysis was incorporated into the economic model. Costs were updated to reflect the current cost year.
Hospitalisations [Section A.7.7]	TMM1 IA2 Costed using 2014/2015 inputs.	TMM1 final analysis Costed using 2018/2019 inputs.	The TMM1 final analysis was incorporated into the economic model. Costs were updated to reflect the current cost year.
Concomitant medications [Section A.7.8]	TMM1 IA2 Costed using 2014/2015 inputs.	TMM1 final analysis Costed using 2018/2019 inputs.	The TMM1 final analysis was incorporated into the economic model. Costs were updated to reflect the current cost year.

Model input and cross reference	Original parameter /assumption (Committee preferred)	Updated parameter /assumption	Source/Justification
Costs [Section A.7.9]	Cost year 2014/15	Cost inputs were updated to the most recent cost year of 2018/2019	Costs were updated to reflect the current cost year.
Ixazomib costs [Section A.7.9]	List price of ixazomib included within the model. Scenarios conducted based on original discounts and CAA required for CDF.	List price of ixazomib presented within the main body of this submission dossier. Results based on the proposed PAS presented in Appendix F.	Takeda is currently in discussions with NHS England regarding potential future commercial arrangements if ixazomib were recommended by NICE for baseline commissioning. Following guidance from NICE's project team, all analyses in the main body of this submission have been presented using the list price of ixazomib. Arising from the initial discussions with NHS England, Takeda have already applied to reinstate a [redacted] which [redacted] offered through the CAA in the CDF, thus offering a [redacted]% discount off the NHS list price (a net price of £[redacted] per capsule). Appendix F shows the cost-effectiveness results including the proposed PAS for ixazomib. Once commercial discussions are concluded with NHS England, Takeda will, if necessary, submit an updated Appendix that shows the cost-effectiveness results incorporating the final commercial agreement.
Lenalidomide costs [Section A.7.9]	List price of lenalidomide included within model	List price of branded lenalidomide (Revlimid®) included in the model for the first [redacted], followed by an estimated cost for generic lenalidomide – estimate based on [redacted]	To reflect upcoming changes to the cost of lenalidomide in UK clinical practice, an estimated cost for generic lenalidomide has been applied. It is assumed that lenalidomide will be available as a generic medicine from [redacted]. Based on the assumed timing of the FAD publication for this CDF review, the model assumes [redacted] of branded lenalidomide costs before applying an assumed generic price for lenalidomide.

A.9 Cost-effectiveness results (deterministic)

Table 17 presents the cost-effectiveness results from the original NICE submission dossier, these results reflect the NICE Committee's preferred base case and were deemed to demonstrate plausible potential for cost-effectiveness at CDF entry – based on the IA2 data from TMM1. Results have been provided based on the original agreed CAA which led to the CDF recommendation ([redacted]) and using the list price for ixazomib. Under the agreed base case assumptions from the original appraisal and the agreed CAA, the ICER was £31,691. The original base case can be reverted to within the economic model on the 'Main Settings' sheet using the 'Reset to Original Submission' button.

Table 18 presents the cost-effectiveness results for the new company base case, which incorporates the updated clinical evidence from the final analysis of TMM1 relating to: OS (with two-stage adjustment and re-censoring), subsequent therapies, ToT, HRQoL, adverse events, hospitalisations and concomitant medications. The new base case also reflects the 2018/2019 cost year, list price for ixazomib and the list price for lenalidomide for [redacted] followed by a generic price reflecting a [redacted] discount. The updated base case results, using the list price of ixazomib, generate an ICER per QALY gained of £[redacted].

Note: all results presented for the new company base case within the main body of the submission dossier relate to the list price for ixazomib. Appendix F presents the cost-effectiveness results for the new company base case incorporating the proposed PAS for ixazomib.

Table 17: Cost-effectiveness results from the original NICE submission based on IA2 (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Including the original CDF CAA for ixazomib							
IXA+LEN+DEX	[redacted]	4.85	3.68				
LEN+DEX	[redacted]	3.58	2.70	[redacted]	1.2675	0.97	£31,691
Based on list price for ixazomib							
IXA+LEN+DEX	[redacted]	4.85	3.68				
LEN+DEX	[redacted]	3.58	2.70	[redacted]	1.2675	0.97	[redacted]

Table 18 Cost-effectiveness results from the new company base case based on the final analysis of TMM1 and list price for ixazomib (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
IXA+LEN+DEX	[redacted]	4.86	3.18				
LEN+DEX	[redacted]	3.78	2.47	[redacted]	1.08	0.71	[redacted]

A.10 Probabilistic sensitivity analysis

To characterise the uncertainty in the parameter inputs, a probabilistic sensitivity analysis (PSA) was performed for 5,000 iterations. All inputs were simultaneously varied based upon distributional information. Results were then recorded and used to estimate a mean probabilistic ICER.

The base case probabilistic results are summarised in Table 19 and depicted in a cost-effectiveness plane (CEP) in Figure 10. The CEP illustrates the simulated estimates of expected incremental costs and QALYs of IXA+LEN+DEX compared with LEN+DEX in the PSA against a willingness to pay (WTP) threshold of £30,000 per QALY gained. The cost-effectiveness acceptability curve (CEAC) (Figure 11) shows the probability of IXA+LEN+DEX being cost-effectiveness versus LEN+DEX at varying WTP thresholds.

Based on the list price for ixazomib, the PSA estimated mean incremental QALYs gained from IXA+LEN+DEX compared to LEN+DEX of 0.71 (95% CI: [0.61–0.80]) and mean incremental costs of £[redacted] (95% CI:[redacted]). Resulting in a probabilistic ICER of £[redacted] – based on the list price for ixazomib.

Table 19 Updated base-case results (probabilistic; based on list price for ixazomib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QAL
IXA+LEN+DEX	[redacted]	4.87	3.18				
LEN+DEX	[redacted]	3.79	2.48	[redacted]	1.08	0.71	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 10 Cost-effectiveness plane of probabilistic results (based on list price for ixazomib)

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

Figure 11 Cost-effectiveness acceptability curve (based on list price for ixazomib)

Abbreviations: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide.

A.11 Key sensitivity and scenario analyses

One-way sensitivity analyses were performed to evaluate the sensitivity of the modelled ICER to individual inputs. Inputs were varied in turn based on their lower and upper bound values. Results were then recorded to estimate the most influential parameters in descending order of ICER sensitivity.

Figure 12 depicts the results in a tornado diagram based on the list price for ixazomib; the parameters with the greatest impact on model outcomes were coefficients relating to the estimation of utility. This is to be expected as utility is a key driver of the total QALYs accrued by each treatment arm in the model, which directly impacts the ICER calculation. To a lesser extent, the proportion of patients receiving specific types of subsequent therapy were shown to impact the ICER.

Figure 12 Tornado diagram (based on list price for ixazomib)

Abbreviations: FA, final analysis; PD, progressed disease; IXA+LEN+DEX, ixazomib-lenalidomide-dexamethasone; LEN+DEX, lenalidomide-dexamethasone.

Four key areas of uncertainty were explored in scenario analyses: (1) adjustments for subsequent therapy, (2) treatment waning, (3) generic cost for lenalidomide and (4) [redacted]. Table 20 presents the results of these based on the list price for ixazomib.

Firstly, the impact of using the unadjusted OS data from TMM1 was considered. This scenario uses efficacy and applies subsequent therapy costs based on the TMM1 trial. The ICER increases (i.e., less cost-effective for IXA+LEN+DEX) when the unadjusted OS data are used

– this is to be expected as the relative treatment effect for OS outcomes of IXA+LEN+DEX vs. LEN+DEX is confounded by the subsequent therapies received in the TMM1 clinical trial. This confounding is greater in the LEN+DEX arm, resulting in a less favourable relative treatment effect when using the unadjusted data. This effect is only partially offset by the reduction in incremental costs, which occurs due to more expensive subsequent therapies being used in the LEN+DEX arm when compared to the IXA+LEN+DEX arm. However, the unadjusted analysis is not reflective of the routinely funded treatment pathway in England and is not consistent with the NICE Position Statement regarding the inclusion of CDF medicines in a treatment sequence. [10] As such, the unadjusted analysis should not inform the base case, and this scenario is presented for completeness only.

To further explore the impact of adjusting for subsequent therapies, the two-stage without re-censoring and the IPCW approaches are considered, alongside naïve comparisons of OS outcomes across switchers and non-switchers. The ICER worsens for IXA+LEN+DEX when the two-stage approach without re-censoring is used compared to the base case in which the two-stage with re-censoring approach is used. Re-censoring is an important component of the two-stage analysis as, without it, informative censoring can be introduced if there is an association between switching and prognosis – which is very likely to be the case in this context where the treatments defining a switcher are novel therapies with efficacious profiles. Additionally, naïve comparisons of the OS outcomes across switchers and non-switchers indicate a trend towards superior outcomes for those patients switching – see Figure 2 and Figure 3. For this reason, it has been recommended that re-censoring should be applied in adjustment analyses and the results without re-censoring are presented as illustrative only. The IPCW method also worsens the ICER for IXA+LEN+DEX compared to the base case. However, the predicted survival from this method does not align with clinical expectations (discussed in Section A.7.1).[9] Therefore, it is not used to inform the base case. Both scenarios provide an exploration around the assumptions underpinning the treatment switching adjustments.

As discussed in Section A.7.2 , with any impact of waning on the treatment effect captured for 96–99% of patients (in the IXA+LEN+DEX and LEN+DEX arms, respectively) in the observed data, further treatment waning adjustments are not applied in the base case. However, there are a small proportion of patients remaining on treatment in TMM1 (4% and 1% of patients receiving IXA+LEN+DEX and LEN+DEX, respectively) for whom the effect of treatment waning has not been reflected. Therefore, a scenario explores the impact of waning for these patients. As expected, there is a minimal impact on the ICER due to the majority of the waning effect being implicitly captured within the observed data.

The base case assumes the list price of lenalidomide – although a confidential discount does exist – for [redacted] followed by an estimate of the generic cost. The rationale behind this assumption is that lenalidomide will be available as a generic medicine from [redacted]. The generic cost of lenalidomide has been informed intuitively based on a comparison with [redacted] and results in a [redacted] discount applied to the list price. However, this is a key source of uncertainty which is explored in scenarios looking at a [redacted], [redacted] and [redacted] discount applied to the list price of lenalidomide to reflect the generic pricing. As expected, reducing the discount to [redacted] results in an increase in the ICER of [redacted]. Whereas, increasing the discount to [redacted] and [redacted] results in a decrease in the ICER of [redacted] and [redacted], respectively.

Finally, the base case presented within the main body of this submission assumes a list price for ixazomib. As part of the CAA for inclusion in the CDF, an [redacted] (i.e., [redacted] per capsule). To explore the sensitivity of the results to [redacted], a scenario analysis explores the impact of applying [redacted]. In Table 20 this is applied alongside the list price of ixazomib and is shown to have a [redacted] impact on the ICER – reducing the ICER in favour of IXA+LEN+DEX by [redacted]. In Appendix F the results are shown including the proposed PAS for ixazomib.

Table 20 Key scenario analyses

Scenario and cross reference	Scenario detail	Brief rationale	ICER	Impact on base-case ICER
Base case			[redacted]	
Unadjusted TMM1 OS data [Section A.7.2]	Use TMM1 OS data unadjusted for subsequent therapies	The base case includes an adjustment for subsequent therapies using the TSE method with re-censoring. This scenario uses efficacy and applies subsequent therapy costs based on the TMM1 setting (i.e., unadjusted). However, it is not considered reflective of the routinely funded treatment pathway in England, is not consistent with the NICE Position Statement re CDF medicines,[10] and was not considered reflective of UK treatment based on feedback from UK clinicians.	[redacted]	[redacted]
Adjusted OS using two-stage methods with re-censoring [Section A.7.2]	Adjusted OS using the two-stage treatment switching analyses without re-censoring	The two-stage method with re-censoring is applied in the base case. To further explore the impact of adjusting for subsequent therapies, the two-stage method without re-censoring and the IPCW approaches are considered. However, as discussed in Section A.7.1, the output from these methods do not align with the NICE TSD, or clinical expectations, respectively. They provide an exploration around the assumptions underpinning the treatment switching adjustments.	[redacted]	[redacted]
	Adjusted OS using the IPCW treatment switching analyses		[redacted]	[redacted]
Treatment waning [Section A.7.2]	Include adjustment for treatment waning effect in both treatment arms	The base case excludes treatment waning as the observed data reflects this effect for the majority of patients. However, there are a small proportion of patients remaining on treatment in TMM1 (4% and 1% of patients receiving IXA+LEN+DEX and LEN+DEX, respectively). Therefore, a scenario explores the impact of waning for these patients.	[redacted]	[redacted]
	Assume a generic LEN cost at a [redacted]	The base case assumes list price of lenalidomide – although	[redacted]	[redacted]

Scenario and cross reference	Scenario detail	Brief rationale	ICER	Impact on base-case ICER
Generic LEN costing [Section A.7.9]	discount of the list price	a confidential discount does exist for lenalidomide – for [redacted] followed by an estimate of the generic cost. The generic cost of lenalidomide has been informed based on a comparison [redacted] discount applied to the list price. However, this is a key source of uncertainty which is explored in scenarios looking at a [redacted], [redacted] and [redacted] discount applied to the list price of lenalidomide to reflect the generic pricing.		
	Assume a generic LEN cost at an [redacted] discount of the list price		[redacted]	[redacted]
	Assume a generic LEN cost at a [redacted] discount of the list price		[redacted]	[redacted]
IXA costing [Section A.7.9]	Assume [redacted] for ixazomib	The base case presented within the main body of this submission assumes a list price for ixazomib. As part of the CAA for inclusion in the CDF, [redacted]. To explore the sensitivity of the results to [redacted], a scenario analysis explores the impact of applying [redacted]. This is applied alongside the list price of ixazomib.	[redacted]	[redacted]

Abbreviations: CDF, Cancer Drugs Fund; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IPCW, inverse probability of censoring weighting; IXA, ixazomib; LEN, lenalidomide; MAA, managed access agreement; OS, overall survival; TMM1, TOURMALINE-MM1; TSE, two-stage estimation.

A.12 Key issues and conclusions based on the data collected during the CDF review period

During the three years that IXA+LEN+DEX has been available on the CDF for patients who have received 2 or 3 prior therapies, the significant uptake by clinicians has demonstrated the important role that ixazomib continues to play in the management of RRMM. More than 2,500 patients received treatment with IXA+LEN+DEX during its first 2.5 years on the CDF (December 2017 to June 2020), an average of about 80–90 patients per month.[8] Clinical experts report that this regimen is well-tolerated and easy to use. Therefore, patients are able to stay on treatment and control their disease. Clinical experts say this is a potential treatment option for up to 90% of all patients with 2 or 3 prior lines of therapy that they see in clinic.[9]

During the original NICE appraisal, the magnitude of the OS benefit for IXA+LEN+DEX was the key clinical uncertainty leading to a recommendation for use within the CDF. The final analysis of the TMM1 trial is now available at a median follow-up of 85-months, and it provides more mature OS data. At this timepoint, the vast majority of patients had progressed and only 4% and 1% of patients in the IXA+LEN+DEX and LEN+DEX trial arms, respectively, remained on treatment.[14]

At the final analysis, IXA+LEN+DEX provided a 10-month median OS advantage vs. LEN+DEX, consistent with the 9-month median PFS benefit seen at IA2. The opinion of UK clinical experts is that this represents a clinically meaningful OS benefit.[14] Takeda acknowledges that the hazard ratio for the between-group difference in OS has increased from the IA2 data cut-off. However, based on discussions with UK clinical experts, Takeda believes this is due to the confounding of the OS analysis arising from the impact of subsequent treatments received in TMM1.

As explored in Sections A.6.1, A.7.1 and Appendix B, there were differences in subsequent therapies received between treatment arms in TMM1 that are prognostically important for OS in RRMM. Specifically, more patients in the LEN+DEX arm received subsequent therapies that are known to have prognostic importance, namely daratumumab, elotuzumab or autologous SCT compared with the IXA+LEN+DEX arm. In addition, 35% of patients who received IXA+LEN+DEX and at least one subsequent anti-cancer therapy received a PI as their next-line therapy despite having progressed on ixazomib and having PI refractory disease. In the March 2021 advisory board, 12 UK MM experts unanimously informed Takeda that this would not happen in routine clinical practice.[9] The effect of the imbalance in the novel subsequent therapies has been to reduce the OS benefit seen with IXA+LEN+DEX in the TMM1 trial. After adjusting for subsequent therapies – as described in Section A.7.1 and A.7.2,

and consistent with NICE's Position Statement on adjusting for subsequent therapies that are not routinely commissioned[10] – the hazard ratio for IXA+LEN+DEX vs. LEN+DEX was shown to improve for OS for all methods. The most clinically plausible of the methods, the two-stage method with re-censoring, estimated a hazard ratio of 0.713 [95% CI: 0.535, 0.952, p=0.0216] and median OS of 50.89 vs. 40.91 months (i.e. an estimated 9.98 month survival gain for IXA+LEN+DEX vs. LEN+DEX arms, respectively). These analyses demonstrate that the confounding introduced through subsequent therapies reduces the relative treatment effect of IXA+LEN+DEX and that the hazard ratio would likely be improved had the subsequent therapy profile in TMM1 aligned with UK clinical practice.

OS data from TMM1 for patients who had 2 or 3 prior therapies can be compared to that reported for carfilzomib (CARF; another PI) in combination with LEN+DEX in the ASPIRE trial (Appendix F). Unlike TMM1, clinicians in ASPIRE were not blinded to study drug treatment allocation when selecting subsequent therapy. At the final analysis of the ASPIRE trial, median OS for patients who had received 2 or 3 prior therapies was 48.8 months and 42.3 months for the CARF+LEN+DEX and LEN+DEX arms, respectively. While the LEN+DEX arm performed similarly in TMM1 and ASPIRE (median OS: 43.0 months and 42.3 months, respectively), unadjusted median OS is approximately 5 months longer for IXA+LEN+DEX in TMM1 than for CARF+LEN+DEX in ASPIRE (53.0 months vs. 48.8 months, respectively), despite the impact of subsequent therapy on OS in TMM1 as discussed above. Notably, there was less use of subsequent therapies in ASPIRE than in TMM1 and, as an open-label trial, ASPIRE was not subject to the blinding issue seen in TMM1 (discussed further in Appendix G). Hence, there is less potential for the OS benefit to be confounded in ASPIRE than in TMM1.

Based on the use of IXA+LEN+DEX in the CDF (captured in SACT), some initial real-world OS data have been reported from the SACT dataset. While the data from SACT are informative, care should be taken in trying to compare it with the data from TMM1. The SACT data lack a LEN+DEX comparator arm, have a much shorter median follow-up than TMM1 (median: 15-months, maximum: 35-months for SACT vs. a median follow-up of 85 months for TMM1) and there are important differences in patient populations between SACT and TMM1, including age and rates of previous autologous SCT. As discussed in Section A.6.2 , the patient population in SACT was heavily skewed towards more elderly individuals (median age, 72 years; 18% of patients aged >80 years) compared with the IXA+LEN+DEX arm in TMM1 (median age 67 years). As is common for real-world datasets when compared to clinical trials, the patients from SACT are generally older, less fit and had a poorer prognosis than patients in TMM1.

Prolonging PFS remains an important treatment goal for patients with MM and their clinicians. PFS was the primary endpoint for TMM1, and unlike the OS analysis it is not confounded by issues regarding subsequent therapies. At IA2, IXA+LEN+DEX demonstrated a 9-month improvement in median PFS for patients with 2 or 3 prior therapies vs LEN+DEX,[4] a clinically meaningful benefit. The magnitude of the PFS benefit for the 2 or 3 prior therapy subgroup is consistent with the 10-month OS benefit for IXA+LEN+DEX vs. LEN+DEX at the final (unadjusted) TMM1 analysis.

Moreover, the 22-month median PFS for patients receiving IXA+LEN+DEX in TMM1 at IA2 is consistent with the PFS reported for patients receiving IXA+LEN+DEX in real-world clinical practice (see Appendix D). Across several studies that included patients generalisable to UK clinical practice, including the ixazomib Named Patient Program in the UK [UVEA-IXA], patients receiving IXA+LEN+DEX had a median PFS between 16.6 months and 23.3 months,[24,25] demonstrating that the PFS benefit reported in TMM1 translated into real-world patient outcomes.

Duration of treatment was another residual uncertainty from the original appraisal. Duration of treatment is shorter in SACT than would be expected based on the TMM1 trial. Median treatment duration in SACT (11.5-months) was calculated based on the full analysis set (N=2,460). However, of these patients, 1,106 (41%) were still receiving IXA+LEN+DEX at the data collection cut-off. SACT is also continually including new patients in its database, as new patients initiate therapy each month. Both of these factors are expected to shorten the median treatment duration in SACT compared to the TMM1 trial. By contrast, the median duration of treatment in the UVEA-IXA study ([redacted]-months) is closer to that reported for IXA+LEN+DEX in TMM1 at IA2 and the final analysis.

During the time that ixazomib has been in the CDF, clinicians and patients have benefited from having access to an effective, well-tolerated, easy to use, all-oral triplet regimen. That over 2,500 patients have received IXA+LEN+DEX via the CDF – approximately 80–90 new patients per month – is testament to the ongoing clinical need for this regimen, and its importance to patients and clinicians in England and Wales. Although new treatment combinations for MM have been assessed by NICE since the initial ixazomib appraisal, the majority are not available through baseline commissioning, and clinicians at a March 2021 advisory board were unanimous in their desire to see continued access to IXA+LEN+DEX. Key strengths of IXA+LEN+DEX cited by clinical experts were its advantageous tolerability profile, low discontinuation rates and the fact that it can be used in up to 90% of the third- and fourth-line patients that they see in clinic, regardless of age or performance status. All clinicians stated that they would regard losing access to ixazomib as a retrograde step for their

patients, for the NHS and for myeloma care in the UK. In particular they were concerned that it would leave a gap at third line in the MM pathway.

The real-world value of the all-oral IXA+LEN+DEX regimen has been seen clearly during the COVID-19 pandemic. NHS England's decision in May 2020 to provide interim funding for IXA+LEN+DEX at second line during the pandemic has allowed clinically extremely vulnerable patients with MM to shield at home while continuing to receive effective treatment. While the immediate need to have fewer face-to-face appointments due to COVID-19 transmission risk may decrease in the coming months, there will be an ongoing need to relieve pressure on infusion services while the NHS addresses the inevitable delays to some treatments that occurred during the height of the pandemic. IXA+LEN+DEX is well-placed to support this effort and we note that this interim funding for ixazomib has recently been extended until the end of August 2021.[26]

The results of the base-case cost-effectiveness analysis, using list prices of ixazomib, show that IXA+LEN+DEX compared to LEN+DEX accrues an additional 0.71 QALYs at an additional cost of £[redacted] per patient. This results in an ICER of £[redacted] per additional QALY gained. Appendix F outlines the cost-effectiveness results including the proposed PAS for ixazomib. Applying the proposed PAS to ixazomib reduces to ICER to £65,703 per QALY. Takeda is currently in discussions with NHS England regarding potential future commercial arrangements if ixazomib were to be recommended by NICE for baseline commissioning. Once commercial discussions are concluded with NHS England, Takeda will if necessary update the cost-effectiveness results.

In summary, IXA+LEN+DEX provides patients with MM, clinicians and the NHS with an easy to use, effective and well-tolerated treatment regimen. For patients who have received 2 or 3 prior therapies, the 9-month median PFS advantage over LEN+DEX that was seen at IA2 has translated into a 10-month median OS advantage at the final analysis, despite confounding from subsequent therapies received. Takeda is in ongoing commercial discussions with NHS England and reaffirms its commitment to working with all stakeholders to find a solution that allows patients and the NHS to continue to benefit from having access to this effective and important all-oral triplet regimen.

A.13 References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund review

Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (CDF review of TA505) [ID1635]

Response to clarification questions

October 2021

File name	Version	Contains confidential information	Date
ID1635 Company response to ERG clarifications [ACIC]	**1.0**	**Yes**	**5/10/2021**

Section A: Clarification on effectiveness data

Treatment pathway

A.1 Please present a diagram indicating the company's conception of the treatments used in the "*UK treatment pathway*" for people whose disease has progressed after 3 or 4 previous treatments that may or may not have included previous exposure to a proteasome inhibitor (PI) therapy. The ERG believe that the company interpret this as best supportive care only, please confirm.

Response: The natural history of multiple myeloma, as a progressive disease, is characterised by repeated periods of patients becoming refractory to treatment. At an advisory board in March 2021, clinical experts highlighted that later lines of treatment for MM typically involve multiple, varied combinations of therapies depending on what patients have previously responded to, or become refractory to. Table 14 (page 36) of the Takeda submission dated July 5th provides an overview of some of the therapeutic combinations used in later lines in T-MM1.

As indicated on pages 25 and 26 of the July 5th CS, and consistent with the NICE Position Statement,[1] the treatment switching analysis adjusted for patients in T-MM1 "who received a subsequent treatment which is not routinely available in UK clinical practice." This comprised "carfilzomib (CARF)-based, elotuzumab (ELOT)-based, bortezomib (BORT)+lenalidomide (LEN)+ dexamethasone (DEX), pomalidomide (POM)+BORT+DEX, re-treatment with ixazomib (IXA) or LEN, stem-cell transplants (SCT), plitidepsin, cetuximab, pembrolizumab and nivolumab". In addition, "daratumumab (DARA)-based and isatuximab (ISA)-based regimens were adjusted for as they are only funded via the CDF."

The remaining therapies included bendamustine (BEN)+ prednisone (PRED), cyclophosphamide (CYC), BORT+ doxorubicin (DOX), BORT+DEX, melphalan (MELPH)+PRED, POM+DEX, thalidomide (THAL)+DEX, panobinostat (PANO)+BORT+DEX, BORT+BEN+DEX, and DEX monotherapy. All of these combinations are available for patients in the UK. It would not be appropriate to characterise these therapies as best supportive care; they represent active therapies

that may be used by treating clinicians based on individual patient characteristics, prognosis and previous treatment history.

A.2 Please list the company's conception of all available therapies for people with multiple myeloma (MM) whose disease has progressed after 3 or 4 lines of treatment (i.e., 2 or 3 lines plus IXA+LEN+DEX or LEN+DEX) broken down according to the headings shown in Table 1.

Table 1: Therapies available for people with MM whose disease has progressed after 3 or 4 lines of treatment

UK therapies available within the company's conception of the UK clinical pathway	Therapies currently under consideration by NICE within the Cancer Drugs Fund scheme	Therapies considered potentially useable by Takeda's clinical advisors but not reimbursed in routine UK commissioning	Therapies used / available elsewhere than in the UK

Response: The response to A.1 above provides the detail requested for this clarification. The Company would highlight that column 1 – UK therapies available within the company's conception of the UK clinical pathway – is detailed in the response to A.1, based on the NICE Position Statement on adjustment for therapies not routinely funded in UK practice.[1] For column 2, DARA-based and ISA-based regimens are only funded within the CDF. While the relevance of the distinction between columns 3 and 4 is not clear to the Company, the July CS – and A.1 above – clearly states which therapies are not routinely funded in England and Wales.

Treatment switching adjustments

A.3 PRIORITY QUESTION: For each of the 4 Kaplan-Meier plots shown in Figure 7 (Two-stage adjustment with re-censoring), Company submission (CS) Document, pg. 33. Please supply data in the form shown in Table 2. It would be appreciated if this information could be supplied in Microsoft Excel.

Table 2: Patient-level information

Timepoint	Number at risk	Event	Censored	Survival(t)
T=0	N=???	0	0	100%
T=???	N=???	N=???	N=???	???
T=???	N=???	N=???	N=???	???
Etc…	Etc…	Etc…	Etc…	Etc…

Response: Please see the accompanying Microsoft Excel file ('IXAZOMIB_ERGQuestionsA3_A4') that includes these data for the four Kaplan-Meier plots shown in Figure 7 of the CS. These data are also available within the submitted economic model in the "Lifetable(OS)" sheet.

A.4 PRIORITY QUESTION: For each of the 4 Kaplan-Meier plots shown in Figure 9 (Time-on-treatment), CS Document, pg. 39, please supply data in the form shown in the Table 3. It would be appreciated if this information could be supplied in Microsoft Excel.

Table 3: Patient-level information

Timepoint	Number at risk	Event	Censored	Survival(t)
T=0	N=???	0	0	100%
T=???	N=???	N=???	N=???	???
T=???	N=???	N=???	N=???	???
Etc…	Etc…	Etc…	Etc…	Etc…

Response: As discussed with NICE and the ERG during the clarification stage, there are only two Kaplan Meier plots in Figure 9 of the CS. Please see the accompanying Microsoft Excel file ('IXAZOMIB_ERGQuestionsA3_A4') for the data corresponding to these two Kaplan-Meier curves. These data are also available within the submitted economic model under the "Lifetable(ToT)" tab.

A.5 Figures 2 and 3, CS Document, pg. 27, identify 186 '*non-switchers'*, 89 in IXA+LEN+DEX arm and 97 in LEN+DEX arm. Please complete **Table 4** to list treatments received by these people according to line of treatment after progression (i.e., the immediate next line after IXA+LEN+DEX or LEN+DEX, being defined as first line).

Response: Of the N=186 'non-switchers' only N=96 received an active subsequent therapy; N=90 did not receive an active subsequent therapy. Note: this aligns with the CS and the economic model where 207/297 received subsequent active therapies. **Table *4*** presents the subsequent therapies received by the non-switchers in the IXA+LEN+DEX arm. **Table *5*** presents the subsequent therapies received by the non-switchers in the LEN+DEX arm.

Table 4: Subsequent therapies received by the 'non-switchers' in the IXA+LEN+DEX treatment arm

Ixazomib + LenDex	**Next line**	**Next line 2**	**Next line 3**	**Next line 4**
Azacitidine	2	0	0	0
BEN+BORT+DEX	0	0	0	1
BEN+DEX	2	0	0	0
BEN+PRED	1	0	0	0
BEN+THAL+DEX	0	1	0	0
BORT	2	1	0	0
BORT+BEN+DEX	1	1	0	0
BORT+CYC	1	0	0	0
BORT+CYC+DEX	6	2	1	0
BORT+CYC+DEX+CIS+ETOP	0	1	0	0
BORT+DEX	4	0	2	0
BORT+DOX+DEX	2	0	0	0
BORT+DOX+MELPH+DEX	1	0	0	0
BORT+THAL+DEX	0	1	0	0
CLARITHROMYCIN	1	0	0	0
CYC+DEX	1	1	0	0
CYC+DOX+VIN+DEX	1	0	0	0
CYC+MELPH+DEX	1	0	0	0

CYC+methylPRED	1	1	0	0
CYC+PRED	0	1	0	0
CYC+VIN+DOX	0	1	0	0
DEX	1	0	1	0
HYDROCORTISONE	2	0	0	0
LEN	2	0	0	0
LEN+DEX	1	0	0	0
MELPH+DEX	0	2	1	0
MELPH+PRED	2	1	0	0
POM	1	1	0	0
POM+CYC+DEX	2	1	0	0
POM+DEX	5	2	3	1
POM+methylPRED	1	0	0	0
PRED	1	0	0	0
PREDNISONE, ETOPOSIDE, PROCARBAZINE AND CYCLOPHOSPHAMIDE (PEP-C)	0	1	0	0
PROCARBAZINE+PRED+CYC+ETOP+MELPH	1	0	0	0
THAL+CYC	1	0	0	0
THAL+CYC+DEX	1	0	0	0
THAL+DEX	0	0	1	0
THAL+MELPH+PRED	1	0	0	0
Total	**49**	**19**	**9**	**2**

Table 5: Subsequent therapies received by the 'non-switchers' in the LEN+DEX treatment arm

LenDex	**Next line**	**Next line 2**	**Next line 3**	**Next line 4**
Azacitidine	1	0	0	0
BEN+BORT+DEX	1	0	0	0
BEN+BORT+PRED	1	0	0	0
BEN+DEX	1	0	0	0
BEN+PRED	1	1	0	0
BORT+BEN+CYC+DEX	0	1	0	0
BORT+CYTARA+METHO+DEX	0	1	0	0
BORT+BEN+DEX	3	0	0	0
BORT+BEN+THAL+DEX	0	0	0	1
BORT+CYC/DEX	1	0	0	0

BORT+CYC+DEX	2	0	0	0
BORT+CYC+methylPRED	1	0	0	0
BORT+DEX	6	1	0	0
BORT+DOX+DEX	1	1	0	0
BORT+MELPH+PRED	4	0	0	0
BEN+methylPRED	0	0	1	0
BORT	0	0	1	0
BORT+BEN	0	0	1	0
BORT+DOX+DEX	0	0	1	0
BORT+THAL+ETOP+CYC+CIS+DOX+DEX	1	0	0	0
CYC+DEX	1	0	0	0
CYC/MELPH+DEX	0	1	0	0
CYC+DEX	0	3	0	0
CYC+PRED	0	1	0	0
CYC+methylPRED	1	0	1	0
CYTARA + HYDROCORTISONE + METHO	0	0	0	1
DEX	3	0	0	0
ETOP+DEX+CYTARA+CIS	0	1	0	0
HYDROCORTISONE+DEXTROMETHORPHAN	1	0	0	0
LEN+CYC+PRED	1	0	0	0
MELPH+PRED	2	1	0	0
MELPH+THAL+PRED	1	0	0	0
PANO+BORT+DEX	0	1	0	0
POM	0	1	0	0
POM+CYC+CLARITROMICIN+DEX	0	1	0	0
POM+CYC+DEX	1	1	0	0
POM+DEX	6	2	2	0
PRED	3	0	0	0
THAL	1	0	0	0
THAL+CYC+DEX	1	0	0	0
THAL+DEX	0	1	0	0
THAL+PRED+DEX	1	0	0	0
VINCRISTINE-ADRIAMYCINE-DEX	0	0	1	0
Total	**47**	**19**	**8**	**2**

A.6 Please present Kaplan-Meier plots of unadjusted overall survival (OS) restricted to those who were "*switchers to next-line therapies"* (N=51) in Table 11, CS Document, pg. 26, and broken down by IXA+LEN+DEX (N=24) and LEN+DEX (N=27) arms.

Response: Following discussions with NICE and the ERG during the clarification call held on September 30th, it was agreed that the split of next-line subsequent therapy vs. later-line subsequent therapy was no longer relevant. This was an artefact from an earlier version of the model and submission where an error was subsequently identified. This has since been rectified. Importantly, patients receiving next-line PI in the IXA+LEN+DEX arm are no longer adjusted for in the treatment switching analyses due to an inability to account for both next-line PI use and subsequent novel therapies in published methodologies (see Section A.7.1/page 25 of the Takeda submission dated July 5th). As the use of PIs in the next-line is thought to worsen outcomes for patients in the IXA+LEN+DEX arm, this is considered to be a conservative approach.

A.7 Please present Kaplan-Meier plots of unadjusted OS restricted to people who were *"switchers to later line (subsequent) therapies"* (N=60) in Table 11, CS Document, pg. 26, and broken down by IXA+LEN+DEX (N=35) and LEN+DEX (N=25).

Response: Following discussions with NICE and the ERG during the clarification call held on September 30th, it was agreed that the split of next-line subsequent therapy vs. later-line subsequent therapy was no longer relevant. This was an artefact from an earlier version of the model and submission where an error was subsequently identified. This has since been rectified. Importantly, patients receiving next-line PI in the IXA+LEN+DEX arm are no longer adjusted for in the treatment switching analyses due to an inability to account for both next-line PI use and subsequent novel therapies in published methodologies (see Section A.7.1/page 25 of the Takeda submission dated July 5th). As the use of PIs in the next-line is thought to worsen outcomes for patients in the IXA+LEN+DEX arm, this is considered to be a conservative approach.

A.8 CS Document, pg. 26, section A7.1 provides a definition of switchers: *"For clarity, consistent with the NICE Position Statement,[10] switchers were defined as patients who received a subsequent treatment which is not routinely available in UK clinical practice"*, and CS Document, pg. 25, section A7.1 provides a further definition of switchers: *"the term "switchers" refers to patients who have received a subsequent therapy that requires adjustment and the term "switch date" refers to the date at which they received the subsequent therapy of interest"*. Since the line of therapy is unspecified (i.e., Table 11, CS Document, pg. 26 suggests it can include many subsequent lines) many *"switchers"* that will have multiple *"switch dates"*. Please explain how this situation was resolved in the 2-stage adjustment process.

Response: Patients were defined as switchers if they received therapies unavailable in UK routine practice in any subsequent line of therapy. This is consistent with the NICE Position Statement.[1] The point at which they switched was the first date that such a therapy was received. Once a qualifying therapy had been received, patients were considered switchers from the date of receipt, irrespective of later treatment patterns. No explicit adjustment for receipt of multiple lines of subsequent therapy irrelevant to UK routine practice was performed. This was considered a simplifying assumption to overcome the complexities suggested by the question.

A.9 Table 6, CS Document, pg. 17 is titled "Influence of blinding versus unblinding of study drug allocation on clinician choice of next-line therapy in TMM1 for all patients who received at least one subsequent therapy[14]". The therapies received are listed under "Next line of therapy". Please present this data so that "Next line of therapy" is broken down into:

1. Next immediate line of therapy and
2. Subsequent line of therapy and classified as PI-based, Non-PI based and Total, (e.g., as in Table 6).

Table 6: Immediate next line and subsequent line of therapy

Therapy	Non-PI/PI-based	Immediate next line of therapy			Subsequent line of therapy		
		Unblinded n (%)	Blinded n (%)	Total receiving next-line therapy, n (%)	Unblinded n (%)	Blinded n (%)	Total receiving next-line therapy, n (%)
IXA+LEN+DEX	PI-based						
	Non-PI-based						
	Total						
LEN+DEX	PI-based						
	Non-PI-based						
	Total						

Response: For clarity, Table 6 CS Document, pg. 17 only includes data for immediate next line therapy. The data cannot therefore be further categorized by immediate and subsequent line of therapy. Furthermore, following discussions with NICE and the ERG during the clarification call held on September 30th, it was agreed that the split of next-line subsequent therapy vs. later-line subsequent therapy was no longer relevant. The response to clarification question A.6 provides further details.

A.10 PRIORITY QUESTION: The ERG requests information regarding further treatments and *"switchers"*:

1. Table 6, CS Document, pg. 17 implies that a maximum of 40 people randomized to IXA+LEN+DEX received a PI as a next line of therapy. However, CS Document, pg. 25 states: *"in total 42 patients in the IXA+LEN+DEX arm received a PI as their immediate next line of therapy".* Please clarify this discrepancy.

Response: Following discussions with NICE and the ERG during the clarification call held on September 30th, it was agreed that the split of next-line subsequent

therapy vs. later-line subsequent therapy was no longer relevant. This was an artefact from an earlier version of the model and submission where an error was subsequently identified. This has since been rectified. Importantly, patients receiving next-line PI in the IXA+LEN+DEX arm are no longer adjusted for in the treatment switching analyses due to an inability to account for both next-line PI use and subsequent novel therapies in published methodologies (see Section A.7.1/page 25 of the Takeda submission dated July 5th). As the use of PIs in the next-line is thought to worsen outcomes for patients in the IXA+LEN+DEX arm, this is considered to be a conservative approach.

Note: 42 patients in the IXA+LEN+DEX arm received a PI as a next-line therapy.

The discrepancy between the number presented on page 17 vs page 25 relates to the way the subsequent therapy data were organised into line of therapy. Information about subsequent therapies is available from TOURMALINE-MM1 based on clinician input with regards to the type of subsequent therapy, the start date and the end date. These were not input based on line of therapy and no other data are available. For the majority of data, lines of therapy were easily identifiable. However, there were some which were more ambiguous; for example: DEX followed immediately by CARF+DEX or BEN+DEX followed immediately by BORT+BEN+DEX. Therefore, it was assumed where there were less than three months between combinations with only the addition or removal of one therapy that this was the same line of therapy. This assumption was only required in a minority of instances and was supported by clinicians experienced in treating patients with RRMM in the UK; clinicians indicated this was reflective of clinical practice where patients may have a treatment holiday from one component to manage an adverse event or patients may build up to the whole treatment combination over time.

2. Of the 42 PI recipients mentioned, 25 of these received later therapies included within the list of treatments “requiring adjustment”. Nevertheless, the CS classified all 42 people as *“non-switchers”*, please confirm this interpretation is correct and that all PI recipients in the LEN+DEX arm were also classified as *“non-switchers”* and were not adjusted for in the 2-stage

analysis. Please confirm for each arm the numbers classified as *"non-switchers"* because they received PI therapy.

Response: This is a mis-interpretation. Switchers were identified based on receipt of a subsequent treatment which is not routinely available in UK clinical practice, this resulted in N=59 and N=52 switchers in the IXA+LEN+DEX and LEN+DEX arms, respectively. These include the N=25 patients in the IXA+LEN+DEX arm who also had a PI as a next line of therapy. However, the survival relating to these patients was not adjusted based on receipt of PI at the next line, rather the survival was adjusted based on the receipt of novel therapies. We were unable to identify a method to disentangle these two effects (see Section A.7.1/page 25 of the Takeda submission dated July 5th). Therefore, the effect of next line PI remains a potential confounding factor when interpreting the adjusted OS data. The total number of non-switchers were: N=89 and N=97 for IXA+LEN+DEX and LEN+DEX, respectively. The N=89 includes N=17 patients who had a next-line PI.

A.11 PRIORITY QUESTION: Information provided in CS Document, pgs. 17 and 26, Table 6 and Table 11 lacks clarity. For each arm separately please complete Table 7 indicating the number of people in each category. The ERG realises that some rows in Table 7 can be derived from other rows but for unambiguous clarity please complete all rows.

Response: Following discussions with NICE and the ERG during the clarification call held on September 30th, it was agreed that the split of next-line subsequent therapy vs. later-line subsequent therapy was no longer relevant. This was an artefact from an earlier version of the model and submission where an error was subsequently identified. This has since been rectified. Importantly, patients receiving next-line PI in the IXA+LEN+DEX arm are no longer adjusted for in the treatment switching analyses due to an inability to account for both next-line PI use and subsequent novel therapies in published methodologies (see Section A.7.1/page 25 of the Takeda submission dated July 5th). As the use of PIs in the next-line is thought to worsen outcomes for patients in the IXA+LEN+DEX arm, this is considered to be a conservative approach. Therefore, the split of next-line vs subsequent lines has been

removed from the Table template provided by the ERG - Table 7 is completed below for the remaining rows.

Table 7: Number of participants

	IXA+LEN+DEX	LEN+DEX	TOTAL
Total N	148	149	297
Did not receive post-progression therapy	40	50	90
Received post-progression therapy	108	99	207
Number classified as Switchers	59	52	111
Number classified as Non-switchers	89	97	186

A.12 Confounding is considered as *"the difference (error) between the estimated treatment effect and the effect that would have been observed if the treatment pathway had reflected UK clinical practice or if the distribution of subsequent therapies were balanced between treatment arms"*. The numbers of next line switchers in each arm seem well balanced in terms of numbers (24/148 and 27/149 for IXA+LEN+DEX and LEN+DEX arms, respectively) and types of therapies (Table 11, CS Document, pg. 26). Please confirm these data are correct and explain why adjustment seems necessary.

Response: The data presented in Table 11 in the CS are correct. The adjustment is necessary as a large number of the subsequent therapies received through the follow-up of TOURMALINE-MM1 do not reflect current UK clinical practice as per baseline commissioning/routine funding (i.e. excluding treatments available through the Cancer Drugs Fund). Therefore, as per the NICE Position Statement,[1] the effect of these should be removed from the analysis.

A.13 PRIORITY QUESTION: The ERG noted that there were some discrepancies between information reported in the CS Document and CS Document Appendix B.

1. Table 11, CS Document, pg. 26 indicates that there were 7 people in the IXA+LEN+DEX arm and 5 people in the LEN+DEX arm who were adjusted for in the treatment switching analyses as they received a DARA-based or DARA+LEN-based regimen during next line therapy. However, in Table 11, CS Document Appendix B, pg. 22, different numbers of people who received daratumumab during next line therapy are reported (3 people in the

IXA+LEN+DEX arm and 5 people in the LEN+DEX). Can the company provide an explanation?

Response: The discrepancy between the number presented in Table 11 in the CS vs Table 11 in the Appendix relates to the way the subsequent therapy data were organised into lines of therapy.

Information about subsequent therapies is available from TOURMALINE-MM1 based on clinician input with regards to the type of subsequent therapy, the start date and the end date. These were not input based on line of therapy and no other data are available. For the majority of data, lines of therapy were easily identifiable. However, there were some which were more ambiguous; for example: DEX followed immediately by DARA+DEX or BEN+DEX followed immediately by BORT+BEN+DEX. Therefore, for the treatment switching analyses, it was assumed that where there were less than three months between combinations with only the addition or removal of one therapy that this was the same line of therapy. This assumption was only required in a minority of instances and was supported by clinicians experienced in treating patients with RRMM in the UK; clinicians indicated this was reflective of clinical practice where patients may have a treatment holiday from one component to manage an adverse event or patients may build up to the whole treatment combination over time. This approach differs from the raw data pulled out from TOURMALINE-MM1 and so may result in minor differences.

Note: this differing approach does not impact the treatment switching analyses as no start dates were changed or imputed. It only impacts how the data are summarised by line.

2. Accounting for all subsequent lines, a similar discrepancy is noted as Table 12, CS Document Appendix B, pg. 23 indicates that 31 people in the LEN+DEX arm received daratumumab. However, Table 11, CS Document, pg. 26 reports that only 10 people in the LEN+DEX arm who received daratumumab were adjusted for in the treatment switching analyses. Can the company provide an explanation?

Response: As stated on page 26 of the CS, Table 11 in the CS presents the first novel subsequent therapy which categorised the patient as a switcher (see the text above Table 11 in the CS which states *"**Note:** some patients received multiple lines*

of novel therapies, ***Error! Reference source not found.*** *reflects the first of the novel t herapies received which was used as the switch date"*). For example, a patient may have received CARF as their first novel subsequent therapy, at this point they are marked as "switching". However, the same patient may have gone on to receive DARA at a later line. Therefore, the numbers in Table 11 from the CS are not comparable to those in Table 12 in the Appendix.

A.14 PRIORITY QUESTION: Table 12, CS Document, pg. 30, reports unadjusted and adjusted OS hazard ratios, please provide median OS for both arms based on each method.

Response: The treatment switching adjusted analyses presented in the CS adjust for both treatment switching and differences in baseline characteristics. As such, corresponding estimates of median survival for these scenarios can only be made conditional on a given distribution of baseline characteristics. Therefore, to provide estimates of median survival for the adjusted two-stage analyses, median survival was predicted for each individual in the trial based on their baseline covariate values with and without the use of IXA+LEN+DEX. The aggregated median survival was then calculated as the average median survival across all patients – calculated separately for patients in the IXA+LEN+DEX and LEN+DEX treatment arms. This approach has previously been referred to as the corrected group prognosis (CGP) method.[REF] Note: this will provide different estimates of median survival to predictions from the economic model, as the analysis below provides the average median survival across all patients. Whereas, the economic model predicts survival for the average patient.

An equivalent analysis could not be performed for the IPCW approach due to the structure of the resulting dataset – the dataset splits the observed data into intervals with different weights applied to each patient in each interval to reflect the probability of switching treatment. Therefore, median survival estimated for the IPCW analysis are provided without adjustment for differences in baseline characteristics and should be interpreted with caution.

Table 8 presents the estimated hazard ratios and median survival relating to adjusted treatment switching analyses.

Table 8: Estimates hazard ratios and median survival relating to treatment switching adjustments

	Hazard ratio (95% CI), p-value IXA+LEN+DEX vs. LEN+DEX	**Median survival (months)**	
		IXA+LEN+DEX	LEN+DEX
Unadjusted	0.845 (0.642 - 1.114; p=0.2316)	53.0	43.0
Naïve – censor at switch	0.712 (0.507 - 0.999; p=0.0484)	70.7	44.7
Naïve – 'per protocol'‡	0.699 (0.493 - 0.990; p=0.0428)	34.5	25.9
TSE (no re-censoring + adjust for baseline characteristics†)	0.785 (0.596 - 1.035; p=0.0857)	52.5	43.4
TSE (re-censored* + adjust for baseline characteristics†)	0.713 (0.535 - 0.952; p=0.0216)	51.4	41.5
IPCW (stabilised weights + adjust for baseline characteristics†)	0.674 (0.465 – 0.979; p=0.0383)	54.6[α]	38.6[α]

Abbreviations: CI, confidence interval; IPCW, inverse probability of censoring weighting; IXA+LEN+DEX, ixazomib-lenalidomide-dexamethasone; LEN+DEX, lenalidomide-dexamethasone; OS, overall survival; TSE, two-stage estimator.

Note: p-values from stratified log-rank tests for analyses which do not adjust for baseline characteristics. For analyses which adjust for baseline characteristics, p-values are those associated with the coefficient from a Cox regression model including treatment arm and baseline characteristics as covariates.

† Adjusts for high risk, age>65, ISS stage at screening, and history of bone lesions.

‡ Excludes all patients who switched from the analysis.

[α]Median estimates for ICPW do not adjust for baseline covariates

A.15 PRIORITY QUESTION: Please can the company present Kaplan-Meier plots for time to next subsequent treatment after PI for:

1. The 40 or 42 IXA+LEN+DEX people who received a PI as first therapy following progression.
2. The 25 of these that received a subsequent treatment classified as requiring adjustment.
3. The remaining 20 people.

Response: Following discussions with NICE and the ERG during the clarification call held on September 30th, it was agreed that the split of next-line subsequent therapy vs. later-line subsequent therapy was no longer relevant. This was an artefact from an earlier version of the model and submission where an error was subsequently identified. This has since been rectified. Importantly, patients receiving next-line PI in the IXA+LEN+DEX arm are no longer adjusted for in the treatment switching analyses due to an inability to account for both next-line PI use and subsequent novel therapies in published methodologies (see Section A.7.1/page 25 of the Takeda submission dated July 5th). As the use of PIs in the next-line is thought to worsen outcomes for patients in the IXA+LEN+DEX arm, this is considered to be a conservative approach.

Note: there were 42 patients receiving a PI as an immediate next-line in the IXA+LEN+DEX arm. N=25 of these patients also received a novel subsequent therapy not routinely available in UK clinical practice; these 25 patients were included in the treatment switching analyses and were adjusted for based on the receipt of a subsequent therapy not routinely available in the UK and **not** in relation to the next-line PI use. The remaining N=17 patients were not classified as switchers.

A.16 Please present Kaplan-Meier plots (for each arm of TMM1) showing time-on-treatment with a PI used as immediate next subsequent therapy.

Response: Following discussions with NICE and the ERG during the clarification call held on September 30th, it was agreed that the split of next-line subsequent therapy vs. later-line subsequent therapy was no longer relevant. This was an artefact from an earlier version of the model and submission where an error was subsequently identified. This has since been rectified. Importantly, patients receiving next-line PI in the IXA+LEN+DEX arm are no longer adjusted for in the treatment switching analyses due to an inability to account for both next-line PI use and subsequent novel therapies in published methodologies (see Section A.7.1/page 25 of the Takeda submission dated July 5th). As the use of PIs in the next-line is thought to worsen outcomes for patients in the IXA+LEN+DEX arm, this is considered to be a conservative approach.

A.17 CS Document, pg. 28 states that *"to ensure that the most important prognostic factors for switching and survival are captured, this list was informed and validated through feedback from the clinical advisory board and follow-up communication with clinicians."* The ERG was unable to identify *"advisory board"* material received by the ERG that documents or describes this validation. Please can the company clarify or supply this information.

Response: While the full report from the advisory board remains confidential, the Company has provided below an excerpt from the report that addresses the ERG clarification.

"Advisors were presented with the following prognostic factors: Treatment arm, Age, Gender, Time since diagnosis, Race, Region, Prior PI, Baseline laboratory values (corrected calcium, serum protein, urine M-protein and platelets). Advisors did not expect Race and Gender to be prognostic. Advisors recommended including one or more additional factor(s) related to current disease status/severity. Suggestions included: Time from last treatment, Performance status, Comorbidities, PFS, Renal function, Prior lenalidomide, Cytogenetic status (high-risk vs standard risk), R-ISS (or, in lieu of this, ISS and cytogenetics) and Time since diagnosis."

Further details of the March advisory board are provided in the reference pack accompanying the submission ('Takeda_Data on File_UKDOFIXA21001_Ad board [CIC]').

A.18 Please combine the known/observed progression times available for 58 switchers with time-on-treatment for the remaining 53 switchers for whom progression time was unavailable (total switches 111), CS Document, pg. 29, and present resulting Kaplan-Meier plots by treatment arm.

Response: It is not appropriate to compare the PFS and ToT for switchers only; this breaks randomisation from the trial and there are important prognostic factors and treatment effect modifiers which are adjusted for as part of the treatment switching analyses to address this.

A.19 PRIORITY QUESTION: It appears that the use of *"subsequent therapies"* (post-progression therapies) is different in the present submission to that in the April 2021 (aborted) submission (see Table 9 and Table 10). Please clarify if this is the case, and if it is different, please explain why this change has occurred.

Table 9: Proportion of participants receiving post-progression anti-cancer therapy

Therapies	April 2021 submission		Current submission	
	LEN+DEX	IXA+LEN+DEX	LEN+DEX	IXA+LEN+DEX
Bendamustine + Prednisolone as a subsequent therapy	7.92%	11.17%	14.32%	10.34%
Cyclophosphamide as a subsequent therapy	19.80%	26.06%	30.43%	22.16%
Bortezomib + doxorubicin as a subsequent therapy	7.92%	0.00%	10.74%	8.86%
Bortezomib + dexamethasone as a subsequent therapy	53.47%	3.72%	62.64%	54.66%
Carfilzomib + dexamethasone as a subsequent therapy	0.00%	0.00%	0.00%	0.00%
Lenalidomide + dexamethasone as a subsequent therapy	0.00%	0.00%	0.00%	0.00%
Melphalan + Prednisolone as a subsequent therapy	21.78%	37.23%	39.38%	23.64%
Pomalidomide + dexamethasone as a subsequent therapy	45.54%	78.18%	69.80%	63.53%
Thalidomide + dexamethasone as a subsequent therapy	13.86%	22.34%	14.32%	23.64%
Panobinostat + Bortezomib + Dexamethasone as a subsequent therapy	3.96%	0.00%	8.95%	7.39%
Bortezomib + bendamustine + dexamethasone as a subsequent therapy	19.80%	0.00%	21.48%	10.34%
Carfilzomib + lenalidomide + dexamethasone as a subsequent therapy	0.00%	0.00%	0.00%	0.00%
Daratumumab as a subsequent therapy	0.00%	0.00%	0.00%	0.00%
Daratumumab + lenalidomide + dexamethasone as a subsequent therapy	0.00%	0.00%	0.00%	0.00%
Dexamethasone as a subsequent therapy	5.94%	7.45%	5.37%	5.91%
Elotuzumab + thalidomide + dexamethasone as a subsequent therapy	0.00%	0.00%	0.00%	0.00%
Elotuzumab + pomalidomide + dexamethasone as a subsequent therapy	0.00%	0.00%	0.00%	0.00%
Isatuximab + pomalidomide + dexamethasone as a subsequent therapy	0.00%	0.00%	0.00%	0.00%
Ixazomib + dexamethasone as a subsequent therapy	0.00%	0.00%	0.00%	0.00%

Therapies	April 2021 submission		Current submission	
	LEN+DEX	IXA+LEN+DEX	LEN+DEX	IXA+LEN+DEX
Ixazomib + lenalidomide + dexamethasone as a subsequent therapy	0.00%	0.00%	0.00%	0.00%
Pomalidomide + carfilzomib + dexamethasone as a subsequent therapy	0.00%	0.00%	0.00%	0.00%
Autologous stem cell transplant as a subsequent therapy	0.00%	0.00%	0.00%	0.00%

Table 10: Proportion of participants receiving post-progression anti-cancer therapy

Therapy	April Submission						Current submission					
	Adjusted OS		Unadjusted OS		Original submission		Adjusted OS		Unadjusted OS		Original submission	
	IXA+LEN +DEX	LEN +DEX	IXA+LEN +DEX	LEN +DEX	IXA+LEN+ DEX	LEN +DEX	IXA+LEN +DEX	LEN +DEX	IXA+LEN +DEX	LEN +DEX	IXA+LEN + DEX	LEN +DEX
Bortezomib + bendamustine + dexamethasone as a subsequent therapy	11.17%	7.92%	5.38%	6.20%	11.11%	11.11%	10.34%	14.32%	6.67%	8.60%	11.11%	11.11%
Carfilzomib + lenalidomide + dexamethasone as a subsequent therapy	26.06%	19.80%	11.54%	13.18%	41.41%	41.41%	22.16%	30.43%	14.29%	18.28%	41.41%	41.41%
Daratumumab as a subsequent therapy	0.00%	7.92%	4.62%	4.65%	9.09%	9.09%	8.86%	10.74%	5.71%	6.45%	9.09%	9.09%
Daratumumab + lenalidomide + dexamethasone as a subsequent therapy	3.72%	53.47%	28.46%	27.13%	0.00%	0.00%	54.66%	62.64%	35.24%	37.63%	0.00%	0.00%
Dexamethasone as a subsequent therapy	0.00%	0.00%	18.46%	15.50%	0.00%	0.00%	0.00%	0.00%	22.86%	21.51%	0.00%	0.00%
Elotuzumab + thalidomide + dexamethasone as a subsequent therapy	0.00%	0.00%	22.31%	17.05%	21.21%	21.21%	0.00%	0.00%	27.62%	23.66%	21.21%	21.21%
Elotuzumab + pomalidomide + dexamethasone as a subsequent therapy	37.23%	21.78%	12.31%	17.05%	18.18%	18.18%	23.64%	39.38%	15.24%	23.66%	18.18%	18.18%

Isatuximab + pomalidomide + dexamethasone as a subsequent therapy	78.18%	45.54%	33.08%	30.23%	0.00%	0.00%	63.53%	69.80%	40.95%	41.94%	0.00%	0.00%
Ixazomib + dexamethasone as a subsequent therapy	22.34%	13.86%	12.31%	6.20%	12.12%	12.12%	23.64%	14.32%	15.24%	8.60%	12.12%	12.12%
Ixazomib + lenalidomide + dexamethasone as a subsequent therapy	0.00%	3.96%	3.85%	3.88%	79.80%	79.80%	7.39%	8.95%	4.76%	5.38%	79.80%	79.80%
Pomalidomide + carfilzomib + dexamethasone as a subsequent therapy	0.00%	19.80%	5.38%	9.30%	0.00%	0.00%	10.34%	21.48%	6.67%	12.90%	0.00%	0.00%
Autologous stem cell transplant as a subsequent therapy	0.00%	0.00%	1.54%	2.33%	0.00%	0.00%	0.00%	0.00%	1.90%	3.23%	0.00%	0.00%
Bortezomib + bendamustine + dexamethasone as a subsequent therapy	0.00%	0.00%	10.77%	20.93%	0.00%	0.00%	0.00%	0.00%	13.33%	29.03%	0.00%	0.00%
Carfilzomib + lenalidomide + dexamethasone as a subsequent therapy	0.00%	0.00%	3.85%	5.43%	0.00%	0.00%	0.00%	0.00%	4.76%	7.53%	0.00%	0.00%
Daratumumab as a subsequent therapy	7.45%	5.94%	3.08%	2.33%	0.00%	0.00%	5.91%	5.37%	3.81%	3.23%	0.00%	0.00%
Daratumumab + lenalidomide + dexamethasone as a subsequent therapy	0.00%	0.00%	0.00%	1.55%	0.00%	0.00%	0.00%	0.00%	0.00%	2.15%	0.00%	0.00%

Dexamethasone as a subsequent therapy	0.00%	0.00%	2.31%	3.88%	0.00%	0.00%	0.00%	0.00%	2.86%	5.38%	0.00%	0.00%
Elotuzumab + thalidomide + dexamethasone as a subsequent therapy	0.00%	0.00%	0.77%	0.78%	0.00%	0.00%	0.00%	0.00%	0.95%	1.08%	0.00%	0.00%
Elotuzumab + pomalidomide + dexamethasone as a subsequent therapy	0.00%	0.00%	1.54%	2.33%	0.00%	0.00%	0.00%	0.00%	1.90%	3.23%	0.00%	0.00%
Isatuximab + pomalidomide + dexamethasone as a subsequent therapy	0.00%	0.00%	2.31%	1.55%	0.00%	0.00%	0.00%	0.00%	2.86%	2.15%	0.00%	0.00%
Ixazomib + dexamethasone as a subsequent therapy	0.00%	0.00%	1.54%	0.78%	0.00%	0.00%	0.00%	0.00%	1.90%	1.08%	0.00%	0.00%
Ixazomib + lenalidomide + dexamethasone as a subsequent therapy	0.00%	0.00%	0.77%	7.75%	0.00%	0.00%	0.00%	0.00%	0.95%	10.75%	0.00%	0.00%

Response: This question makes comparisons between an earlier, incorrect version of the economic model and submission - which was submitted to NICE in April but was then superseded by an updated, correct version submitted in July – with the current, correct version from July. Following discussions with NICE and the ERG during the clarification call held on September 30th, it was agreed that the previously submitted model is no longer relevant due to the identification of an error in how the the treatment switching analyses was performed. This error impacted subsequent treatment distributions and explains why the values differ between the two submissions. In addition to this error, the most recent treatment switching analyses no longer adjust for patients receiving next-line PI in the IXA+LEN+DEX arm due to an inability to account for both next-line PI use and subsequent novel therapies in published methodologies. This also contributes to the differences in the adjusted subsequent treatment distributions between the two submissions. The error has since been rectified and the correct subsequent treatment distributions are reported in the updated July submission.

A.20 PRIORITY QUESTION: Please can the company identify the *"fundamental flaw"* noted by the company in the company's previous submission and provide an explanation of how this was rectified.

Response: Following discussions with NICE and the ERG during the clarification call held on September 30th, it was agreed that the April submission has been superseded by the updated and correct July version. It was concluded that the April submission should not be considered for the remainder of this appraisal.

For completeness, the error in the previous model was due to incorrect definition of "switchers" in the treatment switching analysis, and the methodology that followed. This incorrect analysis censored all the "invalid" subsequent therapies at point of receipt, with treatment switching methods then applied to the remaining dataset and adjusting for receipt of any subsequent therapy versus no subsequent therapy. This approach was not as intended and did not address the objective of aligning the survival data with routine clinical practice in the UK.

In correcting the error in methodology it became evident that it was not possible to disentangle the effects of multiple switches for one patient. Therefore, the updated

analyses define switchers based on first receipt of subsequent therapies which are not routinely available in UK clinical practice – in line with the NICE Position Statement.[1] Importantly, the effect of next-line PI in the IXA+LEN+DEX treatment arm is not adjusted for. As the use of PIs in the immediate next-line is thought to worsen outcomes for these patients, this is considered to be a conservative approach. Additionally, the effects of multiple novel subsequent therapies are not fully addressed in this approach, this is also thought to be conservative because more patients in the LEN+DEX arm than in the IXA+LEN+DEX arm received subsequent therapies which are known to have prognostic importance (e.g. daratumumab).

Section B: Clarification on cost-effectiveness data

B.1 PRIORITY QUESTION: The ERG undertook an analysis that compared the disaggregated life years (LYs) post-progression results using the adjusted OS: 2-stage re-cens (novel therapies) to the unadjusted OS (Table 11). The results show that by including subsequent therapies which are not routinely funded or available in UK practice the gain in post-progression LYs is greater in people randomised to LEN+DEX compared to IXA+LEN+DEX, for which the impact is negligible. These results seem contradictory with the statement in the CS (page 30) indicating that clinical experts considered that OS should reduce when adjusting for the effects of efficacious subsequent therapies. Please can the company explain this finding?

Table 11: Disaggregated LYs by TOURMALINE-MM1 OS analyses (post-progression)

Therapy	Base-case [adjusted OS: 2-stage re-cens (novel therapies)] - (excluding the effect of efficacious subsequent therapies)	Unadjusted OS (including the effect of efficacious subsequent therapies)
IXA+LEN+DEX	2.615	2.648
LEN+DEX	2.287	2.589

Response: Consistent with the Company's position in the CS, and the advice received from clinical experts (CS, page 30), the ERG's analysis demonstrates that OS reduces for both treatment arms when subsequent therapies which are not routinely funded or available in UK practice are adjusted for.

The observed difference in LY adjustment on removal of novel therapies between the two treatment arms is due to the differences in subsequent therapies received by these patients. As described on pages 16 and 17 of the CS dated July 5th, "more patients in the LEN+DEX arm than in the IXA+LEN+DEX arm received subsequent therapies which are known to have prognostic importance, for example: daratumumab (31/149=21% in LEN+DEX vs. 19/148=13% in IXA+LEN+DEX), elotuzumab (7/149=5% vs. 3/148=2%) and autologous stem-cell transplant (9/149=6% vs. 1/148=0.7%). These treatments are either not available in the UK or are only funded by the CDF. The imbalance in these therapies confounds the

interpretation of the survival benefit, as more patients in the LEN+DEX arm received therapies that extend survival for patients with MM." This is consistent with the LYs in the ERG's analysis decreasing more for patients in the LEN+DEX arm vs the IXA+LEN+DEX arm.

B.2 PRIORITY QUESTION: The ERG noted that there is little uncertainty in the probabilistic sensitivity analysis (PSA) results (Figure 1) for incremental QALYs in the most recent model compared to the results (Figure 2) for the previous model. Please can the company explain why there is a discrepancy?

Figure 1: Incremental scatterplot of the PSA results for the comparison between IXA+LEN+DEX versus LEN+DEX

(Obtained from "PSA Results" worksheet, ID1635 ixazomib Takeda submission model list price 05072021CM [CIC])

Figure 2: Incremental scatterplot of the PSA results for the comparison between IXA+LEN+DEX versus LEN+DEX

(Obtained from "PSA Results" worksheet, ID1635 ixazomib Takeda clarification model LISTprice 07052021KM [CIC])

Response: This question makes comparisons between an earlier, incorrect version of the economic model and submission - which was submitted to NICE in April but was then superseded by an updated, correct version submitted in July – with the current, correct version from July. The error in the earlier version related to treatment switching analyses which directly influenced the incremental life years and, thus, quality adjusted life years (QALYs). The uncertainty relating to the incorrect approach was much greater due to a number of (incorrect) assumptions feeding into the analysis. Figure 1 presented above is the correct representation of the uncertainty in the relevant model version.

B.3 PRIORITY QUESTION: In the PSA a normal distribution was used to show the uncertainty around costs. Please can the company provide justification for using this distribution? Can the company clarify if there is functionality in the model to select other distributions?

Response: A normal distribution was selected for costs because often only the mean value was available and this was considered to be the simplest distribution. A limiting factor of the normal distribution is the potential for negative costs. However, when varying the standard deviation based on 10% of the mean, as was done in the analyses presented in the CS, none of the costs were estimated as negative. There is not an option to change this distribution within the model. However, the top ten most influential parameters on the ICER as shown by the tornado plots do not reflect costs being key drivers. Therefore, this is expected to have limited impact.

B.4 PRIORITY QUESTION: The ERG noted that on the "PARAM" worksheet in the economic model that the lower bound (LB) and upper bound (UP) for the *"FA-coefficient associated with-Age"* (cell C444) was -0.002 and -0.007, respectively. Please can the company confirm that the LB and UB should be -0.007 and -0.002, respectively on the "PARAM" (cells K444 and L444) and "HRQL" (cells L51 and N51) worksheets.

Response: The Company can confirm that the lower and upper bounds should be -0.007 and -0.002, respectively on the "PARAM" (cells K444 and L444) and "HRQL" (cells L51 and N51) worksheets. This results in a minimal difference to the OWSA, only resulting in a switch in the lower and upper bound results for the "FA-coefficient associated with-Age" parameter.

B.5 The ERG noted that on the "PARAM" worksheet that the base values for Rate-Anaemia (row 523), Rate-Nausea (row 530), Rate-Neutropenia (row 531) and Rate-Pneumonia (row 533) are not within lower and upper bounds. Please can the company clarify?

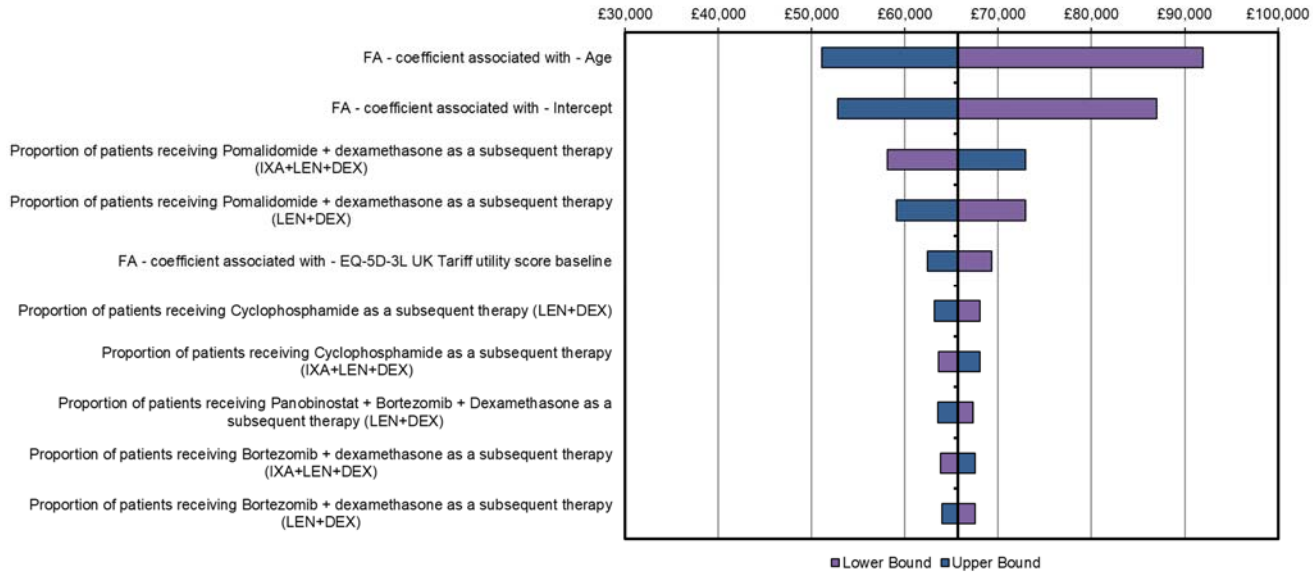
Response: The Company can confirm that the beta distributions for these variables were incorrectly calculated; based on total number of patients as opposed to patient

years of exposure. This error only impacted the rates of adverse events and has now been corrected in: 'ID1635_Ixazomib_UpdatedCEA_withLIST_CIC_v2.0_ERGQ'. The updated tornado diagram based on the list price for ixazomib is presented in Figure 3. The tornado diagram based on the proposed PAS for ixazomib is presented in Figure 4, this is an updated version of Figure 14 in Appendix F.3 of the Company Submission. As the rates of adverse events are not key drivers of the model, this error does not impact results of either OWSA.

Figure 3: Updated Tornado diagram (based on list price for ixazomib)

Abbreviations: FA, final analysis; IXA+LEN+DEX, ixazomib-lenalidomide-dexamethasone; LEN+DEX, lenalidomide-dexamethasone.

Figure 4: Updated Tornado diagram (based on proposed PAS for ixazomib)



Abbreviations: FA, final analysis; IXA+LEN+DEX, ixazomib-lenalidomide-dexamethasone; LEN+DEX, lenalidomide-dexamethasone.

References

1. NICE. Position statement: consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product. January 2019. Available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/cancer-drugs-fund/CDF-comparator-position-statement.pdf [Accessed 04 October 2021].

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund review

Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (CDF review of TA505) [ID1635]

Additional clarification question

October 2021

File name	Version	Contains confidential information	Date
ID1635 Company response to additional ERG clarifications [redacted]	1.0	No	13/10/2021

Additional clarification question on effectiveness data

The ERG has additional points of clarification regarding the company's response to question A3 of the original clarification questions. There appears to be small discrepancies in the data sent by company in file ID1635 ixazomib Takeda clarification questions A3_A4 05102021CM noACIC, summarised in Table 1.

Table 1: Number of deaths and censored by treatment

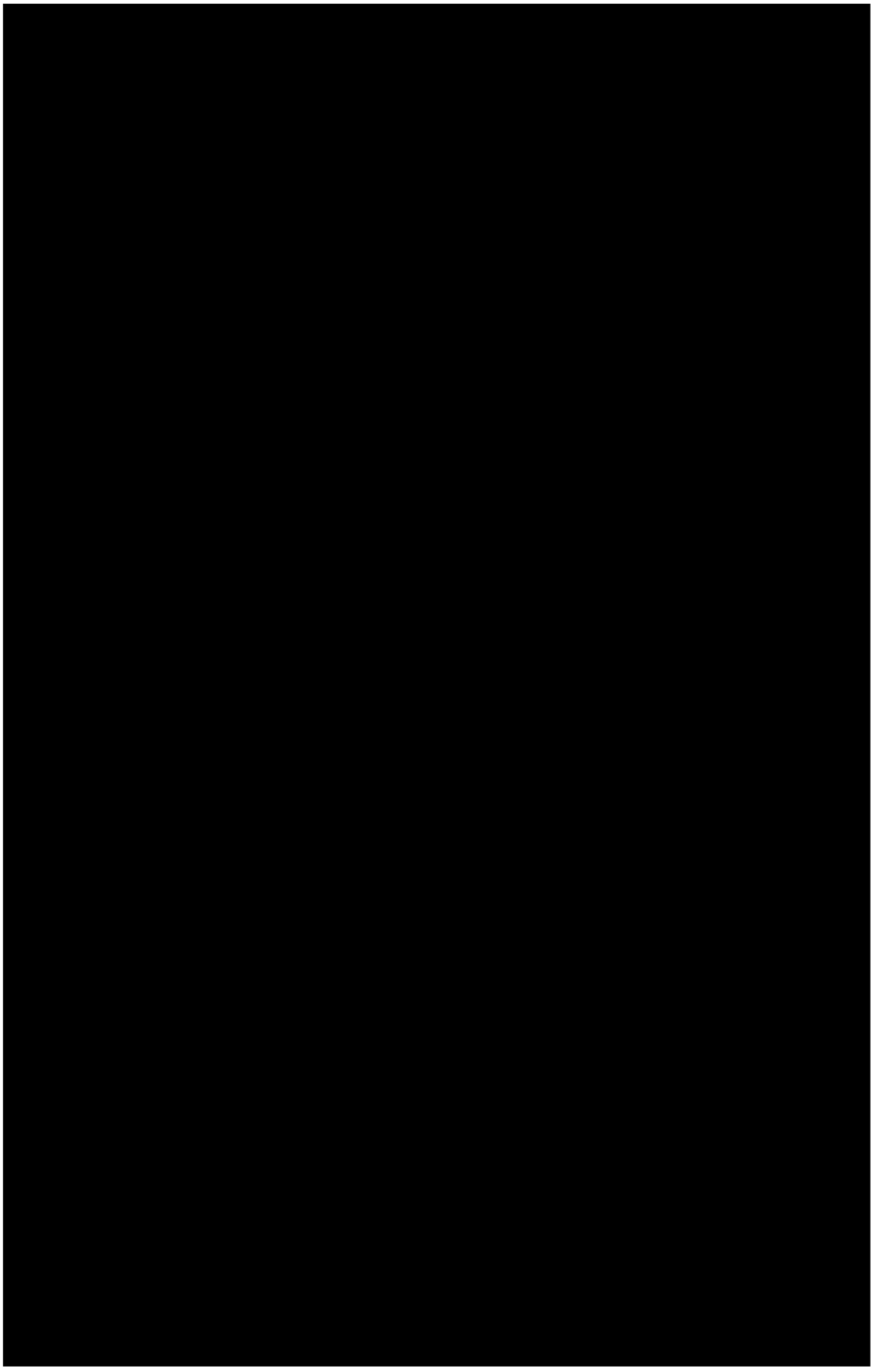
Outcome	IXA+LEN+DEX				LEN+DEX			
	Total	Deaths	Censors	Deaths +censors	Total	Deaths	Censors	Deaths +censors
OS unadjusted	148	104	43	147	149	104	44	148
OS adjusted	148	89	57	146	149	101	47	148
ToT	148	138	9	147	149	140	8	148
OS, overall survival; ToT, time-on-treatment								

1. The numbers of deaths and censors don't seem to tally with the quoted total number of patients; in particular, for OS adjusted in the IXA+LEN+DEX arm. There are 146 deaths and censors whereas the total patients expected is 148. Please can the company clarify.

Response: The Kaplan–Meier plots were produced using STATA – example code for the first ten lines of the 2+ prior lines subgroup unadjusted OS data are presented in Figure 1. The code *sts list, by (arm_e)* gives you the raw output – which makes sense when you add up the columns and is easy to interpret. To provide the input for the Lifetable(OS) and Lifetable (ToT) sheets in the economic model based on weekly cycles the code: *sts list, by (arm_e) at (0(1)10)* is used. This is designed to give you a snapshot of the full Kaplan–Meier curve and the numbers may not always add up exactly as would be expected. STATA state that: the Beg. Total information is that for the last observed failure time (before the failures occur). When the at() option is used, the Beg. Total column in the output does not contain the number at risk at the time indicated in the Time column. It shows the number at risk at the time just before the previous failure.[1] This has no impact within the base case economic model, as these Kaplan–Meier curves are not implemented in the model calculations.

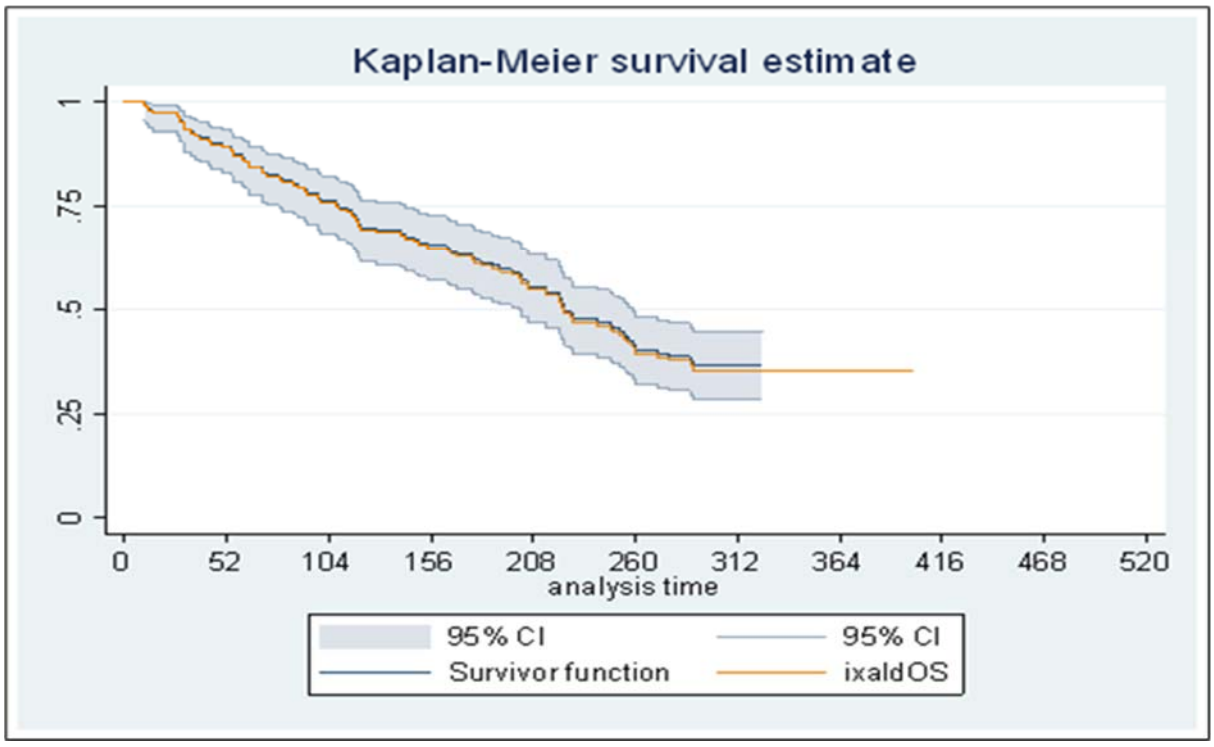
[1] https://www.stata.com/manuals13/ststslist.pdf

Figure 1: Example of STATA code deriving the Kaplan-Meier data for the unadjusted OS in the 2+ prior lines subgroup



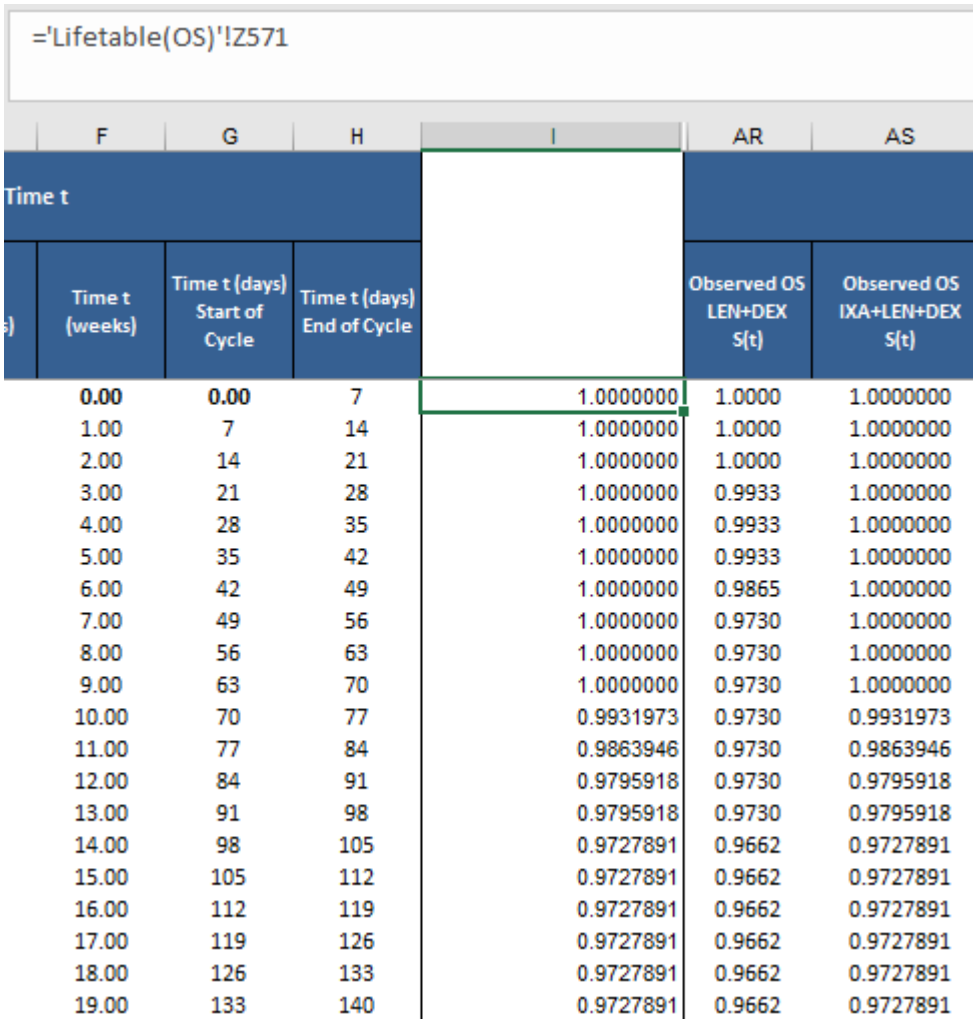
2. Using the company's data from clarification response the ERG gets the Kaplan–Meier plot in black (with CIs). The company's last time for any death or censoring in the clarification is 321 weeks. However, from the Kaplan-Meier data from the economic model has a last time point of about 400 weeks, a much longer flat tail. In the Figure 1 we have plotted both: the orange is taken from the economic model KM (columns AS versus column D in the comparator 2 worksheet). Using the company's IPD, the KM graph although almost the same as from economic model (apart from long tail) is slightly different (displaced down). Please can the company clarify.

Figure 2: Kaplan-Meier curves from information supplied and from economic model



Response: Firstly, we have been unable to replicate the small differences between the orange and black Kaplan–Meier curves observed in Figure 2 within the economic model. When looking at the unadjusted OS data as an example the Kaplan–Meier estimates in column AS (Comp2) are identical to those in the Lifetable(OS) sheet – see Figure 3 below. To provide further clarification we would need more information with regards to how the black curve was derived.

Figure 3: Screenshot from the Comp2 sheet



='Lifetable(OS)'!Z571

	F	G	H	I	AR	AS
	Time t					
	Time t (weeks)	Time t (days) Start of Cycle	Time t (days) End of Cycle		Observed OS LEN+DEX S(t)	Observed OS IXA+LEN+DEX S(t)
	0.00	**0.00**	7	1.0000000	1.0000	1.0000000
	1.00	7	14	1.0000000	1.0000	1.0000000
	2.00	14	21	1.0000000	1.0000	1.0000000
	3.00	21	28	1.0000000	0.9933	1.0000000
	4.00	28	35	1.0000000	0.9933	1.0000000
	5.00	35	42	1.0000000	0.9933	1.0000000
	6.00	42	49	1.0000000	0.9865	1.0000000
	7.00	49	56	1.0000000	0.9730	1.0000000
	8.00	56	63	1.0000000	0.9730	1.0000000
	9.00	63	70	1.0000000	0.9730	1.0000000
	10.00	70	77	0.9931973	0.9730	0.9931973
	11.00	77	84	0.9863946	0.9730	0.9863946
	12.00	84	91	0.9795918	0.9730	0.9795918
	13.00	91	98	0.9795918	0.9730	0.9795918
	14.00	98	105	0.9727891	0.9662	0.9727891
	15.00	105	112	0.9727891	0.9662	0.9727891
	16.00	112	119	0.9727891	0.9662	0.9727891
	17.00	119	126	0.9727891	0.9662	0.9727891
	18.00	126	133	0.9727891	0.9662	0.9727891
	19.00	133	140	0.9727891	0.9662	0.9727891

Secondly, the maximum time we have Kaplan–Meier data for IXA+LEN+DEX is 401 weeks for the unadjusted OS analysis and 324 weeks for the adjusted OS analysis – see the screenshots below from the response to A3 from the Clarification Questions. When the adjusted OS data are selected there is no Dynamic Chart function set up in the model. Therefore, the tail of the Kaplan–Meier curve is defaulting to the last survival estimate until 401 weeks; from week 324 to week 401 the same survival estimate is used resulting in a longer flat tail. This has no impact on any of the model calculations and did not influence the parametric curve selected in the base case.

Figure 4: Screenshot from A3 clarification question, unadjusted OS

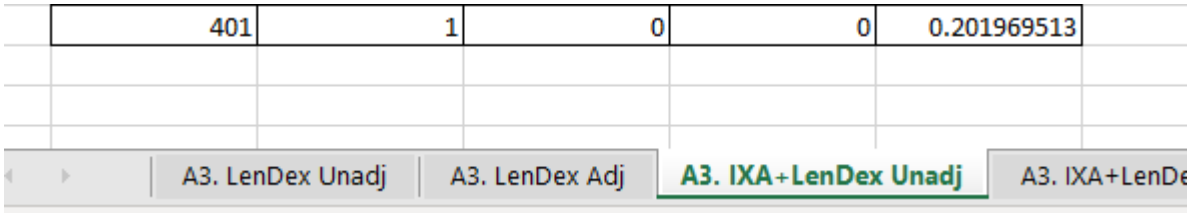
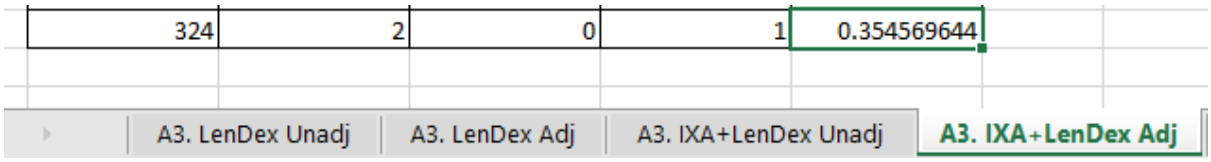


Figure 5: Screenshot from A3 clarification question, adjusted OS



NICE National Institute for Health and Care Excellence

Patient organisation submission

Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (CDF review of TA505) [ID1635]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

<table>
<tr><td>2. Name of organisation</td><td>Myeloma UK</td></tr>
<tr><td>3. Job title or position</td><td>[redacted]</td></tr>
<tr><td>4a. Brief description of the organisation (including who funds it). How many members does it have?</td><td>Myeloma UK is the only organisation in the UK dealing exclusively with myeloma. Our broad and innovative range of services cover every aspect of myeloma from providing information and support, to improving standards of treatment and care through research and campaigning. We receive no government funding and rely almost entirely on the fundraising efforts of our supporters. We also receive some unrestricted educational grants and restricted project funding from a range of pharmaceutical companies. We are not a membership organisation.</td></tr>
<tr><td>4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]

If so, please state the name of manufacturer, amount, and purpose of funding.</td><td>The table below shows the audited 2019 income from the relevant manufacturers. Funding is received for a range of purposes and activities namely core grants, project specific work including clinical trials, and gifts, honoraria or sponsorship.
<table>
<tr><th>Name of Company</th><th>Grants and project specific funding</th><th>Gifts, Honoraria and Sponsorship</th><th>Total (£)</th></tr>
<tr><td>Takeda</td><td>40,000</td><td>869</td><td>40,869</td></tr>
<tr><td>Celgene</td><td>110,000</td><td>12,337</td><td>122,337</td></tr>
<tr><td>Janssen-Cilag</td><td>20,000</td><td>327</td><td>20,327</td></tr>
</table>
</td></tr>
</table>

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We designed and widely circulated a Patient Treatment Survey specifically to support this appraisal. The survey was open to patients who have been treated with Ixazomib in combination with lenalidomide and dexamethasone (IRd) at third and fourth line of treatment, patients who had received IRd as an interim treatment option due to COVID-19 and those who have accessed IRd through a clinical trial. The survey received responses from 139 patients who shared their experience of being treated with IRd for myeloma. **Therefore, this survey has important experience and insight data from a large number of patients whose clinical condition is highly relevant and have received the treatment being appraised.** **A full analysis of the survey can be found in Appendix A attached to the submission.** Information in the survey has been augmented by insight and data gathered through our research and services programmes, including: - A multi-criteria decision analysis study of 560 myeloma patients. The study, funded by Myeloma UK and run by the European Medicines Agency (EMA) and University of Groningen, explored patient preferences for different benefit and risk outcomes in myeloma treatment. - It has also been informed by the experiences and views of patients, family members and carers gathered through ongoing engagement with our Myeloma Infoline, Patient and Family Myeloma Infodays and online Discussion Forum.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**What is it like to live with myeloma?** *"The uncertainty of not knowing when it will come back but the certainty of knowing it will is particularly difficult."* Myeloma is a highly individual and complex cancer originating from abnormal plasma cells in the bone marrow. There is currently no cure, but treatment can halt its progress and improve quality of life. The complications of myeloma can be significant, debilitating and painful and include severe bone pain, bone destruction, kidney damage, fatigue and a depleted immune system which can lead to increased infections. Myeloma is also a relapsing and remitting cancer which evolves over time and becomes resistant to treatment. Most patients can be successfully retreated at relapse; however, remission is usually associated with diminishing duration and depth of response over time. Multiply relapsed patients, the patient population covered in this appraisal, often experience an even more significant disease burden. They not only face a worse prognosis but also a greater symptomatic burden, due to the progressive nature of the disease and the cumulative effects of treatment which can result in reduced quality of life. Treatment side-effects and frequent hospital visits have a social and practical impact on patients' lives, including significant financial implications. Reduction in mobility over time and a perceived increase in reliance on carers and family members, also impacts on patients' sense of control. Treatment related adverse events also generally increase with number of lines of therapy; the proportion of patients with one or more toxicity or comorbidity at the end of treatment increases with lines of treatment. That said, patients often see symptoms and side effects as something to be expected and accept it as part of their disease and/or treatment, with many patients developing self-care strategies.

	"I find the mental aspect most challenging. Not knowing what it's going to do even though you understand it is coming back. It clipped my wings. I live in a world of before and after. Certain things become insignificant. But I do not give in to it." **What do carers experience?** *"I feel angry that I'm not going to get the future I wanted, but the hardest thing to feel is how my life at the moment is in limbo".* A Myeloma UK study into the experiences of carers and family members found that looking after someone with myeloma has a significant emotional, social and practical impact: - 94% of carers are emotionally impacted and found the uncertainty of myeloma a major factor. - 25% of those in work had been unable to work or had to retire early to care for the person with myeloma. - 84% always put the needs of their relative or friend with myeloma before their own. - Only 42%of carers were not given enough information at diagnosis about how myeloma may affect them. Living with myeloma is therefore often extremely challenging physically and emotionally for patients, carers, and family members. *"I had to think of my husband. You are in this as a team, it is not an individual battle."*

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers appreciate the wider range of effective treatments that are now available for treating relapsed and refractory myeloma which has delivered significant improvements in survival in myeloma over the past decade. However, myeloma remains a challenging cancer to treat, often particularly so for multiply relapsed patients. Myeloma is a relapsing and remitting cancer which evolves over time and becomes resistant to treatment; a range of treatment options with different mechanisms of action at each stage of the pathway is therefore vital for myeloma patients. Myeloma patients and their carers place a very high value on treatments that: • **Prolong their life.** • **Put their myeloma into remission for as long as possible.** • **Allow them to enjoy normal day-to-day life.** The Myeloma UK, EMA and the University of Groningen study showed that, achieving a lasting remission from treatment was the most important factor for most (75%) participants. This was true across all patient groups regardless of demographic and clinical characteristics. Treatments with minimal negative impact on quality of life are very important, particularly those with as few side effects as possible and of low severity. That said, data shows that patients will accept even severe side effects if the treatment has a superior efficacy, suggesting that efficacy is the strongest driver of treatment choice. **IRd** IRd is currently licenced through the CDF for multiply relapsed patients who have received two or three prior therapies. We know from our engagement with clinicians that IRd is the current standard treatment for patients at 3rd line of treatment in England.

	Myeloma UK's Patient Treatment Survey shows what patients think of this current treatment: - 81% of respondents rated their experience of IRd as either very positive or positive. - 97% of respondents would recommend IRd to other myeloma patients - 81% of patients felt that IRd is effective in controlling their Myeloma. - 95% of respondents rated the way it was given as an all-oral treatment as very positive or positive. - 77% of patients said their Quality of Life improved or stayed the same while receiving IRd - 87% of patients said their levels of mental health improved or stayed the same while receiving IRd A full analysis can be seen in appendix 1 however it is clear that IRd is a welcome addition the myeloma treatment pathway. *"My main hope is for the myeloma to be controlled as far as possible and it's meant a lot to me that this treatment has been available and has been effective up to now. Although I find the side effects difficult at times it's worth it for a treatment that's helping me."*
8. Is there an unmet need for patients with this condition?	Yes. As stated, above Myeloma UK know from our engagement with patients that IRd is a popular treatment. We also know through our engagement with the clinical community that since 2018 IRd has become the standard treatment at 3rd line for treating multiple myeloma. This has been emphasised in other Myeloma appraisals including TA10510. If this treatment were not to be approved for routine commissioning it would leave a significant gap at third line for patients. Currently IRd is the only triplet combination therapy available to patients at this part in the pathway and if it were to be removed then patients would be receiving sub-optimal treatments. This would be hugely damaging for myeloma patients who want to be receive the best treatments possible at each line of therapy. *"Greatest drug against Myeloma that I have taken. Please let me carry on taking it as it increases my chance of living longer."*

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	We know from our engagement that patients value treatments which put their myeloma into remission for as long as possible, prolong their life and allow them to enjoy a normal day to day life. Using our survey data and clinical trial data from TOURMALINE-MM1 we analysed if IRd can deliver on these patient treatment preferences. **Improved efficacy and improved progression free survival:** Clinical trial data from TOURMALINE-MM1 on efficacy, response rate, duration of response and progression free survival shows that IRd is more effective at controlling a patient's myeloma compared to lenalidomide and dexamethasone alone (Rd). The median progression free survival was 20.6 months in the IRd group and 14.7 months in the Rd group (95% confidence interval [CI], 0.59 to 0.94; P=0.01), representing a 40% longer median progression free survival with IRd as compared with Rd. Overall response rate was 78.3% in the ixazomib group and 71.5% in the Rd group (P = 0.04). The corresponding rate of complete response plus very good partial response were 48% in the IRd group and 39% in Rd group. The corresponding median duration of response was 20.5 months and 15.0 months. From the survey 81% of respondents felt that IRd was effective in controlling their myeloma. *"A long period of remission with few side effects. It brought my paraproteins down to "undetectable" for several months for the first time since diagnosis."* *"IRd is an easier treatment for the patient to deal with and seems to be really effective in dealing with myeloma."* **Improved OS:** We understand that OS benefits had still to be determined by data collection through the managed access agreement over the period that IRd has been available to patients through the CDF.

	However, it must be noted that studies have shown for myeloma patients and their families and carers, and particularly those that are multiply relapsed, the worry of whether there are further effective treatment options available is a major issue. Knowing that a good treatment will be there when they relapse is hugely important; not having that certainty is a significant psychological burden.[1] Patients can experience a positive psychological benefit with the knowledge that the treatment is prolonging their life. *"I feel more confident that the chemotherapy regime will control the myeloma as well as may be expected, and hence increase the time between relapses and extend survival time."* *"It's given my wife and I hope for the future - being able to do the things we want to do - alongside seeing my daughters and their families grow up."* **Quality of Life:** The survey asked a number of questions exploring whether quality of life was affected while taking IRd. A majority of patients (77%) said their Quality of Life improved or stayed the same while receiving IRd. Respondents who said it improved their QoL provided comments that IRd had effectively controlled their myeloma, was easy to take and gave them hope for the future. For the same reasons as above a majority of patients (87%) also said their levels of mental health improved or stayed the same while receiving IRd. *"My mental health is very related to my ability to exercise, to walk and to lead a very active life. IRd has allowed me to stay active, even during the pandemic."* Further to this when asked if the side effects impacted on their ability to carry out daily activities 49% of respondents said the side effects did not impact on their daily life. The patient population receiving IRd are multiply relapsed and may carry a high disease burden. It is clearly significant that IRd can improve efficacy without negatively impacting on patients QoL.

[1] Hulin C., et al (2017) Living with the burden of relapse in multiple myeloma from the patient and physician perspective. Leukaemia research, 59, pp.75-84

	"I have felt normal, in terms of my general health and wellbeing, and have been able to carry on with all my normal daily activities." **Method of Administration:** We know from our engagement that patients value treatments which are easy to use and can give them greater control over their lives. In the survey 95% of respondents rated the way it was administered as an all-oral treatment as either very positive or positive Most patients viewed having an all-oral treatment as a positive and commented that this gave them more control over lives. *"Once the prescription is in my hands I am in total control and do not have to go out of my way or involve anybody else. I just build the tablet regime into my daily routine."* *"It's a much easier form of treatment which helps especially if working as not having to go to hospital for infusions, saves a lot of time."* The method of administration also has an impact on the family/carer. Pre-covid many patients would be accompanied on their hospital visits to receive treatment by family/carers. By receiving an all-oral treatment, it also relives some of the treatment burden from families. *"Much better for my husband as I only leave the house for two short visits to the hospital; blood test and prescription collection."*

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	In our Patient Treatment Survey, it was clear that side effects had an impact on a proportion of patients. More than half of respondents to the survey reported mild peripheral neuropathy, GI issues and fatigue as a side effect. *"It does play havoc with my stomach and bowels and can make me very tired for certain days during the cycle".* Almost a quarter of patients said that their QoL (23%) and mental health (13%) decreased while receiving IRd. From qualitative comments provided by patients the levels of side effects experienced was a theme that emerged here. *"The side effects caused depression due to feeling constantly unable to do the things I wanted to do (activities of daily life)."* However, only 4% said the side effects entirely stopped them from completing daily activities, with 47% stating it partially stopped them from completing daily activities. It is to be expected that a triplet anti-cancer therapy would have some effect on patients' quality of life, and it should be borne in mind that a partial effect on daily activities is likely to encompass a range of impacts, including those that are slight and do not have a significant negative effect on quality of life. *"Having to deal with the side effects of IRd makes it less pleasurable, comfortable and energising in all I attempt to achieve whether this is a country walk, shopping, cooking, yoga, drawing, talking to friends on zoom etc.....it doesn't stop me getting on with tasks, but it does entail more effort and less spontaneous enjoyment."* It must be noted that **75%** (102/139) of respondents to the survey were at third line or beyond and will be living with the combined symptoms of relapsed myeloma and multiple treatment burden. The Myeloma UK survey data on toxicity should also be viewed alongside the clinical trial data which records adverse events in comparison to lenalidomide and dexamethasone. The trial data underlined the fact that QoL was similar in the two groups, while IRd delivers significant additional benefit.

	Patient engagement in Myeloma UK has shown that most patients see side effects as something that has to be managed in their daily lives or tolerated for an effective treatment that keeps their myeloma in remission. At third and fourth line of treatment patients will have experience of managing side effects. This was emphasized by respondents: *"Primarily tiredness and interrupted sleep patterns but small price to pay set against the benefits IRd provides. Irrespective, I just get on with life tired or not".* *"The main side effect was sickness in conjunction with the ixazomib. This was identified and effectively controlled with anti-sickness medicine."* *"When you understand the treatment, you know what side effects are coming on what days."* Finally, it should be noted that taking the impact of side effects into account 81% of our survey respondents rated their experience of IRd as very positive or positive and 97% of patients would recommend IRd to other myeloma patients. *"Continued to work, less financial worries, continue to be a mum. Bashed the myeloma down to nothing which gives positivity which can only be a good thing. Read other people's side effects with other treatments and feel lucky, but patients are all different and trying to find a treatment that works for the individual can sometimes be hard."*
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No
Other issues	
13. Are there any other issues that you would like the committee to consider?	The method of administration as an all-oral treatment is clearly highly valued by patients. This was particularly significant over the pandemic as many patients were greatly appreciative of the flexibility and protection taking IRd gave. All Myeloma patients were classified in the clinical extremely vulnerable category and were told shield over all periods of lockdown. IRd was part of NHS England Interim Treatment Options and access was extended to patients who had received one prior therapy in England. Patients valued the benefits of taking an all-oral treatment throughout the pandemic and the protection it gave them. Many patients did not have to go into a hospital setting and it took a massive amount of stress away from patients who knew they were being treated with an effective triplet combination whilst not being exposed to the risk of COVID-19. Many comments to our survey reflect the appreciation that patients showed for having access to an all-oral treatment over the pandemic: *"An all-oral treatment is far better for the patient than having to have part of the triple medication administered by injection or infusion in a hospital setting, particularly in the Covid pandemic."* *"It is so convenient, and with hospital visits reduced this has been a significant factor with the Covid-19 pandemic. I get a blood test every 4 weeks at a local small hospital in Ashbourne which is then followed by a consultation with a consultant from the Royal Derby Hospital Haematology Team which is then*

	followed by a courier delivery of the drugs etc for the next 4-week cycle. All very efficient and impressive. I am grateful and feel lucky". *"Having this treatment orally has proved invaluable during the covid 19 pandemic. It has reduced the need for hospital visits for treatment and gives the patient more control i.e. which day to have the Ixazomib on (obviously using the same day through the cycle)."* *"Receiving IRd during the pandemic has definitely been an advantage and led to peace of mind at not having to visit the hospital."* *"Given that Myeloma patients are in shielding, oral medication has taken the worry out of visiting hospital and exposing oneself and carer to possible Covid infection."* *"Oral treatment has meant I have had less exposure to COVID-19 risks."*

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- IRd delivers improved efficacy and PFS, more effectively controlling myeloma, the benefit which is most valued by patients.
- The all-oral administration is hugely beneficial for patients, even more so during the COVID-19 pandemic.
- The significant additional clinical benefit of IRd is gained without impacting negatively impacting on patients' quality of life.
- The psychological benefit of accessing an effective triplet combination for a multiply relapsed patient group is significant.
- Despite the existence of alternative treatments there remains significant unmet need for the patient population covered in this appraisal. IRd has become the standard treatment of choice for patients at their third line of treatment. We cannot emphasise too strongly how devastating it would be if IRd were no longer available to this patient group. The impact on patient outcome, patients' mental health, quality of life and on their family and friends would be highly damaging.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

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Myeloma UK Patient Treatment Survey Report

Myeloma UK have conducted a Patient Treatment Survey on ixazomib (Ninlaro®) in combination with lenalidomide and dexamethasone (IRd) to understand more about patient experience of the treatment. Results from this survey will inform Myeloma UK's evidence submission for the NICE CDF review of the treatment.

Summary/Key Points

- 81% of respondents rated their experience of IRd as either very positive or positive.
- 97% of respondents would recommend IRd to other myeloma patients
- 95% of respondents rated the way it was administered as an all-oral treatment as either very positive or positive.
- IRd delivers the treatment preferences most important to patients including, treatment effectively controlling myeloma and increased progression free survival.
- A majority of patients said their quality of life while on IRd stayed the same or improved.
- Side effects can have an impact on patients' ability to carry out daily activities.

Introduction

In 2018, ixazomib (Ninlaro®) in combination with lenalidomide (Revlimid®) and dexamethasone (IRd) was approved by the National Institute for Healthcare Excellence (NICE) for the treatment of myeloma in patients who had received two or three prior therapies.

The treatment was conditionally approved for use through the NHS in the Cancer Drugs Fund (CDF) and was available to patients at third and fourth line of treatment. (It has since also been made available at second line as an interim treatment option for COVID-19.)

This is the first myeloma treatment which has been conditionally approved through the CDF that has come to NICE for re-appraisal. With an estimated high patient population who accessed this treatment Myeloma UK designed a survey to capture the insight and experience of patients who received IRd.

The survey was created with the help of three patients who had received the treatment combination. The three patients took part in a semi-structured interview to inform the question design, reviewed the questions and tested the survey. The survey was also reviewed by a clinician.

The Patient Treatment Survey was hosted online through Survey Monkey and was open from the 2nd of March until the 21st of March 2021. It was open to patients who have been treated with IRd at third and fourth line of treatment, patients who had received IRd as interim treatment option due to COVID-19 and those who have accessed IRd through a clinical trial. Patients were recruited through engagement via email and social media.

The survey received responses from 139 patients who shared their experience of being treated with IRd for myeloma. (Only two questions were mandatory and answered by all 139 respondents. Therefore, response figures will be in brackets (n)).

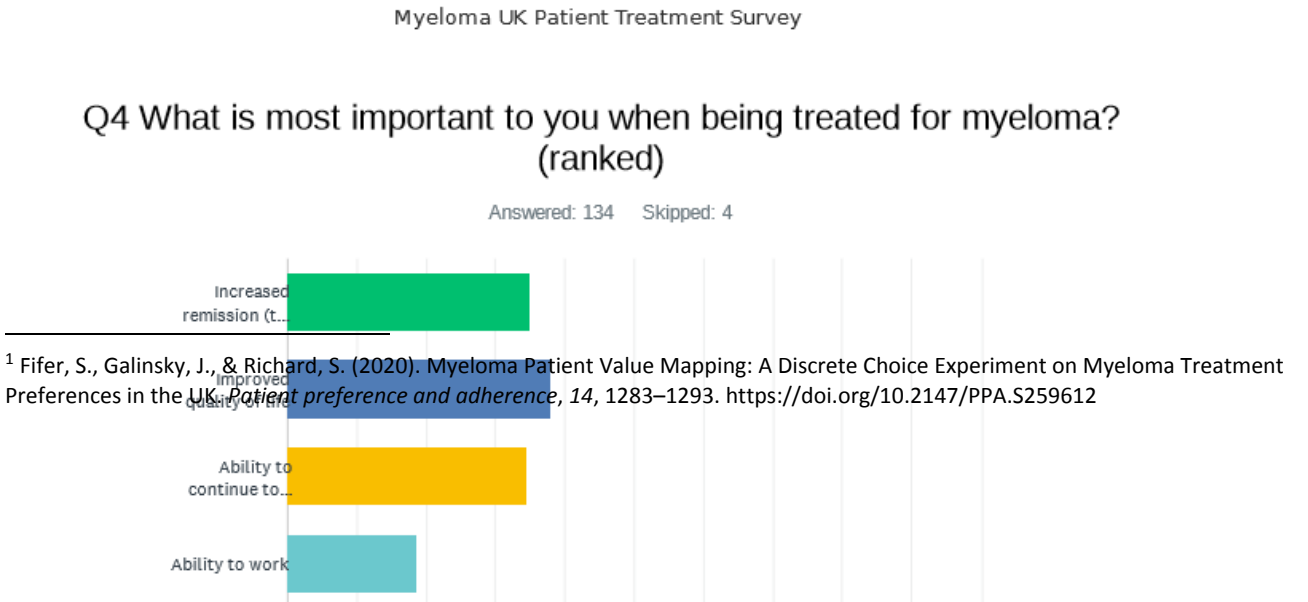
What did the survey tell us?

The survey was designed to answer two research questions:

1. Does IRd deliver the treatment preferences of patients?
2. How did patients feel IRd affected Quality of Life (QoL)?

Does IRd deliver the treatment preferences of patients?

To answer question number one the survey asked patients *'what is most important to you when being treated for myeloma?'* It provided six answer options and asked them to rank in order of importance. (Answer options were informed by Myeloma UK research[1] and the patient interviews conducted to inform survey design.)



[1] Fifer, S., Galinsky, J., & Richard, S. (2020). Myeloma Patient Value Mapping: A Discrete Choice Experiment on Myeloma Treatment Preferences in the UK. *Patient preference and adherence*, *14*, 1283–1293. https://doi.org/10.2147/PPA.S259612

From the results patients ranked their treatment preferences as:

1. Treatment effectively controlling my myeloma
2. Improved overall survival
3. Improved quality of life
4. Increased remission time
5. Ability to continue daily activities
6. Ability to work

Does IRd deliver these treatments preferences to patients?

Answers to the questions in the Patient Treatment Survey combined with clinical trial data can answer if IRd delivers these treatment preferences to patients.

Is IRd effective in controlling myeloma?

Clinical trial data from TOURMALINE-MM1 on efficacy, response rate, duration of response and progression free survival shows that IRd is more effective at controlling a patient's myeloma compared to lenalidomide and dexamethasone alone (Rd).[2]

The median progression free survival was 20.6 months in the IRd group and 14.7 months in the Rd group (95% confidence interval [CI], 0.59 to 0.94; P=0.01), representing a 40% longer median progression free survival with IRd as compared with Rd.

Overall response rate was 78.3% in the ixazomib group and 71.5% in the Rd group (P = 0.04). The corresponding rate of complete response plus very good partial response were 48% in the IRd group and 39% in Rd group. The corresponding median duration of response was 20.5 months and 15.0 months.

In the Patient Treatment Survey when asked '*Do you feel IRd was effective in controlling your myeloma*' **81%** of respondents said yes, **9%** said no and **10%** did not know.

Analysis: Through the clinical trial data the treatment combination has shown that it can effectively control a patient's myeloma. A large majority of patients who took part in the survey would agree that IRd has been effective in controlling their myeloma.

"IRd is an easier treatment for the patient to deal with and seems to be really effective in dealing with myeloma."

"My main hope is for the myeloma to be controlled as far as possible and it's meant a lot to me that this treatment has been available and has been effective up to now. Although I find the side effects difficult at times it's worth it for a treatment that's helping me."

Does IRd improve overall survival?

When IRd was conditionally approved through the CDF in 2018 overall survival (OS) had yet to be determined.

The Managed Access Agreement for IRd focused on determining a final OS analysis. Once this had been achieved it was expected that the treatment would be re-appraised by NICE. The process for re-appraisal has formally started and the manufacturing company, Takeda, will publish the final overall survival analysis through the re-appraisal.

Analysis: OS had still to be determined however respondents to the survey were confident that IRd was an effective treatment. Studies have shown for myeloma patients and their families and carers, and particularly those that are multiply relapsed, the worry of whether there are further effective treatment options available is a major issue. Knowing that a good treatment will be there when they relapse is hugely important; not having that certainty is a significant psychological burden.[3]

[2] Moreau P et al. Oral Ixazomib, Lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;374(17):1621–34. https://doi.org/10.1056/NEJMoa1516282.

[3] Hulin C., et al (2017) Living with the burden of relapse in multiple myeloma from the patient and physician perspective. Leukaemia research, 59, pp.75-84

Patients can experience a positive psychological benefit with the knowledge that the treatment is prolonging their life.

"I feel more confident that the chemotherapy regime will control the myeloma as well as may be expected, and hence increase the time between relapses and extend survival time."

"It is reducing myeloma and giving me hope of prolonged survival."

"More positive outlook as I feel I am going to live longer".

"Probably about 12 months more than I expected thus hopefully prolonging life."

Does IRd improve quality of life?

The survey asked patients several questions related to their quality of life (QoL) while receiving IRd. This was designed to help answer research question number two: *'How did patients feel IRd affected QoL',* and a further analysis will be set out in part two below.

In the clinical trial QoL data was measured through a EORTC QLQ-C30 and QLQ-MY20 questionnaires. Results at 23 months indicated similar patient reported QoL in the IRd group and the Rd group.[4] This suggest that addition of ixazomib to the currently approved treatment of Rd did not negatively impact QoL and by adding a third treatment to this combination patient QoL was not affected. Indeed, in a further analysis of the HRQoL data it was found that the future perspective's questions showed that there was a more positive outlook for patients who received IRd compared to Rd.[5]

The Patient Treatment Survey asked specific questions on the impact of IRd on QoL and mental health:

- When asked '*how do you feel IRd affected your QoL*', **23%** (26) of respondents said their QoL improved, **54%** (59) said it stayed the same; and **23%** (26) said that taking IRd decreased their quality of life.

The majority of respondents said their quality of life stayed the same however equal numbers (23%) said taking IRd had both improved or decreased their QoL. Respondents who said it improved their QoL provided comments that IRd had effectively controlled their myeloma, was easy to take and gave them hope for the future. The same number of respondents said that IRd had decreased their QoL, and the impact of side effects was a theme here. A third of patients who noted a decrease in QoL also reported that their myeloma had progressed.

[4] Moreau P et al. Oral Ixazomib, Lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;374(17):1621–34. https://doi.org/10.1056/NEJMoa1516282.

[5] Leleu, Masszi, et al. Patient-reported health-related quality of life from the phase III TOURMALINE-MM1 study of ixazomib-lenalidomide-dexamethasone versus placebo-lenalidomide-dexamethasone in relapsed/refractory multiple myeloma. Am J Hematol. 2018; 93: 994– 1001. https://doi.org/10.1002/ajh.25134

- When asked '*how do you feel IRd affected your mental health*,' **12%** (14) said it had improved their mental health, **75%** (84) said it had stayed the same and **13%** (15) said that their mental health had decreased while taking IRd.

As above most respondents said their level of mental health stayed the same but a similar number each said that their mental health improved/decreased. Those who stated it had improved provided comments focusing on the effectiveness of IRd controlling their myeloma and giving them hope for the future. In those respondents who stated that their mental health decreased they provided comments focusing on the impact of side effects and the fact that their myeloma had progressed.

Analysis: Most patients said that when taking IRd there QoL and levels of mental health improved or were maintained. This is significant as IRd is a triplet combination therapy for multiply relapsed patients. Many patients who received this treatment will already have been gone through multiple cycles of treatment and experience a significant disease burden. When receiving IRd they feel that their QoL and levels of mental health improve or are maintained.

A significant proportion of patients stated that their QoL and levels of mental health decreased due to the impact of the side effects or the treatment not being effective for them. This will be explored further in part 2 of the report.

Does IRd give increased remission time?

As referenced above, in the clinical trial IRd was shown to increase progression free survival when compared to Rd alone. (20.6 months vs 14.7 months). [6]

- Most of the respondents to the survey were still receiving IRd and the survey was not designed to capture PFS data. However, when asked *'how long has your remission period been',* **20%** (19) of respondents had been in remission longer than 25 months after receiving IRd.

Analysis: The Clinical trial data is the most important source of evidence for establishing a PFS gain. It is clear from the clinical trial data the IRd gives increased PFS for patients compared to Rd alone. However, it should be noted that a small number of respondents to our survey reported periods of remission longer than the median PFS gain outlined in the clinical trial. Most patients understand this, and this is reflected in qualitative comments:

"A long period of remission with few side effects. It brought my paraproteins down to "undetectable" for several months for the first time since diagnosis."

Does IRd give you the ability to continue daily activities?

A number of factors can impact on a patient's ability to continue daily activities including how the treatment is administered and the side effects of the treatment.

[6] Moreau P et al. Oral Ixazomib, Lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;374(17):1621–34. https://doi.org/10.1056/NEJMoa1516282.

- When asked *'How would you rate the way IRd is given,'* a combined **95%** of respondents rated the way it was given as either very positive or positive.

Most patients viewed having an all-oral treatment as a positive and commented that this gave them more control over lives.

"Once the prescription is in my hands I am in total control and do not have to go out of my way or involve anybody else. I just build the tablet regime into my daily routine."

- When patients were asked '*how do you feel the side effects of IRd affect your daily life*,' **49%** (55) said the side effects did not impact on their daily life; **47%** (53) said it partially stopped them from completing daily activities; and, **4%** (5) said the side effects entirely stopped them from completing daily activities.

From the survey just under half of patients' daily activities were not impacted by IRd. Patients at this point in their myeloma journey will be multiply relapsed and receiving a triplet combination treatment. It is therefore significant that nearly half of respondents stated that the side effects of this treatment do not impact their daily lives and only 4% stated that it stopped them entirely from completing daily activities.

A similar proportion of respondents said they were only partially affected. The survey did not define *partially* and therefore it can have a wide interpretation, including only relatively minor impact. Qualitative comments show that patients will manage and put up with a degree of side effects, and its impact, if the treatment is effective.

"I have felt normal, in terms of my general health and wellbeing, and have been able to carry on with all my normal daily activities."

"Although I have the odd "off" day, in general the side effects have been minimal and manageable, not significantly impacting on the ability to do what I want to."

"Having to deal with the side effects of IRd makes it less pleasurable, comfortable and energising in all I attempt to achieve whether this is a country walk, shopping, cooking, yoga, drawing, talking to friends on zoom etc.....it doesn't stop me getting on with tasks but it does entail more effort and less spontaneous enjoyment."

Analysis: Its clear that side effects can have an impact on patients' ability to carry out daily activities. However, it is significant that almost half of respondents in a patient population who are multiply relapsed and receiving a triple combination treatment for their myeloma said side effects did not impact on their ability to carry out daily activities.

Further to this nearly all respondents stated that the method of administration was a positive benefit of this treatment.

Does IRd give you the ability to continue to work?

The survey had a series of characteristic questions to help analyse the survey data. When respondents were asked their age **78%** (86) respondents were aged over 60 years old.

When asked about their employment status **19%** (21) respondents were either 'working full time', 'working part time' or 'self-employed.' This number of respondents was too small to capture any meaningful data trends. However, these patients did provide qualitative comments on the impact of IRd and myeloma on their working life:

"It's a much easier form of treatment which helps especially if working as not having to go to hospital for infusions, saves a lot of time."

"Depressing relapsing after 11 months from second stem cell, but positive that IRD has done its job in bringing [paraprotein] down to 0. Lockdown may have masked some of the quality of life things as I do less exercise or commuting to work. But I have worked from home full time through my 10 cycles."

"Have always been ok with all treatments and even at nearly 68 continue to work although have obviously been shielding during COVID. Will return to work as a support worker in April."

Analysis

Does IRd deliver treatment preferences to Patients?

From the clinical trial and answers to the Patient Treatment Survey it is clear that IRd delivers the treatment preferences of patients, including: treatment effectively controlling their myeloma and increased remission time. A key benefit all respondents rate as a positive is that IRd is an all-oral treatment giving patients significant control over their daily lives.

For the remaining treatment preferences, it can be argued that IRd delivers these benefits to most patients. Most patients said their QoL, and mental health stayed the same or improved while on IRd with almost half saying that IRd did not impact on their ability to continue daily activities. As stated above the patient population receiving IRd are multiply relapsed and can carry a high disease burden. It is clearly significant that IRd can improve efficacy without negatively impacting on patient QoL.

A number of respondents stated that their QoL and mental health decreased on IRd. Many respondents that the treatment did not work for them or they experienced a negative impact from the side effects. A further analysis on patient QoL while on IRd will be explored below.

……

Part 2: How did patients feel IRd affected Quality of Life (QoL)?

The second research question focuses on patient QoL experience while on IRd.

As discussed above, results from the survey show that that most patients QoL and levels of mental health remain unaffected when being treated with IRd. However, equal numbers of respondents reported improvements in QoL and mental health alongside experiencing decreases in QoL and mental health.

- When asked '*how do you feel IRd affected your QoL*', **23%** (26) of respondents said their QoL improved, **54%** (59) said it stayed the same; and **23%** (26) said that taking IRd decreased their quality of life.
- When asked '*how do you feel IRd affected your mental health*,' **12%** (14) said it had improved their mental health, **75%** (84) said it had stayed the same and **13%** (15) said that their mental health had decreased while taking IRd.

A majority of respondents said their QoL (77%) and mental health (87%) stayed the same or improved while on IRd. This is significant for patients because IRd is positioned at third and fourth line of treatment for patients who are multiply relapsed and receiving a triplet combination treatment. Therefore, it could be argued that many of those who receive this treatment will not experience a reduction in the QoL or mental health.

"My mental health is very related to my ability to exercise, to walk and to lead a very active life. IRd has allowed me to stay active, even during the pandemic."

There was a significant number of respondents who said that their QoL and mental health decreased while receiving IRd. From qualitative comments provided by patients the levels of side effects experienced was a theme that emerged here.

"The side effects caused depression due to feeling constantly unable to do the things I wanted to do (activities of daily life)."

The survey asked patients to describe the main side effects highlighted by patients in the clinical trial between unaffected, mild, serious, and severe. Side effects which impacted on respondents included:

Side Effect (n)	Unaffected	Mild	Serious	Severe
Peripheral Neuropathy (112)	31%	54%	10%	5%
Gastrointestinal issues (111)	23%	54%	16%	7%
Fatigue (110)	20%	56%	20%	4%
Skin Rashes (104)	67%	27%	5%	1%
Neutropenia (103)	51%	38%	10%	1%
Thrombocytopenia (99)	53%	36%	10%	1%
Infection (97)	84%	10%	2%	4%

From the table above most respondents suffered from peripheral neuropathy, GI issues and fatigue. In the other side effects listed most patients were unaffected.

"It does play havoc with my stomach and bowels and can make me very tired for certain days during the cycle".

Further to this many patients provided comments on the effect of the dexamethasone rather than the ixazomib or lenalidomide. Dexamethasone is a key component of many myeloma treatments, including comparator treatments in this appraisal. It should be borne in mind that some side effects reported by respondents in relation to IRd may be present when receiving alternative treatments.

"The side effects are quite bearable and my quality of life is still very good. The steroids meant that I had virtually no sleep at night after taking them."

"Occasionally feel a little unwell two days after taking IRd but believe this is the dexamethasone and not ixazomib as I do not take ixazomib on 4th week but still feel unwell. Some days I feel shaky. Dry and flaky skin on body."

The survey asked related questions to see how patients coped being treated with IRd.

- When patients were asked *'how do you feel the side effects of IRd affect your daily life,'* **49%** (55) said the side effects did not impact on their daily life; **47%** (53) said it partially stopped them from completing daily activities; and **4%** (5) said the side effects entirely stopped them from completing daily activities.

- When respondents were *asked 'if they had received any supportive treatments while on IRd'*, **60%** (67) said yes and **40%** (45) said no. Supportive treatments received by patients focused on handling comorbidities and managing side effects e.g., myeloma bone disease.

- When asked '*if patients had taken a treatment break (time off treatment to allow side effects to settle or other comorbidities to improve)',* **29%** (32) said yes, **70%** (77) said no and **1%** (1) said they did not know. Reasons for a treatment break included to go on holiday, to treat severe side effects, bring down levels of associated toxicity or to treat other illnesses.

It must be noted that **75%** (102/139) of respondents to the survey were at third line or beyond and will be living with the combined symptoms of relapsed myeloma and multiple treatment burden. However, it is clear that treatment related side effects do have an impact on some patients which will need to be managed.

Patient engagement in Myeloma UK has shown that most patients see side effects as something that has to be managed in their daily lives or tolerated for an effective treatment that keeps their myeloma in remission. This was emphasized by respondents' answers:

"Primarily tiredness and interrupted sleep patterns but small price to pay set against the benefits IRd provides. Irrespective, I just get on with life tired or not"

"The main side effect was sickness in conjunction with the ixazomib. This was identified and effectively controlled with anti-sickness medicine."

"When you understand the treatment, you know what side effects are coming on what days."

Of course the impact of side effects is not the only factor to consider when discussing patient QoL.

- When asked to *rate the way IRd is administered (as an all-oral treatment),* a combined **95%** of respondents rated the way it was given as either very positive or positive.

"Taking the drugs orally in a 4-week cycle is manageable and enables me to plan accordingly in relation to days that I am more likely to be well and capable."

Access to oral treatments is highly valued by patients and it has been especially significant over the COVID-19 Pandemic:

"Receiving IRd during the pandemic has definitely been an advantage and led to peace of mind at not having to visit the hospital."

"An all oral treatment is far better for the patient than having to have part of the triple medication administered by injection or infusion in a hospital setting, particularly in the Covid pandemic."

Finally, the survey asked what impact the treatment had on the patient's carer/family. Respondents to the survey stated:

"Family were overjoyed when I started IRd as they had heard only good things from friends in a similar situation as myself. That joy continues today as the paraprotein levels fall. We are just waiting to be able to hug one another - especially the grandchildren."

"We are all pleased that IRd bought me more quality time. Dealing with dex is difficult, so my son and wife had to adapt their contribution to the household pattern, such as cooking on days when that was difficult for me to do. As for my intemperate moods, family were patient and forgiving. It's hard to achieve, so it will have cost them."

"Much better for my husband as I only leave the house for two short visits to the hospital; blood test and prescription collection."

"A very positive impact on my family"

Analysis: Results from the survey show that most patients QoL and levels of mental health improved or were maintained while receiving IRd for their myeloma. This is significant as the patient population who can access this treatment in England are multiply relapsed and likely to be carrying a high disease and/or treatment burden. The fact that a patient at this point of the pathway can receive a treatment with improved efficacy and no negative impact on their QoL must be seen as a benefit for patients.

However, a minority of patients reported decreased QoL and levels of mental health. Side effects can partially stop patients from carrying out daily activities. This is clearly difficult for patients and can lead to use of supportive treatments and treatment breaks.

Some patients did mention that it was the steroid dexamethasone which caused the most trouble. It must also be noted that side effects in this triplet combination can be attributed to each

treatment in the combination. Reported side effects for Rd can be similar to the reported side effects of IRd including fatigue, infections and GI issues.[7]

The Myeloma UK survey data on toxicity should also be viewed alongside the clinical trial data which records adverse events in comparison to lenalidomide and dexamethasone. The trial data underlined the fact that QoL was similar in the two groups, while IRd delivers significant additional benefit.

Multiply relapsed myeloma patients accept the need to manage side effects and are accepting of some quality of life impact in order to receive an effective treatment which keeps them alive for longer.

Finally, most patients agree that having an all-oral treatment is a key benefit as it gives patients more control over their lives. IRd can also have a positive impact on the patient's family knowing that they are receiving an effective, easy to use treatment.

……

Conclusion

IRd is an effective, easy to use treatment for myeloma which delivers on the treatment preferences for patients including effectively controlling their myeloma and increased progression free survival.

Most respondents to the survey stated that their QOL had stayed the same or improved. It is significant that IRd can improve efficacy without negatively impacting on patients QoL.

However side effects can clearly have a negative impact on some patients, affecting their QOL and ability to carry out daily activities. Strategies for managing side effects can be used and patients will tolerate some side effects in the knowledge that they are accessing an effective treatment.

The vast majority of patient respondents think that having an all-oral treatment is positive and can give them more control over their lives.

When asked *'to rate your overall experience of IRd,'* a combined **81%** of respondents rated it as either very positive or positive (45% + 36%).

Finally, an overwhelming **97%** of respondents would recommend IRd to other myeloma patients.

"I am lucky in having a positive mental outlook. The good results from IRd more than compensate for the occasional "off" day and side effects, which enables me and my family to carry on much as before".

[7] Stadtmauer, Edward A et al. "Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma." European journal of haematology vol. 82,6 (2009): 426-32. doi:10.1111/j.1600-0609.2009.01257

“Has given me hope that I have a future.”

“Continued to work, less financial worries, continue to be a mum. Bashed the myeloma down to nothing which gives positivity which can only be a good thing. Read other people’s side effects with other treatments and feel lucky, but patients are all different and trying to find a treatment that works for the individual can sometimes be hard.”

“It’s given my wife and I hope for the future - being able to do the things we want to do - alongside seeing my daughters and their families grow up.”

[redacted]

April 2021

Title: *Multiple myeloma (relapsed, refractory) - Ixazomib (with lenalidomide and dexamethasone) (CDF Review of TA505) Appraisal 1635*

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Contributions of authors
Martin Connock (Honorary Research Fellow) conducted, reviewed and critiqued the survival analysis and undertook additional analyses support by Felix Achana (Associate Professor) and); Mandana Zanganeh (Research Fellow) conducted, reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses; Hesam Ghiasvand (Research Fellow) conducted, reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses, Alexander Tsertsvadze (Independent Consultant) and Xavier Armoiry (Professor/Honorary Clinical Research Fellow) conducted, reviewed and critiqued the clinical effectiveness evidence; Rachel Court (Information Specialist) checked the company searches and undertook any additional searching; Tom Shortland reviewed and critiqued the clinical effectiveness evidence and contributed to report writing, Peter Auguste (Research Fellow) lead the project report and writing support by Amy Grove (Associate Professor). All authors contributed to the draft and final report.

Please note that: *Sections highlighted in [redacted] are [redacted]. Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue.*

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Definition of terms and list of abbreviations

AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
CAA	Commercial Access Agreement
CDF	Cancer Drugs Fund
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence Interval
CS	Company Submission
ERG	Evidence Review Group
HR	Hazard Ratio
IA2	Second interim analysis of TOURMALINE-MM1
ICER	Incremental Cost-Effectiveness Ratio
IPCW	Inverse probability of censoring weighting
ITT	Intention-To-Treat
KM	Kaplan Meier
LYG	Life Year Gained
MSM	Marginal Structural Models
NHS	National Health Service
OS	Overall Survival
PAS	Patient Access Scheme
PFS	Progression-Free Survival
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
RRMM	Relapsed/Refractory Multiple Myeloma
SACT	Systemic Anti-Cancer Therapy
SAP	Statistical Analysis Plan
SCT	Stem-cell Transplants
SoC	Standard of Care
ToE	Terms of Engagement
ToT	Time on Treatment
TMM1	TOURMALINE-MM1
TSE	Two-stage estimator
UK	United Kingdom

Executive Summary

The summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

Table 1 provides an overview of the key issues identified following the ERG's critique of the company submission (CS) that are likely to affect the decision-making process. The key differences between the company's assumptions and the ERG preferences are detailed in Section 6.2. The most influential issue in the cost-effectiveness analysis is the choice of the parametric curve fitted to the adjusted overall survival (OS): 2-stage re-censoring (novel therapies).

Table 1. Summary of key issues

ID 1635	Summary of issues	Report section
Key issue 1: Generalised gamma modelling of the adjusted OS: 2-stage re-censoring (novel therapies)	The company's Weibull models for adjusted OS: 2-stage censoring (novel therapies) appear almost indistinguishable from the generalised gamma. The ERG considers Weibull to be as valid on the grounds of clinical plausibility as the model selected by the company.	Section 3.2.2 and Table 15
Key issue 2: Uncertainty around model selection for adjusted OS: 2-stage re-censoring (novel therapies)	There is uncertainty surrounding the pre-progression and post-progression life year (LY) gains in the adjusted OS: 2-stage re-censoring (novel therapies) modelling. The ERG suggests the lack of detail presented in the CS results in departure from clinical plausibility in terms of LY gains. Lack of detailed breakdown of the pre-progression and post-progression life year (LY) gains in the adjusted OS: 2-stage re-censoring (novel therapies) modelling reveals some departures from plausibility.	Sections 3.1.6.2, 5.5 and Table 18
Key issue 3: The sustained effect of treatment	The ERG queries the sustained effect of ixazomib after treatment has ended. While the ERG acknowledges that waning of treatment (during the treatment itself) has almost completely been captured within the observed time of the trial, we consider that the prolonged sustained effect of the treatment (after treatment has finished) that is currently included in the company models should be considered separately. The ERG provides three scenarios to explore the impact of changes to the sustained effect of treatment for ixazomib (after treatment has finished) on the ICER.	Section 3.3

Additional issue 1:	Lack of progression free survival (PFS) data in the final analysis of the pivotal trial (TMM1). PFS observation lags behind final cut OS observation leading to different handling of the two pivotal inputs for the comparison of clinical effectiveness. The ERG recognises that data on PFS were not collected beyond the second interim analysis of TMM1. Therefore, no updates to PFS are available for consideration in the CDF.	Section 3.2.1
ERG, Evidence Review Group; IXA+LEN+DEX, ixazomib+lenalidomide+dexamethasone; KM, Kaplan Meier; LEN+DEX, lenalidomide+dexamethasone; LY, life-year; OS, overall survival; PFS, progression free survival		

1.2 Critique of the adherence to committee's preferred assumptions from the Terms of Engagement in the company's submission

The company provided updated mature OS data (for both study arms: IXA+LEN+DEX and LEN+DEX) using the final analysis of TMM1 study (data lock point of September 30, 2020) at a median follow-up of 85-months. In the CDF submission, the company have adhered to the majority of the committee's preferred assumptions from the Terms of Engagement (ToE); the key deviations are:

- Updated Time on Treatment (ToT) was derived from the TOURMALINE MM-1 trial (TMM1) however, the generalisability of this data could not be validated.
    - Comparison with the data collected within the Systemic Anti-Cancer Therapy (SACT) dataset, indicates notable differences between the duration of follow-up and important patient characteristics (e.g., age, co-morbidities, prior stem-cell transplants [SCT]).
- The company selected the generalised gamma as an alternative extrapolation to the Weibull parametric curve which was listed as a preferred assumption in the ToE.
    - The ERG note that there was little difference in the predicted survival between the adjusted OS using the generalised gamma and the Weibull parametric curves (See Sections 3.1.6.2, 5.5 and Table 18).
- For the continued treatment effect assumption, the ERG notes that for a small sample of patients still receiving treatment at the end of observation in TMM1 study (4%, IXA+LEN+DEX arm versus 1%, LEN+DEX arm) the effect of treatment waning has not been fully captured.

- o A scenario analysis conducted by the company explored the impact of waning of treatment in this small sample. However, there was a minimal impact on the incremental cost-effectiveness ratio (ICER) due to the very small sample of patients.

1.3 Summary of the key issues in the clinical effectiveness evidence

In this section we highlight our key concerns with the clinical effectiveness evidence submitted by the company, these include:

- Key issue 1: Modelling of the adjusted OS: 2-stage re-censoring (novel therapies)
- Key issue 2: Uncertainty around model selection for adjusted OS: 2-stage re-censoring (novel therapies)
- Key issue 3: The sustained effect of treatment
- Additional issue 1: Lack of progression free survival data in the final analysis

Table 2. Modelling of the adjusted OS: 2-stage re-censoring (novel therapies)

Report section	Section 3.2.2 and Table 15
Description of issue and why the ERG has identified it as important	The company suggested the generalised gamma parametric curves provided a reasonable estimation of long-term outcomes with LEN+DEX and IXA+LEN+DEX. The company justified this assumption via clinical advice they had received. The company's Weibull models for adjusted OS: 2-stage censoring (novel therapies) appear almost indistinguishable from the generalised gamma. The ERG considers Weibull to be as valid on the grounds of clinical plausibility as the model selected by the company. The ERG notes that there is great sensitivity in the economic model even with small changes in modelling of OS. The considerable uncertainty associated with the two-stage estimation OS (TSE-OS) modelling (as exemplified by large differences produced using different methods of adjustment) and the inherent uncertainty in parametric modelling, suggest that the company deterministic base-case point estimate ICER should be viewed with caution.
What alternative approach has the ERG suggested?	Based on the ERG's reconstruction of the company's adjusted OS KM and examination of the parametric models, the ERG found that the Weibull model provided an equally plausible fit and generated modest/conservative OS extrapolation (see section 3.2.2).
What is the expected effect on the cost-effectiveness estimates?	The model is likely to be sensitive to any changes to OS. Given that the Weibull model generated modest/conservative OS extrapolation estimates, this is likely to increase the cost-effectiveness estimates.
What additional evidence or	To explore this issue further using the information we have access to, the ERG reconstructed the company's individual patient data (IPD) of the adjusted OS KM plots and explored alternative parametric models fitted individually to the

analyses might help to resolve this key issue?	IXA+LEN+DEX and LEN+DEX arms to assess goodness-of-fit according to the information criterion scores.

Table 3. Uncertainty around the adjusted OS outcomes

Report section	Section 5.5
Description of issue and why the ERG has identified it as important	There is uncertainty surrounding the pre-progression and post-progression life year (LY) gains in the adjusted OS: 2-stage re-censoring (novel therapies) modelling. After adjustment for treatment switching (i.e., removing the presumed beneficial effect of novel therapies not routinely available within the NHS), the post-progression life expectancy (as obtained from the cost-effectiveness model) reduces in the LEN+DEX arm (2.59 to 2.29 years, approximately 3.6 months), but very marginally in the IXA+LEN+DEX arm (2.65 to 2.62 years, approximately 11 days). The explanation provided by the company suggests that this observation is due to differences in subsequent therapies received in the two arms. However, the ERG considers that this does not appear plausible owing to the small differences observed in the proportion of patients who received specific subsequent therapies. The ERG considers this concern to be of importance. After adjustment, the post-progression LY gain, as obtained from the company's model, represents 0.33/1.08 = 30.5% of total LY gain which is considerable.
What alternative approach has the ERG suggested?	Due to the lack of availability of IPD, the ERG has neither been able to replicate nor validate this adjusted analysis. Nor have we been able to suggest an alternative approach. It is possible that the Company's model has over-adjusted OS analyses.
What is the expected effect on the cost-effectiveness estimates?	The ERG considers that the reduction in post-progression LY after adjustment should have been higher in the IXA+LEN+DEX arm and/or lower in the LEN+DEX arm. Under such a scenario, it is anticipated that the differential post-progression LY gain would reduce, hence reducing the incremental QALY and therefore, increasing the ICER substantially.
What additional evidence or analyses might help to resolve this key issue?	Exploratory analyses would need to be undertaken using the IPD. This was not possible given the ERG restrictions in access to IPD.

Table 4. Key issue 3: The sustained effect of treatment

Report section	Section 3.3
Description of issue and why the ERG has identified it as important	In general, the effect of a treatment in relation to its intended outcomes may be maintained for varying times after treatment ceases, depending on the drug in question and its effect on the outcome. The ERG queries the sustained effect of treatment (after treatment has stopped) for ixazomib. The ERG considers that the period of observation from the end of treatment to the end of observation (approximately 2 years) is too short to fully capture a potential waning of ixazomib's treatment effect. At the end of observation, approximately 35% of patients remain alive and extrapolation of company models assumes that the treatment effect of ixazomib is fully sustained/maintained for a further 18 years. The ERG considers that waning of ixazomib's treatment effect after treatment itself has stopped will likely start to occur before the 18 years have expired.
What alternative approach has the ERG suggested?	The ERG proposes that any waning of the of the sustained treatment effect of LEN+DEX would be experienced in both arms since both groups of patients received this treatment. Therefore, any waning of the ixazomib treatment effect would only be experienced by people randomised to IXA+LEN+DEX. The ERG's alternative approach would be to apply a waning of the post treatment continuing effect to the generalised gamma (or other parametric model) of the adjusted OS for IXA+LEN+DEX after the end of the observation period.
What is the expected effect on the cost-effectiveness estimates?	Depending on the waning of the treatment effect approach applied, it is expected that the OS curves for IXA+LEN+DEX would coincide with the LEN+DEX OS curves at a certain point. This would occur sooner if a more severe waning approach were applied. Likewise, if a less severe approach is taken, then we would expect the OS curves to coincide at a later time point. Given the sensitivity of the economic model to OS, the ERG would expect that applying a waning of the effect of ixazomib after treatment has stopped would result in an increase to the ICER, with more severe waning having a greater impact compared to less severe waning.
What additional evidence or analyses might help to resolve this key issue?	The ERG acknowledge that follow-up data were not collected beyond the 2-year observation period. The ERG undertook exploratory analyses on the company's base-case by applying three waning scenarios to the generalised gamma of the adjusted OS for IXA+LEN+DEX after the end of the observation period. Additionally, the ERG applied three waning scenarios to the Weibull of the adjusted OS.

Table 5. Additional issue 1: Lack of progression free survival data in the final analysis

Report section	Section 3.2.1
Description of issue and why the ERG has identified it as important	The CS included the final analysis of the phase-3 randomised controlled trial TMM1 (CS Document Section A.5 and CS Appendices A-H). The final analysis included updated OS and cost-effectiveness data collected in the TMM1 trial at a median follow-up time of 85-months (Data Lock Point: September 2020). Other updated endpoints were mature data on ToT and health utilities (model-based covariate adjusted EQ-5D questionnaire data) (see Section 1.2, Table 12).

	• The TMM1 trial had progression free survival (PFS) as the primary endpoint (at the median follow-up of 23 months). The ERG acknowledges that PFS data were not collected after the IA2 cut-off as planned in TMM1. The PFS observation lags behind the final cut OS observation leading to different handling of these two pivotal inputs for assessment of clinical effectiveness.
What alternative approach has the ERG suggested?	Additional requests were made during the first round of clarification (number A21) to explore model section and output regarding PFS.
What is the expected effect on the cost-effectiveness estimates?	The effect on cost-effectiveness is indeterminate because the effect on the final PFS findings of continuing collection of data would be altered by collection of data up to the final cut is unknown.
What additional evidence or analyses might help to resolve this key issue?	The ERG recognises that data on PFS were not collected beyond the second interim analysis (IA2) of TMM1. Therefore, there are no updates to PFS available.

1.4 Summary of the key issues in the cost-effectiveness evidence

In this section we highlight our concerns with the cost-effectiveness evidence submitted by the company, including:

- Key issue 4: Generalised gamma modelling of the adjusted overall survival: 2-stage re-censoring (novel therapies)

Table 6. Key issue 4: Generalised gamma modelling of the adjusted OS

Report section	Section 3.2.2 and Table 15
Description of issue and why the ERG has identified it as important	As described in key issue 1 (Table 2), there is considerable uncertainty associated with the TSE-OS modelling and the inherent uncertainty in parametric modelling. The ERG consider that the company's deterministic base-case point estimate ICER should be viewed with caution.
What alternative approach has the ERG suggested?	The ERG considers that the company's 2-stage adjusted generalised gamma model of OS and company's Weibull model are equally plausible to extrapolate OS and for reasons of goodness of fit prefer Weibull to generalised gamma.
What is the expected effect on the cost-effectiveness estimates?	Given the sensitivity of the model to changes to the OS, the ERG would expect that any changes will impact on the cost-effectiveness estimates.

What additional evidence or analyses might help to resolve this key issue?	Unfortunately, the ERG lacked access to the company's IPD and were unable to either replicate or validate the two-stage adjustment: re-censoring (novel therapies). However, the ERG reconstructed the company's IPD of the adjusted OS KM plots and explored alternative parametric models for goodness-of-fit and fitting parametric models individually to the IXA+LEN+DEX and LEN+DEX arms.

1.5 Summary of ERG's preferred assumptions and resulting ICER

The ERG has made the following changes to the company's model to form the ERG's base-case (see Table 7). These changes increased the company ICER by £33,108 to an ERG deterministic ICER of approximately £98,800 (see Table 7 and Table 8).

During the clarification telephone conference with NICE and the company (Thursday 29th April 2021, 15:00), the ERG was advised by the Associate Director to conduct base-case and scenario analyses using the proposed patient access scheme (PAS) for ixazomib. Therefore, this is what is presented in the ERG report.

Table 7. ERG's preferred model assumptions (using the proposed PAS for ixazomib)

ERG preferred assumption	Scenario detail	Brief rationale and section in ERG report	Results (Impact to base-case ICER)
Company base-case			£65,703
Use of Weibull model for OS	In this scenario, the ERG selected 'Weibull' from the 'Main Settings' worksheet.	The ERG considers that the company's 2-stage adjusted KM plots of OS and the Weibull models are plausible to extrapolate OS (see Section 4.1.5).	£71,093
Use the list price for branded lenalidomide throughout the model (commencing from Week 0)	The ERG preferred assumption is to not assume a generic lenalidomide cost (the company base case submission included a list price for branded lenalidomide for [redacted].	The ERG considers that the lenalidomide price reduction presented in the CS is not a reflection of current NHS practice (see Section 4.1.7).	£91,293 (+£25,590)
ERG base-case: use the Weibull model for OS and use	The ERG's base-case analysis comprises making these changes simultaneously.	The ERG implemented these changes simultaneousl	£98,811 (+£33,108)

the list price for branded lenalidomide (commencing from Week 0)		y to assess the cost-effectiveness of IXA+LEN+DEX compared to LEN+DEX for treating relapsed or refractory multiple myeloma based on the ERG's preferred assumptions (see Section 6.2).	
CS, company submission; ERG, Evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival			

Table 8. ERG deterministic results based on cost per QALY gained (using the proposed PAS for ixazomib)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Cost per QALY
LEN+DEX	[redacted]	2.43	[redacted]	-	-
IXA+LEN+DEX	[redacted]	3.08	[redacted]	0.65	£98,811

1.6 Summary of exploratory analyses undertaken by the ERG

In Table 9 and Table 10, we report the results of the ERG scenario analyses based on the company's results and the ERG's base-case results, respectively using the proposed PAS.

Table 9. Exploratory analyses based on the company's base-case results (using the proposed PAS for ixazomib)

Scenario	Section in main ERG report	LEN+DEX		IXA+LEN+DEX		Cost per QALY
		Costs	QALYs	Costs	QALYs	
Company base-case	Section 5.1	[redacted]	2.47	[redacted]	3.18	£65,703
Weibull parametric for adjusted OS: 2-stage re-censoring (novel therapies)	Sections 3.3 and 6.1	[redacted]	2.43	[redacted]	3.08	£71,093
Branded cost of lenalidomide throughout model		[redacted]	2.47	[redacted]	3.18	£91,293
Company's estimate of the		[redacted]	2.47	[redacted]	3.18	£65,594

generic cost of lenalidomide throughout model						
Post treatment waning of effect takes 18 years to complete (generalised gamma model for OS)		[redacted]	2.47	[redacted]	3.14	£69,497
Post treatment waning of effect takes 5 years to complete (generalised gamma model for OS)		[redacted]	2.47	[redacted]	3.03	£85,100
Post treatment waning of effect takes 7.5 years to complete (generalised gamma model for OS)		[redacted]	2.47	[redacted]	3.06	£79,822
Post-treatment waning of effect takes 18 years to complete (Weibull model for OS)		[redacted]	2.43	[redacted]	3.05	£74,026
Post-treatment waning of effect takes 5 years to complete (Weibull model for OS)		[redacted]	2.43	[redacted]	2.99	£83,531
Post-treatment waning of effect takes 7.5 years to complete (Weibull model for OS)		[redacted]	2.43	[redacted]	3.03	£77,375
ERG, Evidence Review Group; QALY, quality-adjusted life year						

Table 10. Exploratory analyses based on the ERG's base-case results (using the proposed PAS for ixazomib)

Scenario	**Section in main ERG report**	**LEN+DEX**		**IXA+LEN+DEX**		**Cost per QALY**
		Costs	**QALYs**	**Costs**	**QALYs**	
ERG base-case	Section 6.3	[redacted]	2.43	[redacted]	3.08	£98,811
Post-treatment waning of effect takes 18 years to complete (Weibull model for OS)	Sections 3.3 and 6.1	[redacted]	2.43	[redacted]	3.05	£102,832
Post-treatment waning of effect takes 5 years to		[redacted]	2.43	[redacted]	2.99	£115,788

complete (Weibull model for OS)						
Post-treatment waning of effect takes 7.5 years to complete (Weibull model for OS)		[redacted]	2.43	[redacted]	3.03	£107,348
ERG, Evidence Review Group; QALY, quality-adjusted life year						

1.7 Probabilistic sensitivity analysis

The mean results of the probabilistic sensitivity analyses are presented in Table 11. These results appear to be in good agreement with the deterministic results.

Table 11. Probabilistic sensitivity analysis results based on ERG's preferred assumptions (using the proposed PAS for ixazomib)

Technologies	Total costs	Incremental costs	Total QALYs	Incremental QALYs	Cost per QALY
LEN+DEX	[redacted]	[redacted]	2.42	-	-
IXA+LEN+DEX	[redacted]	[redacted]	3.08	0.65	£99,022
ERG, Evidence Review Group; QALY, quality adjusted life-year					

Results from the PSA showed that at a willingness-to-pay threshold of £30,000 per QALY, IXA+LEN+DEX has a zero probability of being cost-effective under the proposed PAS for ixazomib.

Evidence Review Group Report

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

Ixazomib (IXA) (Ninlaro®, Takeda), with lenalidomide (LEN) and dexamethasone (DEX), has been available to adults in England since February 2018 through the Cancer Drugs Fund (CDF) for treating relapsed or refractory multiple myeloma if:

- they have already had 2 or 3 lines of therapy and;
- the conditions in the managed access agreement for ixazomib are followed.

In its recommendations, the Appraisal Committee noted that in the TOURMALINE MM-1 (TMM1) trial,[1] ixazomib (plus LEN and DEX [IXA+LEN+DEX]) improves progression-free survival (PFS) and that there was potential for ixazomib to be cost-effective. However, there was uncertainty regarding overall survival (OS) (see original submission).[2] Additional trial data was required to resolve this uncertainty and in turn, establish if ixazomib was to be cost-effective.

The CDF review was preceded by earlier submissions starting at the end of 2016. The CDF review process for ixazomib started in early 2021 with the company presenting a new submission to support the cost-effectiveness of ixazomib based on updated survival analyses obtained from the TMM1 trial.[1] The ERG delivered a report in May 2021 emphasising a number of major concerns regarding the plausibility of estimates presented by the company in their original submission. The company indicated that they had identified a major error in their submission, which resulted in resubmission by the company of a revised version superseding the previous one. This ERG report supersedes the original and pertains to the latest company submission (CS). However, in this report we refer to clarification responses that were received in both the 'first round' and 'second round' of clarification responses.

2.2 Background

For this CDF review, IXA+LEN+DEX was used for adults with multiple myeloma who have received 2 or 3 prior lines of therapy. This was the NICE recommended use in the CDF and was accepted by the ERG as the appropriate place for the technology in the treatment pathway and as the appropriate positioning of the intervention for this review process.

2.3 Critique of company's adherence to committees preferred assumptions from the Terms of Engagement

The company have adhered to the majority of the Committee's preferred assumptions from the Terms of Engagement (ToE); the key deviations/issues are listed in Table 12.

Table 12. Preferred assumption from Terms of Engagement

Assumption	Terms of Engagement	Addressed to by the company submission	Rationale if different	ERG comment
Population	Adults with relapsed or refractory multiple myeloma who have had 2 or 3 lines of therapy.	**Yes.** Adults with relapsed or refractory multiple myeloma who have had 2 or 3 lines of prior therapy is a subgroup of TMM1 study.[1]	Not applicable.	The CS presents the updated safety, efficacy, and cost-effectiveness analysis of IXA+LEN+DEX vs. LEN+DEX for the subgroup of patients who have received 2 or 3 prior lines of therapy using the final T-MM1 study data (median follow-up of 85-months).
Comparators	Lenalidomide plus dexamethasone (LEN+DEX).	**Yes.** LEN+DEX is the comparator arm in TMM1 study.[1]	Not applicable.	The Appraisal Committee concluded that in England the relevant comparator to IXA+LEN+DEX for patients with 2 or 3 prior lines of therapy for relapsed or refractory multiple myeloma would be LEN+DEX. (The committee concluded that Panobinostat (PAN)+Bortezomib (BTZ)+DEX would not be a relevant comparator as it would be used after IXA, as the PAN combination is used after LEN).
Time on treatment	Updated Time on Treatment (ToT) data should be derived from the TMM1 trial and; the generalisability of this assumption should be validated using the data collected within the Systemic Anti-Cancer Therapy (SACT) dataset.	**Yes.** ToT data have been updated using the final analysis from TMM1.[1] (final analysis at 85-months of follow-up). **Partially.** The generalisability of updated ToT data from TMM1 study was checked by directly comparing ToT between TMM1[1] and SACT datasets. The ERG consider that the two	Not applicable	No comment required. Meaningful comparison of updated ToT observed between TMM1 study[1] and SACT dataset is precluded due to notable differences between the two datasets in the duration of follow-up and important patient characteristics (e.g., age, co-morbidities, prior SCT) (see Section 3.1.3).

		datasets (TMM1 and SACT) are not comparable due to differences in important factors independently associated with ToT.		
	Unless the company justifies an alternative extrapolation choice a Weibull curve should be fitted to these data.	**Yes.** Data have been extrapolated using a Weibull curve.		No comment required.
Survival data	The company should use updated survival data from the TMM1 trial.	**Partially.** The company provided updated and adjusted mature OS data (for both study arms: IXA+LEN+DEX and LEN+DEX) using the final analysis of TMM1 study[1] (data lock point of September 30, 2020) at a median follow-up of 85-months.		The company adjusted the OS hazard ratio (HR) estimate for the confounding effects of subsequent therapies that are not routinely funded or available in UK clinical practice.
	Unless the company justifies an alternative extrapolation choice a Weibull curve should be fitted to these data.	**No.** The company have extrapolated OS data using generalised gamma curve. The company stated that *'Following updates to the treatment switching analyses, clinician*	No explicit rational was provided in CS Table A2 page 6-7. However, the company state that curve selection was "*inline with clinical feedback*".	The company suggested the generalised gamma parametric curves provided a reasonable estimation of long-term outcomes with LEN+DEX and IXA+LEN+DEX. The ERG suggest that the company's Weibull models for adjusted OS: two-stage censoring (novel therapies) appear almost indistinguishable from the generalised gamma.

		feedback was sought to validate the parametric curves and survival predictions based on the corrected adjusted Kaplan-Meier data (adjusted based on the TSE with re-censoring). The feedback concluded that the generalised gamma provided a reasonable estimation of long-term outcomes with LEN+DEX and IXA+LEN+DEX. Therefore, this was applied in the base case.' (CS Document, Table 16, page 44)		The ERG considers Weibull to be as valid on the grounds of clinical plausibility as the model selected by the company. Given the uncertainty, the company deterministic base-case point estimate ICER should be viewed with caution.
Utilities	The company should use any updated EQ-5D data from the TMM1 trial.	**Yes.** The company updated EQ-5D data for the final analysis of the TMM1 study.[1] The HRQoL data have been analysed in line with the methods presented in the original STA appraisal (ID TA505) (i.e., regression analyses have been performed which account for multiple observations per patient and a potential list of covariates). Utility regression included: response assessment,	Not applicable.	The company has stated that "*grade 3/4 adverse events, gender and race were shown not to be significant drivers of HRQL in the backwards stepwise selection process with the updated data. Therefore, these were not included in the final regression model. However, to ensure no HRQoL impact is being missed in relation to adverse events, the decrement assumed in the original NICE submission is applied in the base case (CS Document, Table 16 page 45)."* In response to the ERG clarification question B4, the company has stated that since line of treatment was not found to be a significant predictor of HRQoL, these were not included in the final regression model. The ERG accepts these justifications.

		age, hospitalisations, and death within 3 months. The analysis presented was conducted using the data from the population with 2 or 3 prior lines of therapy as per Appraisal Committee preferred assumptions. The regression-model based adjusted utility values and coefficients were used in the updated economic model.		The company has stated that they have included the baseline EQ-5D-3L (0.658) as a covariate; as further exploration of the data and feedback from clinicians indicated that this should be adjusted for (CS Document, Section A.7.5 page 37). The ERG agrees with this statement and accepts that the utilities estimated from the final analysis better align with the literature and, also, better reflect patients' HRQoL with RRMM.
Continued treatment effect	The company should present evidence that the proportional hazard assumption is applicable with the more mature survival data.	**Yes.** The company state that no treatment waning is applied in the base-case.	The TMM1 final analysis captures the impact of discontinuing therapy on the treatment effect for approximately 96% and approximately 99% of patients who have stopped treatment during follow-up in the IXA+LEN+DEX and LEN+DEX arms, respectively. Therefore, no treatment waning is included in the company base case. A scenario analysis applies treatment waning to the approximately 4% and approximately 1% of	The ERG queries the sustained effect of treatment for ixazomib. While the ERG acknowledge that waning of treatment has almost completely been captured within the observed time of the TMM1 trial (for the majority of patients almost all have already stopped treatment during follow-up in the IXA+LEN+DEX (96%) and LEN+DEX (99%) arms). The ERG considers the waning/discontinuation of treatment to be a separate entity (see Section 3.3 for further details). There was a small sample of patients still receiving treatment in TMM1 study (4% vs. 1% in the respective study arms) for whom the effect of treatment waning has not yet been reflected. Therefore, the sustained effect of the treatment after treatment itself has stopped should be considered separately in the economic modelling.

			patients still receiving treatment.	The ERG undertook several scenario analyses to explore the waning of treatment effect.
Subsequent therapies	The company should explore the most appropriate subsequent treatments costs to be included in the model for both arms based on the more mature TMM1 trial data.	**Yes.** Costs were based on subsequent therapy use from the final analysis for TMM1 and adjusted for the impact of subsequent therapies which would not be received in UK clinical practice.	The base case adjusts the OS to adjust for the impact of subsequent therapies which are not routinely funded in the UK (i.e., not available or only funded via the CDF). The costing of subsequent therapies in the base case reflects this.	As mentioned above, there is considerable uncertainty associated with the TSE-OS modelling and the inherent uncertainty in parametric modelling. The ERG consider that the company's deterministic base-case point estimate ICER should be viewed with caution. The costing of subsequent therapies is adequately provided in the company base-case.
End of life	Ixazomib does not meet the EoL criteria.	**Yes.**	Not applicable	No comment required.

3 CLINICAL EFFECTIVENESS

3.1 Critique of new clinical evidence

3.1.1 Updated trial evidence

- The CS includes the final analysis of updated OS and cost-effectiveness data collected in the TMM1 trial[1] at a median follow-up time of 85-months (Data Lock Point: September 2020). Other updated endpoints were mature data on time on treatment (ToT) and health utilities (model-based covariate adjusted EQ-5D questionnaire data). Data on PFS have not been collected beyond the second interim analysis (IA2) of TMM1 (CS Document, Section A.5, page 12).
    - The ERG considers that updated PFS would have been beneficial for the CDF review, as PFS is not affected by the post-progression treatment switching that leads to confounding. However, the ERG acknowledge that it was not in the statistical analysis plan.
- The final analysis of the TMM1 trial pertains to the population of interest for this appraisal, namely patients with RRMM who have had at least two prior therapies and, the intention-to-treat population of the trial, namely patients with RRMM who had at least one prior therapy. The full results of the trial are reported in a paper by Richardson et al.[3]
- As described in Table 12, the company adjusted the updated OS HR estimates to account for the impact of subsequent therapies which are not routinely funded in the UK (i.e., not available, or only funded via the CDF). The company (and company's clinical advisors) propose an expected "*UK clinical practice"* pathway for subsequent line(s) of treatment (CS Document, page 8).
    - As far as the ERG can ascertain, no guidelines exist describing this pathway; even if the proposed expected UK pathway is accurate, it is unlikely to remain unchanged in the near future as more research is published regarding the clinical effectiveness of new treatments beyond three or four lines. However, the company survival analysis assumes that their expected pathway will continue to operate for a further 26 years (from approximately 8 to 34 years) beyond the trial final cut.
    - The ERG clinical advisor notes that the Pan London Myeloma guidelines published in 2020 provide what they consider to be appropriate guidance at the time of publication.[4]

- CS Document Table 11 (page 26) indicates that next line treatments are fairly similar between arms. Thus, additional treatments may be reasonably balanced, and the company suggest that two-stage adjustment may not be required since the main interest is in comparing clinical/cost effectiveness of IXA+LEN+DEX versus LEN+DEX. The two-stage adjustment attempts to determine what might happen regarding patient survival if an "*expected*" but hypothetical UK clinical pathway were to be followed for 34 years; this therefore addresses a subtly different question to that of principal interest here.

- The company noted some between-arm imbalances in the proportion of patients taking certain novel drugs known for their prognostic importance which are either not available in the UK (e.g., CARF-, ELOT-based) or are only funded by the CDF (e.g., DARA-, ISA-based) (CDF-funded treatment sequence products should not be included in economic modelling).

    - Three examples of imbalance in these therapies were highlighted by the Company: daratumumab (received by 31/149=21% in LEN+DEX as opposed to only 19/148=13% in IXA+LEN+DEX), elotuzumab (7/149=5% versus 3/148=2%, respectively) and autologous stem-cell transplant (9/149=6% versus 1/148=0.7%, respectively). The company claimed that "*imbalance in these therapies confounds the interpretation of the survival benefit, as more patients in the LEN+DEX arm received therapies that extend survival for patients with MM*" (CS page 66).

    - Overall, 111 patients (59 in the IXA+LEN+DEX arm and 52 patients in the LEN+DEX arm) required adjustment for receipt of agents not routinely available in the UK.

3.1.2 Adjustment for treatment switching

- Treatment switching adjustments were conducted via two main methods used to remove the effect of subsequent therapies (the inverse probability of censoring weights [IPCW] method and the two-stage method).[5] The OS HR estimates unadjusted and adjusted for treatment switching are presented in Table 13.

    - For OS although the unadjusted HR was not statistically significant (HR=0.845, 95% CI: 0.642, 1.114), the two-stage method (with recensoring) adjusting HR for treatment switching, which was used in the company's base-case, suggests a

statistically significantly improved OS experience in patients receiving IXA+LEN+DEX compared to those receiving LEN+DEX (HR=0.713, 95%CI: 0.535, 0.952).

- The company also considered the Rank Preserving Structural Failure Time (RPSFT) Models method to adjust for bias due to switching to subsequent treatments, but because the TMM1 trial was multicentre, the common treatment effect assumption across multiple trials was not deemed to be valid (CS Document, Section A.7.1, pages 26-29).

- The median OS, (as provided in the second round of clarification responses), and HR for both unadjusted and adjusted analyses are presented in Table 13.

Table 13. Median OS time and HR (unadjusted and adjusted for switching to subsequent treatments)

Endpoint Parameter	**IA2 [median follow-up of 23-months]**		**Final analysis [median follow-up time of 85-months]**	
	IXA+LEN+DEX	**LEN+DEX**	**IXA+LEN+DEX**	**LEN+DEX**
Unadjusted for treatment switching HR (95% CI)	0.645 (0.409, 1.017) Median OS (in months)		0.845 (0.642, 1.114) Median OS (in months)	
	not estimable	not estimable	53.0	43.0
Naïve – censor at switch	N/A		0.712 (0.507, 0.999) Median OS (in months)	
			70.7	44.7
Naïve – 'per protocol'‡			0.699 (0.493, 0.990) Median OS (in months)	
			34.5	25.9
TSE (no re-censoring + adjust for baseline characteristics†)			0.785 (0.596, 1.035) Median OS (in months)	
			52.5	43.4
TSE (re-censored* + adjust for baseline characteristics†)			0.713 (0.535, 0.952) Median OS (in months)	
			51.4	41.5
IPCW (stabilised weights + adjust for baseline characteristics†)			0.674 (0.465, 0.979) Median OS (in months)	
			54.6[α]	38.6[α]

HR, hazard ratio ; IA2, second interim analysis; IPCW, inverse probability of censoring weights; N/A, not applicable; NR=not reported; OS, overall survival
† Adjusts for high risk, age>65, ISS stage at screening, and history of bone lesions.
‡ Excludes all patients who switched from the analysis.
[α]Median estimates for ICPW do not adjust for baseline covariates
*Counterfactual survival times are re-censored for all patients at the minimum of the administrative censoring time of the study (28th September 2020;C_i) and $C_i\psi_2$where $\psi_2$is the adjustment factor associated with group 2 membership. This represents the earliest possible censoring time

3.1.3 Comparison with real-world evidence

- The company provided updated data on ToT from the TMM1 study (final analysis at 85-months of follow-up). Median ToT for patients with 2 or 3 prior therapies was 18.2 months in patients receiving IXA+LEN+DEX versus 13.4 months in patients receiving LEN-DEX (HR for treatment discontinuation=0.76, p=0.0242) (CS Document, Section A.6.1, Table 7, page 18).

- The company provided real-world evidence of OS, ToT, and other patient related factors from the SACT database collected during the CDF period (between December 2017 and June 2020) for 2,460 patients who received IXA+LEN+DEX in England and Wales (CS Document, Section A.6.2, page 20). The generalisability of the TMM1 data could not be validated compared to the real-world evidence. Nevertheless, the updated data were compared;

The updated ToT and OS data for patients receiving IXA+LEN+DEX were directly compared between TMM1 study (median follow-up of 85-months for ToT and OS) and SACT (median follow-up of 8.3 months for ToT; median follow-up of 15 months for OS) datasets. Both median ToT and OS durations were shorter for SACT (ToT: 11.5 months; OS: 30 months) than TMM1 (ToT: 18.2 months; OS: 53 months). At 12- and 18-months, 48% and 38% of patients respectively, were still receiving the treatment (CS Document, Section A.6.2, Table 9, page 20).

  - Meaningful comparisons of updated median ToT duration and median OS time were hindered by notable differences in the duration of median follow-up between the TMM1 study (85-months) and the SACT datasets (8.3 months for ToT and 15 months for OS) and in the distribution of important patient characteristics independently associated with ToT and OS (e.g., age, co-morbidities, prior SCT). Specifically, the patients from SACT tended to be older, less fit, and had a poorer prognosis than patients in TMM1.

  - In the SACT dataset fewer patients received prior stem-cell transplant compared to TMM1 study (CS Document, Section A.6.2, Table 10, pages 21-22).

3.1.4 Updated HRQoL and discontinuation

- Health-related quality of life data (HRQoL - EQ-5D-3L) was used in the final analysis of follow-up of TMM1 trial. HRQoL was measured at baseline, every 4-weeks until

progression and every 12-weeks post-progression until study close. The EQ-5D-3L data were analysed using a regression model with backward stepwise elimination of statistically non-significant independent covariates.

  - The regression analysis included an a priori selected list of covariates identified during the original STA appraisal (ID TA505) and clinical feedback. The final regression model included the EQ-5D-3L utility score at baseline, age, response assessment, death within 3-months of EQ-5D-3L assessment and hospitalisation. The number of prior lines was explored using the ITT population but was not shown to be a significant predictor of endpoint EQ-5D-3L (CS Document, Section A.7.5, page 36).

- The TMM1 final analysis captures the impact of treatment waning after discontinuing therapy for the majority of patients as they have already stopped treatment during the follow-up in the IXA+LEN+DEX (96%) and LEN+DEX (99%) arms. Therefore, no further adjustment for treatment waning was included in the company's base case economic model.

  - However, there was a small sample of patients still receiving treatment in TMM1 study (4% versus 1% in the respective study arms) for whom the effect of treatment waning has not yet been captured (CS Document, Section A.2, Table of Key Committee Assumptions, page 6).

  - The company presents a scenario analysis that explores waning of treatment. This analysis only encompasses changes for < 5% of patients and has minimal impact on cost-effectiveness.

  - The ERG considers this scenario a completely separate issue from the waning of a treatment's effect (see key issues Table 4). The ERG present scenarios for waning of ixazomib's effect encompassing the one-third of patients that the company have modelled (by two-stage adjustment) to be alive at the end of the observation period.

3.1.5 Updated safety

- The company provided safety data from the final analysis after a median follow-up of 85-months. The dataset included a safety population of 720 patients regardless of the number of prior therapies (361 patients in IXA+LEN+DEX arm and 359 patients in the

LEN+DEX arm). The safety population for the subgroup who had had 2 or 3 prior lines of therapy consisted of 297 patients (148 patients in IXA+LEN+DEX arm and 149 patients in the LEN+DEX arm). At the time of this analysis, 96% of patients had discontinued treatment in both arms, mostly owing to disease progression.

- The safety profile of IXA+LEN+DEX was consistent with that seen at the 23-month follow-up analysis (IA2). No new safety signals were observed (CS Document, Section A.6.1, Table 8, pages 18-19).

3.1.6 ERG critique of treatment switching adjustment

The company presented updated OS analyses obtained after median follow up of 85-months for patients enrolled in the TMM1 trial (2+ prior population). These led to a median OS of 53 and 43 months, respectively in the IXA+LEN+DEX and the LEN+DEN arms, a difference that does not reach statistical significance (please see HR on the risk of death summarised in CS Table 5 page 15).

As per the NICE CDF position statement,[6, 7] the OS analyses were adjusted for the presumed "*positive*" impact that subsequent therapies not currently recommended within the NHS may have presented in both IXA+LEN+DEX and LEN+DEX arm. The two-stage adjustment with re-censoring undertaken by the company and used in their base-case model has an effect on OS for both arms: reducing survival in both arms by approximately 1.5 months while at the same time providing a greater survival advantage for IXA+LEN+DEX over LEN+DEX, which reaches statistical significance (OS HR: 0.713, 95%CI [0.535, 0.952]).

3.1.6.1 Statistical approach and definition of confounding

The ERG notes that the final SAP for the TMM1 trial pre-specified that adjustment of OS analyses was to made to account for the "*potential effects of subsequent therapies after patients discontinue study treatment (page 29-30 of TMM1 SAP final version DEC 2014)"*.[8] The ERG considers that the principle of such adjustment is reasonable, although it could be noted that the SAP[8] planned these analyses to be conducted using two methods, namely marginal structural models (MSMs) and IPCW, and not the two-stage method.

The company's adjusted analyses accounted for the use of novel therapies in the TMM1 trial which are neither reimbursed nor routinely available for use in clinical practice in the UK (CS Document page 24).

The company states that they have conducted an analysis according to the methodology described in NICE Decision Support Unit Technical Support Document (NICE TSD) 16.[5] This guideline advocates the use of adjustment methods when patients randomised to the control group who progress, are allowed to switch to the investigational treatment arm, for example for ethical reasons. Switching improves the OS for treatment switchers compared to non-switchers. An intention to treat (ITT)-based (unadjusted) analysis of the OS data, it is postulated, will therefore produce an estimate of HR biased towards the null, thereby underestimating the true treatment effect of the investigational drug. The scenario with switchers in the TMM1 trial was different (there were treatment switchers in both IXA+LEN+DEX and LEN+DEX arms and confounding may have biased OS HR in either direction). The ERG agrees with the company in not using the ITT analysis or per-protocol censoring and exclusion of switchers post-progression.

- However, the NICE TSD 16[5] mainly focuses on treatment switching from the control group onto the experimental treatment. It does not consider situations (as per the TMM1) in which patients randomised to both experimental and control groups switch to receive other treatments. In this case, both arms may reflect part of a realistic clinical pathway which needs to be incorporated into the economic evaluation as opposed to adjusting and or removing the effects.

- The ERG considers that there is no clear definition or guideline outlining the routine clinical pathway in the UK for the treatment of patients with refractory/relapsed multiple myeloma who have received 2 or 3 prior therapies after their disease progression. Moreover, in light of the rapid pace of drug development in oncology, the same clinical routine may not remain stable even over short period of time.

3.1.6.2 Clinical rationale for OS adjustments and plausibility of company's adjusted OS results

As per NICE CDF position statement,[6, 7] the company adjusted both trial arms by removing the impact of non-UK/NHS based treatments, which are presumed to be effective options that can lead to improved survival (see Section 3.1.1). Removing the presumed beneficial

effect of these therapies results in decreased OS for both arms (approximately 1.5 months reduction of median OS in both arms).

As previously indicated, the company suggested that there was an imbalance between subsequent therapies received by patients. They go on to suggest that this confounds the interpretation of the survival benefit, as more patients in the LEN+DEX arm received therapies that extend survival for patients with MM. These imbalances are described as: daratumumab (received by 31/149=21% in LEN+DEX as opposed to only 19/148=13% in IXA+LEN+DEX), elotuzumab (7/149=5% vs. 3/148=2%, respectively) and autologous stem-cell transplant (9/149=6% versus 1/148=0.7%, respectively).

The ERG appreciates that these three therapies are deemed of substantial interest in the management of RRMM as illustrated by their positioning in the latest ESMO guidelines.[9] Had 100% of patients received one or several of these therapies in one arm versus 0% of patients in another arm (as seen in a RCT), the ERG agrees such a scenario could confound OS analyses. However, the extent to which these much smaller differences in the proportion of patients who receive presumed effective options can impact OS analyses is unclear.

The ERG notes that the magnitude of median OS reduction after adjustment is similar, which results in an almost identical median OS gain (10 months in unadjusted analyses vs 9.9 months in adjusted analyses). However, it is sufficient to reach a statistically significant reduction in the risk of death in adjusted analyses (two-stage recensored). The apparent minimal effect of adjustment on median OS estimates contrasts with the statement made by the company regarding the effect of subsequent therapies.

Although the ERG acknowledges that median OS and life-years are very different ways if describing survival estimates, (the latter corresponding to an average), the ERG questions the impact that adjusted analyses have on life-years estimates in the cost-effectiveness section (see Section 5.5).

To examine consistency of the OS results, and in order to verify the impact of adjustment based on a larger sample size and number of events, the ERG has reviewed the final OS analyses of the TMM1 trial beyond the scope of the CDF review, i.e. including the ITT TMM1 population (RRMM with 1+prior therapy) and based on the original analyses planned in the TMM1 SAP.[8] These pre-specified analyses planned to undertake adjustments for the potential effects of subsequent therapies after patients discontinued study treatment, using the two methods described, namely MSMs and IPCW (see page 29-30 of TMM1 SAP final version DEC 2014).[8]

Based on the ITT population, IXA+LEN+DEX did not result in a reduction in the risk of death compared to placebo-LEN+DEX (OS HR: 0.939 95%CI [0.784,1.125]).[3] Although OS HRs were reduced, neither adjustment with MSMs nor with the ICPW method led to a statistically significant reduction in the risk of death (OS HRs of 0.68 95%CI [0.46, 1.00] and 0.70 95%CI [0.48, 1.03] respectively). The 2+ prior population being a subgroup of the entire ITT population, for which overall ixazomib showed no benefit on OS, the ERG considers that the company's post-hoc adjusted analyses provide a very low level of evidence that ixazomib may reduce OS in the 2+ prior population which is the subject of the present appraisal.

While the ERG acknowledges that the use of subsequent therapies (such daratumumab) may have confounded OS analyses, the ERG believes that the question of whether ixazomib improves OS in the 2+ prior population is yet to be determined. Hence, there is still a substantial uncertainty with regards to the effectiveness of ixazomib as assessed by OS.

- In summary, the ERG notes a slight inconsistency between the postulated mechanism of confounding due to novel therapies and the adjustment results. According to this mechanism, the removal of the impact of subsequent therapies not available in the UK (presumed to be effective), which were more frequently used in the LEN+DEX arm, should have been more visible in the LEN+DEX arm. However, the ERG note that the OS dropped by approximately 1.5 months after this adjustment in both arms, yielding to a similar median OS gain between the unadjusted and adjusted analyses. Due to the lack of availability of individual patient data, the ERG has not been able to replicate and validate this adjusted analysis.

- The ERG concludes that there is still a substantial uncertainty with regards to the effectiveness of ixazomib as assessed by OS.

3.1.6.3 Application of the two-stage method

Since randomisation could not be stratified by the post-progression treatments received, the ERG does not consider the proposed OS results comparing IXA+LEN+DEX and LEN+DEX to represent a randomised comparison of treatments. Therefore, the results are likely to be susceptible to appreciable uncertainty.

The ERG has concerns regarding the details of how the two-stage model was used to adjust for switching to subsequent treatments. The two-stage method assumes the use of a secondary baseline, which ideally should represent the time of disease progression. The

violation of this assumption may lead to biased estimation if some of the treatment switchers did not experience disease progression.

It is not clear how many patients whose disease progressed went on to switch to other treatment(s). The ERG could not verify if any of the patients who did not progress, still went on to switch their treatment beyond periods of observation.

The company listed covariates used in the two-stage method to satisfy the 'no unmeasured confounders' assumption. The company have justified their choice of covariates on the basis that it is consistent with clinical opinion. The ERG could not verify this information.

It was not clear what duration of time elapsed between disease progression and treatment switch to subsequent therapies. If the IXA+LEN+DEX patients received new treatments faster after progression than the LEN+DEX patients, then a bias favouring IXA+LEN+DEX is introduced. The existence, direction and magnitude of such bias is unclear.

The ERG had difficulties interpreting and validating the properties of the TSE-OS models presented in the CS because there were apparent contradictions within the CS (KM depictions in Figures 7 and Figure 8), and between the information supplied in clarification document (round two clarification) *ID1635 ixazomib Takeda clarification questions A3_A4 05102021CM noACIC* and information provided within the economic model.

3.1.7 Summary of ERG critique

- The ERG concludes that there is still a substantial uncertainty with regards to the effectiveness of ixazomib as assessed by OS.

- The ERG notes an inconsistency between the postulated mechanism of confounding due to novel therapies and the adjustment results. The median OS dropped by approximately 1.5 months after this adjustment in the two arms, yielding to a similar median OS gain between unadjusted and adjusted analyses.

- There were inconsistences within the CS and between the CS and information supplied by the company in clarification, and between clarification information and the economic model regarding two-stage adjusted OS. For example, in the CS Figure 7 and Figure 8 on pages 33 and 35 presenting the two-stage adjusted OS KM plot for the treatment arms differed substantially with respect to last observation (about 6 years in Figure 7 and nearly 8 years in Figure 8). The clarification document *ID1635*

ixazomib Takeda clarification questions A3_A4 05102021CM noACIC presented alternative estimates.

  - Consequently, the ERG is unsure which data amongst several alternatives have been used by the company (see Section 3.2 Additional work conducted by the ERG). The ERG has therefore, briefly investigated other parametric models of OS.

- ToT and PFS correlated well for the LEN+DEX arm. However, for the IXA+LEN+DEX arm, there was a mismatch as discontinuation preceded progression. Although these comparisons are based on rather unsatisfactory data (in that PFS analysis was only available to IA2 cut off) the mismatch in one arm, but not the other, suggests there may be bias in the costing of treatments that may favour the IXA+LEN+DEX arm.

- The ERG does not agree that the waning of the treatment effect of ixazomib is completely captured within the observed data (whether the data for TSE-OS tare presumed to extend to 6 years or to approximately 8 years). The ERG notes that the period of observation beyond discontinuation of ixazomib in more than 90% patients only lasts for approximately 2 years. This this is an insufficient time to fully capture any waning.
  - Approximately a third of patients are alive in the IXA+LEN+DEX arm at the end of observation. The company have assumed that the treatment effect of ixazomib seen at this time is maintained in the surviving patients for a further 18 years. An assumption that in the ERG's opinion is not likely to hold.
  - The ERG explored waning scenarios applied to the company's generalised gamma model of OS in the ixazomib arm and found that slow waning over 18 years raised the base-case ICER by 5%. Faster waning substantially inflates the ICER beyond a 5% increase.

3.2 Additional work on clinical effectiveness undertaken by the ERG

In the original STA appraisal (ID TA505) the NICE Appraisal Committee recommended that ixazomib be referred to the CDF, so that more mature data could be collected with the aim of reducing uncertainty in the cost-effectiveness analysis and to better inform decision making.[2] OS data was collected up to just over eight years.

3.2.1 Company Kaplan-Meier analyses

In the updated CS (September 2021) the company submitted KM analyses for ToT, PFS and for two-stage adjusted OS. In the following, the KM plots (ToT, PFS, two-stage adjusted OS) are compared between treatments and between each other. The following figures are taken from the economic model submitted with adaptions to allow combination or comparison.

In Figure 1 of this document the KM plots for ToT and TSE-OS are compared between treatments and between each other and are taken from the economic model. The ToT plots extend to about 7.4 years while the TSE-OS plots extend further, these plots correspond to CS (September 2021) Figure 8 (page 35) for TSE-OS and to CS Figure 9 (page 39) for ToT. However, CS Figure 7, in contrast, shows the TSE-OS KM for both arms extending to only about 6.2 years (see enlarged version, ERG Appendix 1).

The KM for TSE-OS, copied from the submitted economic model, implies that the TSE-OS KMs extend to approximately 7.8 years, corresponding to the depiction in CS Figure 8, page 35 (see also ERG Section 9.1) but not corresponding to Figure 7 page 33. The ERG cannot explain these differences.

The unadjusted OS KM plots (CS Figure 1) extend to about 90 months approximately 7.5 years (unfortunately time axis tick marks are lacking in this and other CS figures). The ERG is unsure why OS extends beyond ToT but believe this maybe an error in view of IPD data supplied to the ERG by the company during the second round of clarifications (*received October 7 2021: document ID1635 ixazomib Takeda clarification questions A3_A4 05102021CM noACIC*). This indicates that for the two-stage adjusted OS, the first death event or censoring time occurred at 10 weeks and the last death event or censoring time occurred at 324 weeks (6.21 years). The relevant part of the CS clarification document is shown Table 14. The same time of 324 weeks for last death or censoring was also shown for the LEN+DEX arm.

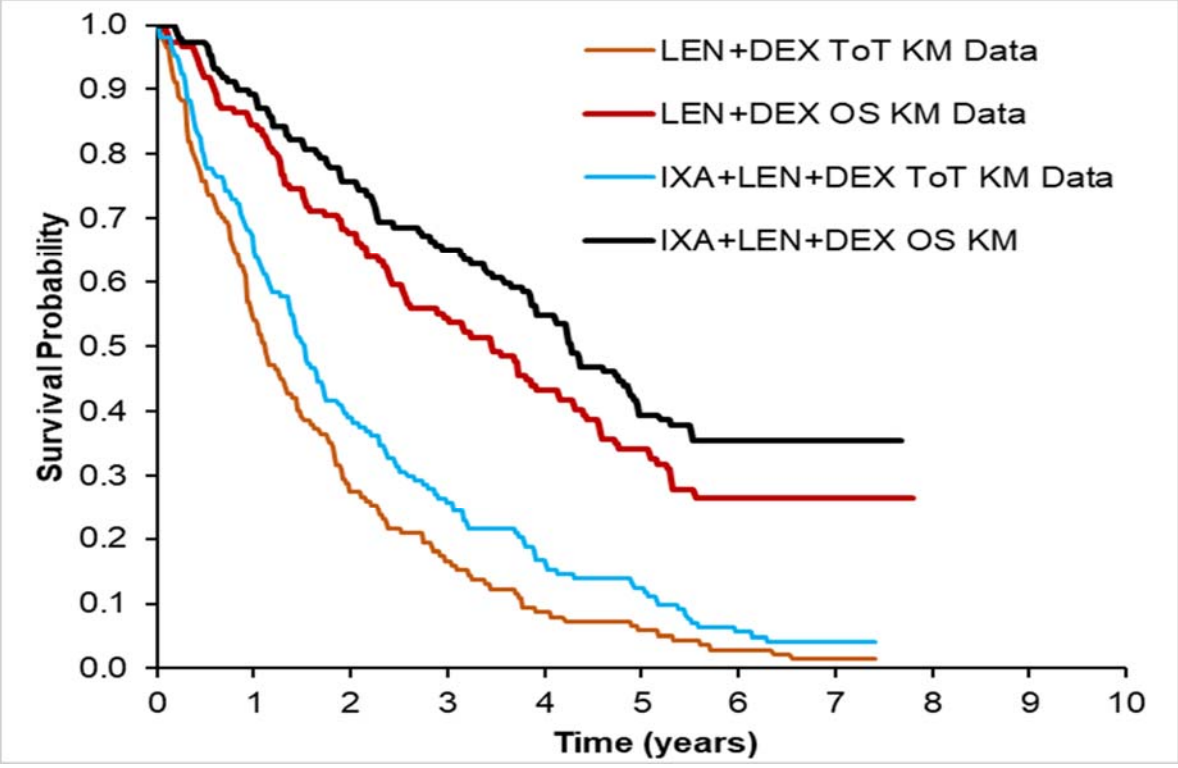

Figure 1: Company KM plots for ToT and 2-stage adjusted OS

Table 14. IXA+LEN+DEX- (FA; Adjusted OS: 2-stage re-censoring [novel therapies]) 2+ prior line patients only

Weeks	Observation	Deaths	Censored	Survival

The corresponding last times for unadjusted OS from this document were 400 weeks (7.7 years) and 397 weeks (7.6 years) for IXA+LEN+DEX and LEN+DEX arms, respectively and 361 and 362 weeks (6.9 years) for ToT.

Figure 1 suggests that after approximately 7.4 years approximately 96% of IXA+LEN+DEX patients have ceased treatment while approximately 35.5% remain alive at end of observation according and have discontinued ixazomib and at some stage have received various subsequent treatments that have been adjusted for in the TSE procedure. In the LEN+DEX arm according to 2-stage re-censoring OS about 26.5% remain after cessation of treatment and observation.

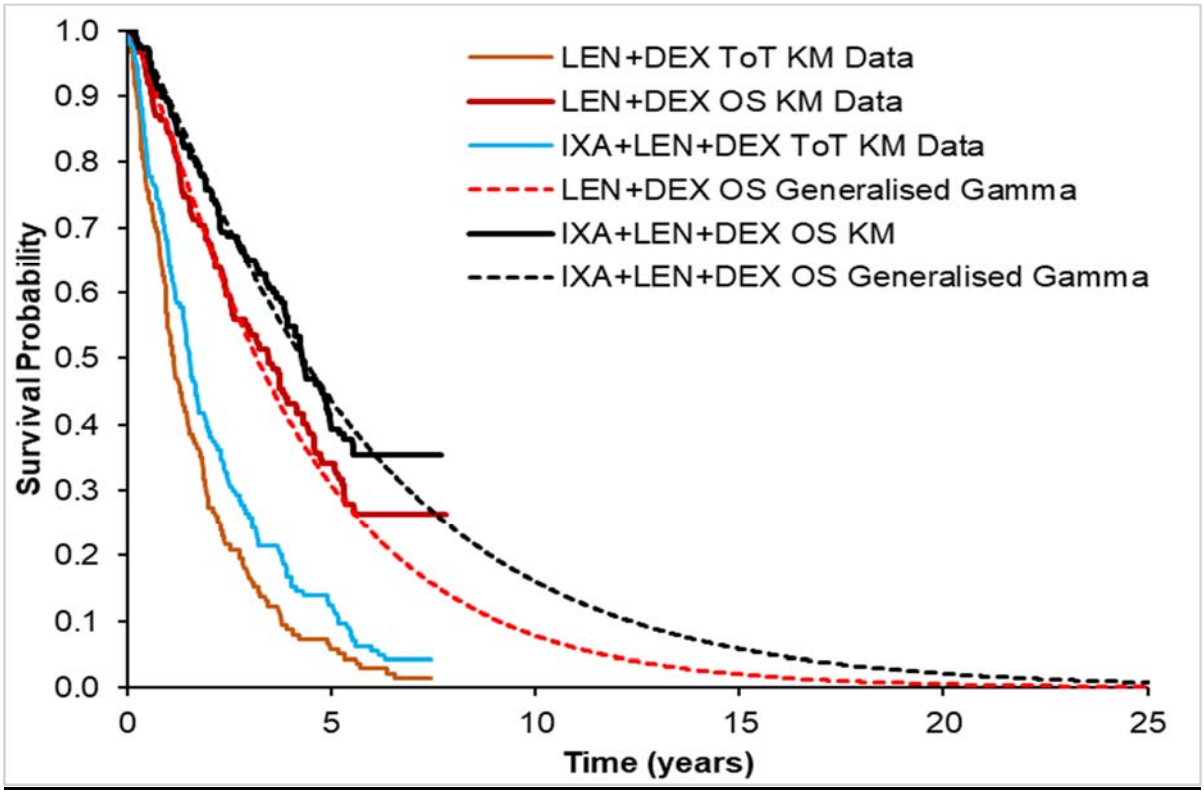

Figure 2: 2-stage adjusted OS KM and company's generalised gamma models extrapolated to 25 years

Figure 2 suggests that after approximately 7.4 years, approximately 96% of IXA+LEN+DEX patients have ceased treatment while approximately 35.5% remain alive at approximately 6 to 7.8 years (according to the two-stage adjusted OS procedure), and have discontinued ixazomib, and at some stage have received various subsequent treatments that have been adjusted for in the two-stage adjusted procedure. In the LEN+DEX arm according to the two-stage adjusted OS, about 26.5% remain alive at approximately 6 to 7.8 years after cessation of treatment.

Figure 3 shows the company two-stage adjusted OS KM and PFS KM plots. These suggest that there is greater OS gain post-progression than pre-progression in both arms. It should be borne in mind however, that the PFS plots are based on the company's IA2 analysis.

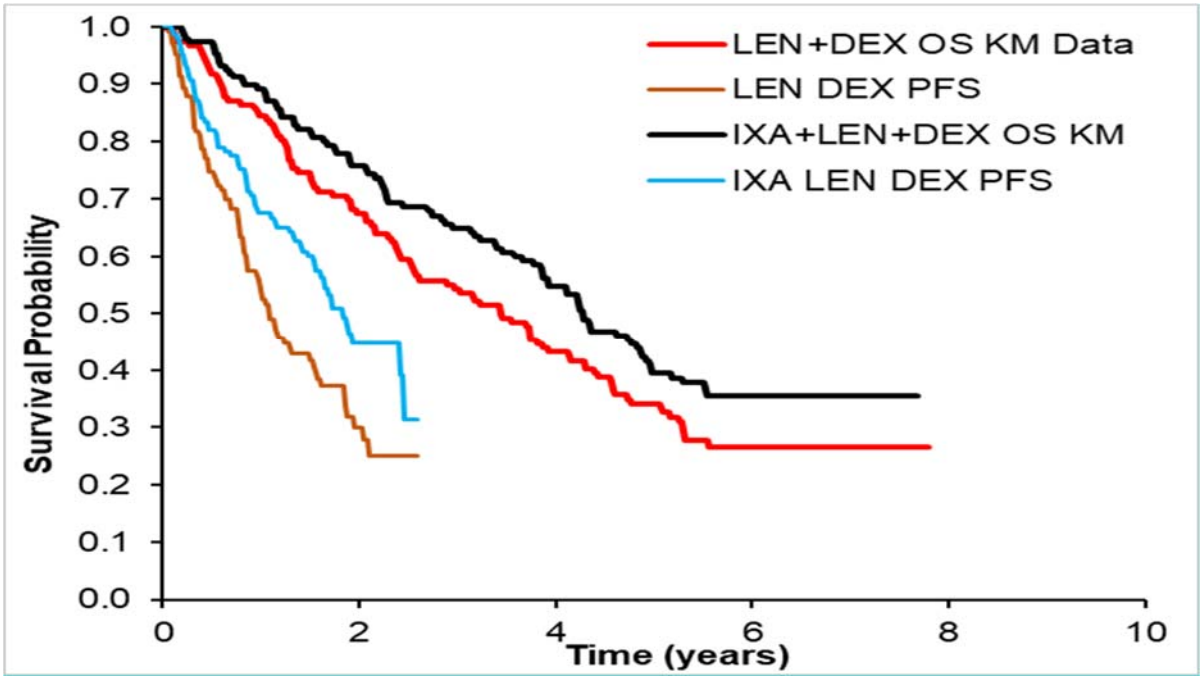

Figure 3: KM plots for 2-stage adjusted OS and for PFS

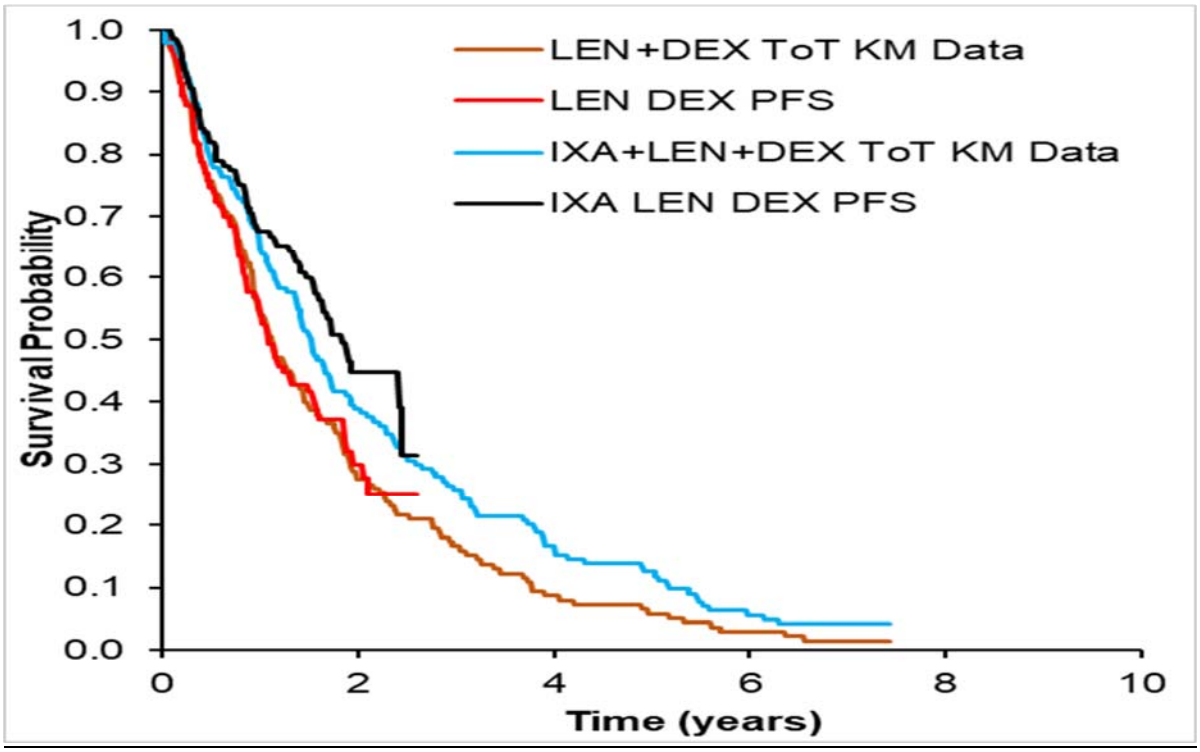

Figure 4: KM plots for ToT and for PFS

Figure 4 compares ToT KM plots with PFS plots. ToT and PFS match very closely and are very similar for the LEN+DEX arm but there is noticeable mismatch between PFS and ToT in the IXA+LEN+DEX arm. Therefore, in the IXA+LEN+DEX arm, there is an apparent discontinuation of treatment before progression which is not seen for the control LEN+DEX

arm. In the economic model the parametric models for discontinuation are used in the costing of treatment arms. The mismatch seen only in the IXA+LEN+DEX arm implies that an equitable assessment of both arms may be compromised, potentially introducing bias that favours the intervention over control. It should be borne in mind that the PFS KM are based on IA2 and are less mature than other KMs.

Data currently available to the ERG does not allow the ERG to cross check the parametric modelling undertaken by the company. Similarly, as already mentioned in section 3.1.6.2, lack of data means the ERG are unable to cross check the TSE-OS undertaken by the company. The ERG is therefore, unable to endorse the current cost-effectiveness analysis submitted by the company; the ERG comment that the ICER is very sensitive to small changes in OS modelling.

At time of writing, the ERG is uncertain what dataset the company used for their parametric modelling of two-stage adjusted OS or exactly what relationship exists between KM plot and fitted generalised gamma models in CS Figures. The ERG assumes that since they are presented in the same graph, the parametric fit is for the same underlying data to that seen in the KM plot. Looking at Figure 2 that depicts the company's generalised gamma models of two-stage adjusted OS, and the two-stage adjusted OS KM plot extending to 7.8 years, it seems more likely that the parametric models may be based on data underlying KMs for two-stage adjusted OS data that terminate at about 6.2 years rather than at approximately 7.8 years.

The ERG is also uncertain what dataset was used by the company to determine the HR of 0.713 (CS Document, Table 12, page 30) for two-stage adjusted OS IXA+LEN+DEX versus LEN+DEX (i.e., whether data extending to approximately 7.8 years or data extending to 6.2 years (the latter as in the second-round clarification document *ID1635 ixazomib Takeda clarification questions A3_A4 05102021CM noACIC*).

3.2.2 Kaplan-Meier analysis of TSE-OS using data supplied

For practical purposes the ERG assumes that the data underlying the company's TSE-OS KM plots is the same as that used to generate parametric models for extrapolation beyond observation. The ERG believes these data are represented in CS Figure 7 and have used the method of Guyot et al.,[10] to develop reconstructed IPD and examine generalised gamma and Weibull parametric models of TSE-OS. The resulting KM plots and 95% CI are superimposed closely to the plots shown in Figure 5.

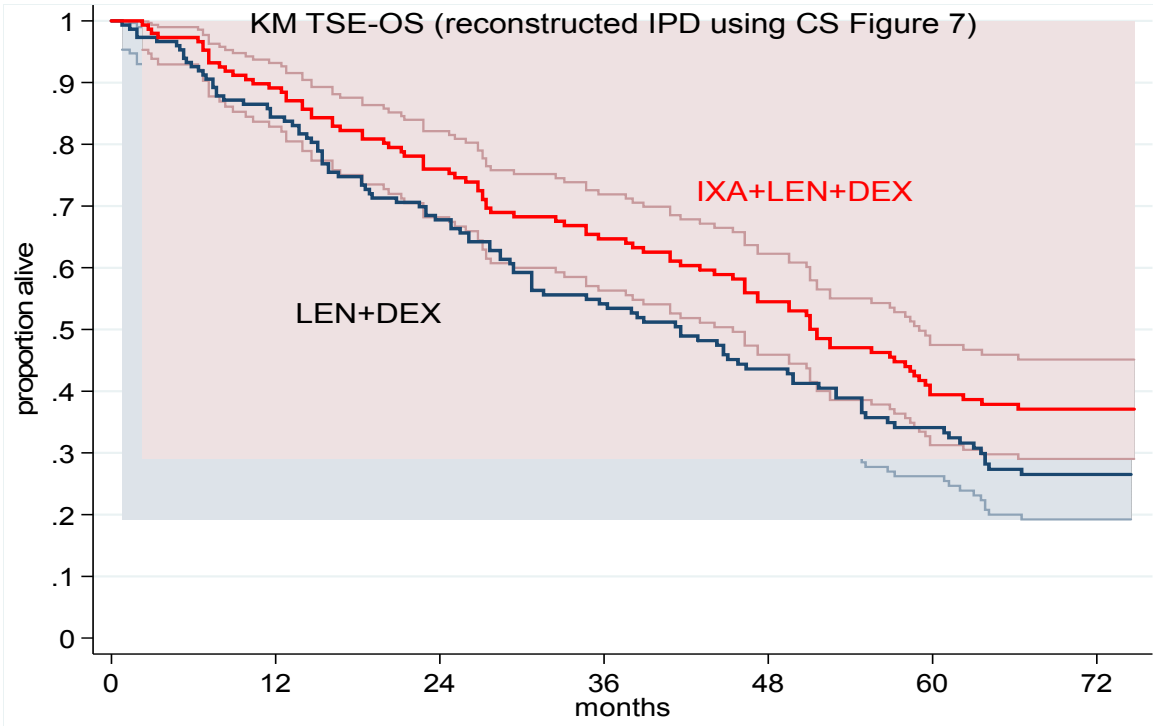

Figure 5: KM plots derived using information supplied by the company in document: ID1635 ixazomib Takeda clarification questions A3_A4 05102021CM noACIC

The unadjusted Cox regression HR based on reconstructed IPD is: 0.743 (95%CI: 0.558, 0.989). This compares to the adjusted HR of 0.713 (95%CI: 0.535, 0.952) provided in CS Table 12. Lack of data on variables precludes the ERG from determining an adjusted HR using reconstructed IPD. Weibull models fit to reconstructed IPD and extended to 28 years are shown in Figure 6.

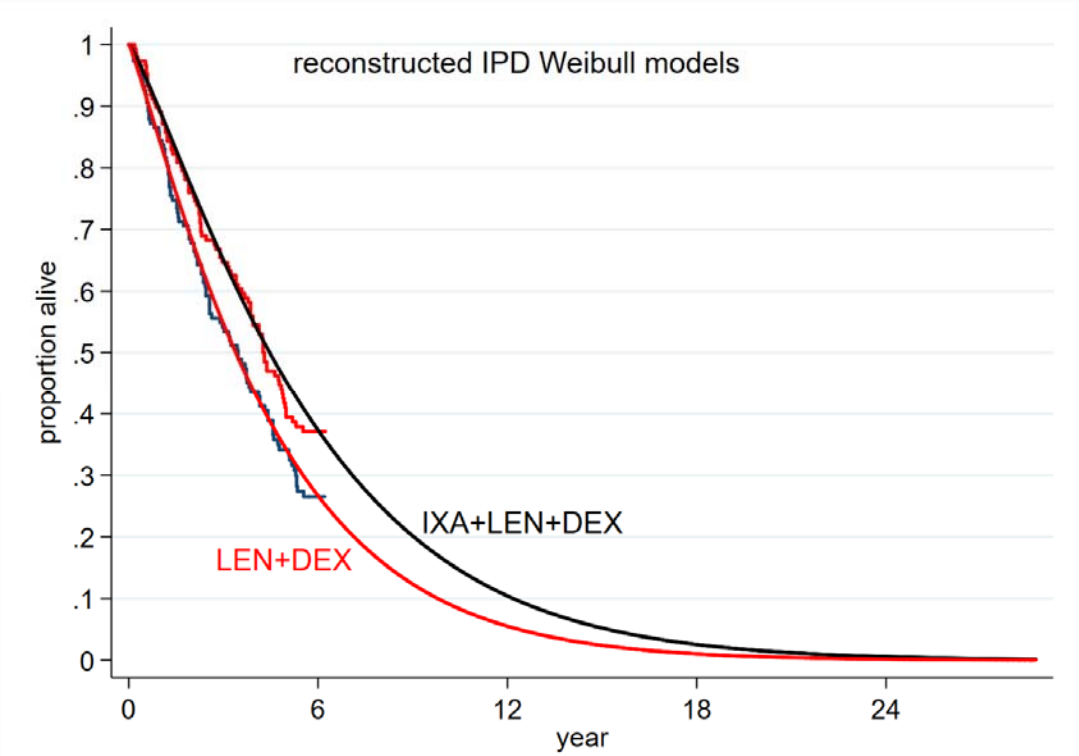

Figure 6: Weibull models using reconstructed IPD from CS Figure 7

When set for generalised gamma models of adjusted OS: 2-stage re-censoring (novel therapies) the company economic model generates an ICER of £65,703 per QALY (PAS company base-case). When the company economic model is set for Weibull models of adjusted OS: 2-stage re-censoring, the ICER is raised to approximately £71,100, an increase of approximately 8%.

The company justify their choice of generalised gamma OS models because *"The generalised gamma curve was considered to provide an estimation of predicted outcomes which most closely aligned with current outcomes observed in the UK by clinical experts"*. Figure 7 compares generalised gamma and Weibull models for each arm to 25 years taken from the economic model. The ERG thinks there is so little difference in predicted survival between generalised gamma (dashed lines) and Weibull (dotted lines) that clinical experts would be unable to distinguish one from the other and therefore on this basis the ERG thinks the Weibull based ICER is as equally valid as the generalised gamma-based ICER.

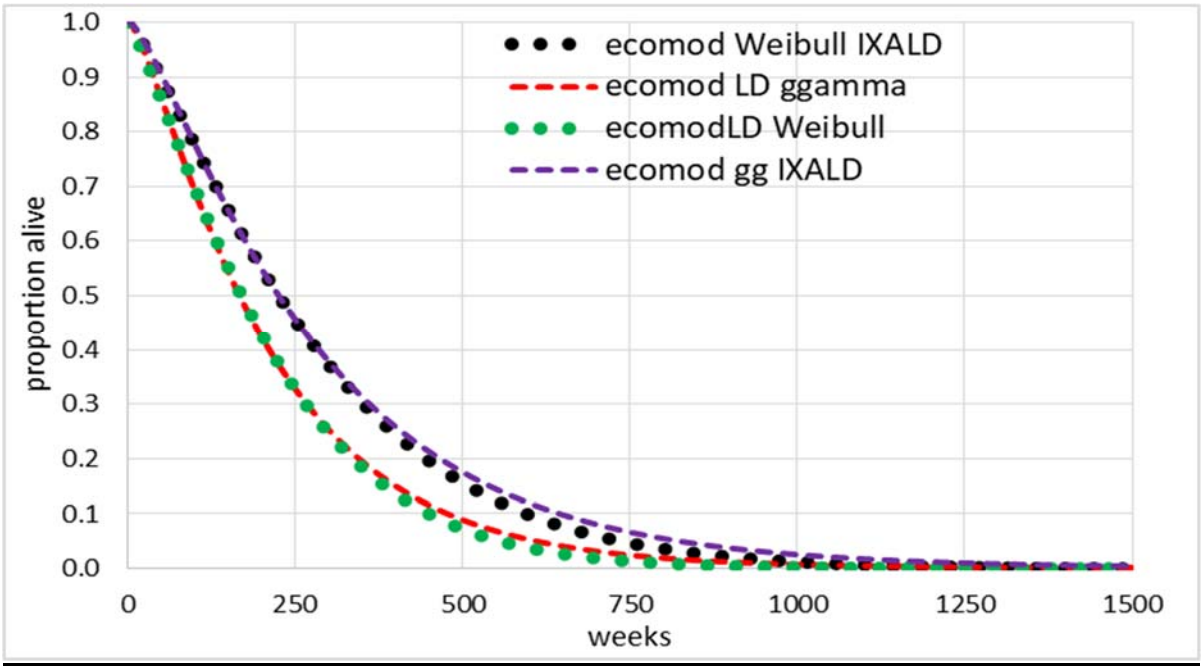

Figure 7: Weibull and generalised gamma models from the company economic model

CS Table 13 presents "*Landmark analyses*" for the generalised gamma models and is shown together with Weibull values (italics) added in by he ERG. Differences beween models are minimal as shown in Table 15.

Table 15. Differences between the overall survival generated from the Weibull and generalised gamma models

Therapies	Parametric model	Proportion alive at			
		10-years	15-years	20-years	25-years
IXA+LEN+DEX	Generalised gamma	16.07%	5.81%	2.10%	0.77%
LEN+DEX		7.84%	1.98%	0.51%	0.13%
IXA+LEN+DEX	Weibull	*14.21%*	*3.99%*	*1.01%*	*0.23%*
LEN+DEX		*6.28%*	*1.04%*	*0.15%*	*0.02%*

The very small difference between generalised gamma and Weibull models generates a 8% increase in ICER and in the ERG opinion indicates great sensitivity of the economic model to small changes in modelling of OS. The appreciable uncertainty associated with the TSE-OS modelling (as exemplified by large differences produced using different methods of adjustment) and the inherent uncertainty in parametric modelling suggest to the ERG that the company deterministic base-case point estimate ICER should be viewed with considerable caution.

When separate parametric modelling for each arm is undertaken using ERG reconstructed IPD (see Figure 5), generalised gamma models perform relatively poorly according to Akaike and Bayesian information criteria scores when compared to Weibull models (see Table 16); across both arms generalised gamma models generate the worst sum information criterion score of six models examined. Therefore, of Weibull or generalised gamma models the ERG prefer the Weibull models for modelling TSE-OS.

Table 16. AIC and BIC scores of parametric models fit to the reconstructed IPD

Model	LEN+DEX arm				Model	IXA+LEN+DEX arm				*Sum across Both arms*
	AIC	BIC	sum	rank		AIC	BIC	sum	rank	
Generalised gamma	403.6	412.7	816.3	5.0	Generalised gamma	376.3	385.3	761.6	5.0	*1577.9*
exponential	403.0	406.0	808.9	1.0	exponential	378.1	381.1	759.2	1.0	*1568.2*
Weibull	402.0	408.0	810.1	2.0	Weibull	376.7	382.7	759.4	4.0	*1569.5*
Gompertz	403.3	409.3	812.6	3.0	Gompertz	379.2	385.2	764.4	6.0	*1577.0*
lognormal	406.3	412.3	818.6	6.0	lognormal	374.8	380.8	755.6	2.0	*1574.2*
loglogistic	403.5	409.5	812.9	4.0	loglogistic	374.8	380.8	755.6	3.0	*1568.5*
AIC Akaike information criteria BIC Bayesian information criteria										

Figure 8 compares the company economic model Weibull models of OS with ERG Weibull models based on ERG reconstructed IPD and fit separately by arm. Median survival (ERG 53.6 and 40.7 months IXA+LEN+DEX and LEN+DEX respectively) are almost the company Weibull model medians (52.2 and 39.1 months respectively); small differences appear in extrapolation beyond approximately 4.5 years. There seems little difference in the gain by IXA+LEN+DEX over LEN+DEX whether company economic models Weibull are considered or the IPD Weibull models. However, the economic model is very sensitive to difference in OS modelling and a difference may emerge if the reconstructed IPD models are implemented with the company economic model.

The ERG used the company's Weibull models in their preferred settings for cost-effectiveness analysis (see Section 6.2).

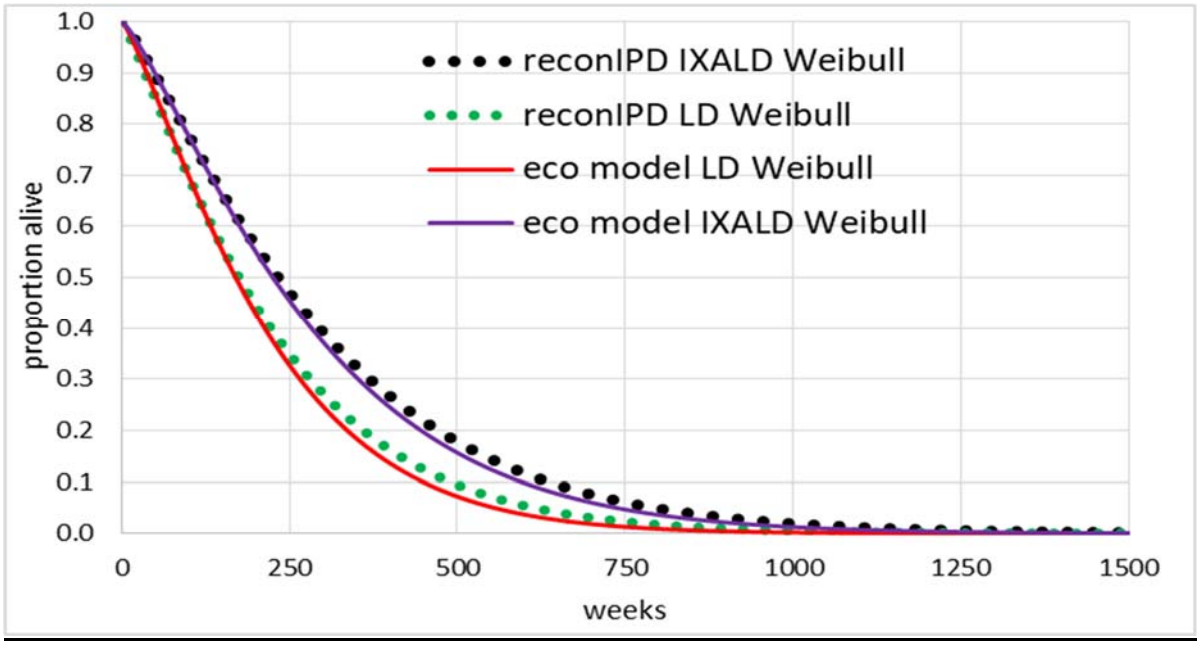

Figure 8: Company economic model Weibull models compared to the reconstructed IPD Weibull models

3.3 Waning of treatment and waning of treatment effect

The company has not included any waning of treatment effect in the CDF submission's base-case analysis. The company has justified this decision saying that any waning is captured adequately in their updated analyses since: *"The updated OS data from TMM1 reflects survival outcomes for >96% of patients who have discontinued treatment with IXA+LEN+DEX and for >99% of patients who have discontinued treatment with LEN+DEX. Therefore, any treatment effect waning is already reflected within these updated OS data"* (CS page 36).

The ERG accept that waning of treatment has almost completely been captured within the observed time of the trial (see Table 12). However, in the opinion of the ERG the waning/discontinuation of treatment is a separate entity from waning of treatment effect. The effect of treatment with regard to outcome may be maintained for various time points after treatment ceases, depending on the drug in question and its effect on the outcome.

It seems clear to the ERG, that the period of observation from the end of treatment to end of observation (approximately 2 years) is too short to fully capture a potential waning of ixazomib's treatment effect. At the end of observation, approximately 35% of patients remain alive and extrapolation of company models assumes that the treatment effect of ixazomib is fully maintained for a further 18 years. It seems to the ERG, that waning of ixazomib's treatment effect will likely start to occur at some point before the 18 years have expired. Waning may start after patients have ceased to be observed. Even if waning should start

immediately after cessation of ixazomib administration, only a small fraction of the potential treatment waning effect would be captured during the subsequent observation period of only approximately two years.

The ERG considers that a lack of waning for a further approximately 18 years (beyond approximately 7.8 or approximately 6.2 years whichever applies) is unlikely and some waning of ixazomib's effect should be included in the models for the 35.5% still alive and at risk at the end of observation. Any waning of treatment effect of LEN+DEX would be experienced by both arms since both receive this treatment, however any waning of the ixazomib treatment effect would only be experienced in the IXA+LEN+DEX arm.

If such waning occurred, the ERG believes that the generalised gamma model (or other model) of OS for the IXA+LEN+DEX after the end of observation would gradually approach and eventually coincide with the model for the LEN+DEX. With very mild waning, this could take until no survivors remain, with more severe waning of IXA+LEN+DEX and LEN+DEX models would occur earlier. The ERG has explored the following three waning scenarios using the company's generalised gamma model.

In all scenarios waning affects only approximately one third of patients and starts at the end of the observation period: a) waning takes 18 years to complete ("slow waning"); b) waning takes 5 years to complete ("fast waning"); c) waning takes 7.5 years to complete. The three scenarios are represented graphically in Figure 9.

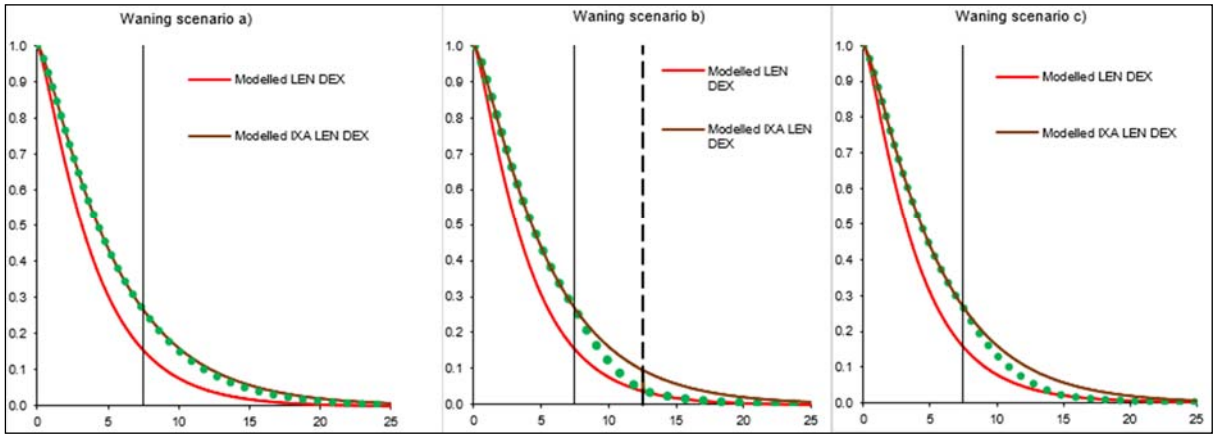

Figure 9: Scenarios of waning of ixazomib treatment effect: the dotted lines represent the waned generalised gamma model of TSE-OS

In section 6.1, the ERG provide the following scenario analyses a) waning takes 18 years to complete ("slow waning"), b) waning takes 5 years to complete ("fast waning"), and c)

waning takes 7.5 years to complete. The impact of making changes in how TSE-OS is modelled (see Section 6.1).

3.4 Conclusions of the clinical effectiveness section

- The ERG suggest that the CS was largely complete with regard to new clinical evidence as outlined in the ToE (Table 12);
    - The phase-3 randomised controlled trial TMM1, was the source of new evidence to support the clinical effectiveness, safety, and cost-effectiveness of IXA+LEN+DEX compared with LEN+DEX for treatment of adults with relapsed or refractory multiple myeloma who have received 2 or 3 prior lines of therapy. The CS included the final analysis of updated OS and cost-effectiveness data collected in the TMM1 trial at a median follow-up time of 85-months.
- The ERG considers that the CS contains potentially biased estimates of the technology's (IXA+LEN+DEX) treatment effects in relation to the control (LEN+DEX) which generate significant uncertainties about the reliability of the clinical effectiveness evidence;
    - The company adjusted the updated OS HR estimate for confounding due to treatment switching after disease progression in patients receiving IXA+LEN+DEX or LEN+DEX. Treatment switching adjustments were conducted via two methods used to remove the effect of subsequent therapies (IPCW method and two-stage method). The two-stage method adjusted HR suggested a statistically significantly improvement in the OS experience in patients receiving IXA+LEN+DEX compared to those receiving LEN+DEX (HR=0.713, 95%CI:0.535, 0.952).
    - The ERG is uncertain regarding the validity and assumptions used in the two-stage model that the company used to adjust for switching to subsequent treatments. No information was provided regarding the secondary baseline, time dependent confounding, or other reasons for switching (besides disease progression) that would be needed for adequate interpretation.
    - The company selected generalised gamma modelling for OS with the only justification that it offered clinically plausible extrapolations. The company Weibull models for OS are almost indistinguishable from the generalised gamma and as valid on grounds of clinical plausibility. Additional analysis conducted by the ERG suggest

that Weibull modelling provides superior fit to the data than does generalised gamma and is a more justified selection for extrapolating OS.

- The assumption that there is no treatment waning of ixazomib does not apply for waning of continuing treatment effect after treatment itself has ceased. These are separate entities. Therefore, the ERG has explored the waning scenarios of waning of treatment effect using the company's parametric modelling (see Section 6.1).

4 COST-EFFECTIVENESS

4.1 Summary and critique of the company's submitted economic evaluation by the ERG

4.1.1 Model structure

The ERG confirms that the economic model used for decision making in the original STA appraisal (TA505), including integration of the ERG scenarios has been updated by the company using the final analysis from TMM1. The company's results and scenarios from the first-round submission can be achieved in the economic model through drop-down options on the 'Main Settings' worksheet.

The updates in the second-round submission describe OS. Please note that they include adjustment for subsequent therapies which are not routinely funded or available in UK clinical practice using the two-stage recensoring and fitted and extrapolated using the generalised gamma parametric model (as described in 3.1.2). They also describe subsequent therapies, time-on-treatment, HRQoL, adverse events, hospitalisations, concomitant medications, costs, ixazomib costs and lenalidomide costs. The ERG's critique of the company's adherence to the Appraisal Committee's preferred assumptions from the terms of engagement are summarised in Table 12 Section 2.3.

4.1.2 Population

Adults with relapsed or refractory multiple myeloma, who have had 2 or 3 lines of prior therapy, (which is a subgroup of patients of final TMM1 study data), have been targeted as per the Appraisal Committee's preferred assumption. The new study has a median follow-up of 85-months (see ToE Table 12 Section 2.3).

4.1.3 Interventions and comparators

IXA+LEN+DEX and LEN+DEX have been used as the intervention and the comparator respectively, as per the Appraisal Committee's preferred assumptions.

4.1.4 Perspective, time horizon and discounting

There have been no changes to the perspective, time horizon and discounting of the model submitted by the company, which was accepted previously by the Appraisal Committee.

4.1.5 Treatment effectiveness and extrapolation

The company submitted the same PFS analysis as submitted in response to ACD following original STA appraisal (ID TA505); this is based on data up to interim analysis IA2 and is therefore less extended follow-up than data now submitted for ToT and for OS, each of which correspond to the final data cut.

- The company's base-case economic model retains Weibull modelling for PFS.
- The company's base-case selects Weibull modelling for ToT. In the base-case setting, whereas PFS and ToT curves for LEN+DEX are similar with ToT slightly ahead of PFS, for IXA+LEN+DEX the difference between ToT and PFS is greater and in contrast ToT lags behind PFS (see Figure 10). This inequity between arms may tend to bias costing in favour of IXA+LEN+DEX.

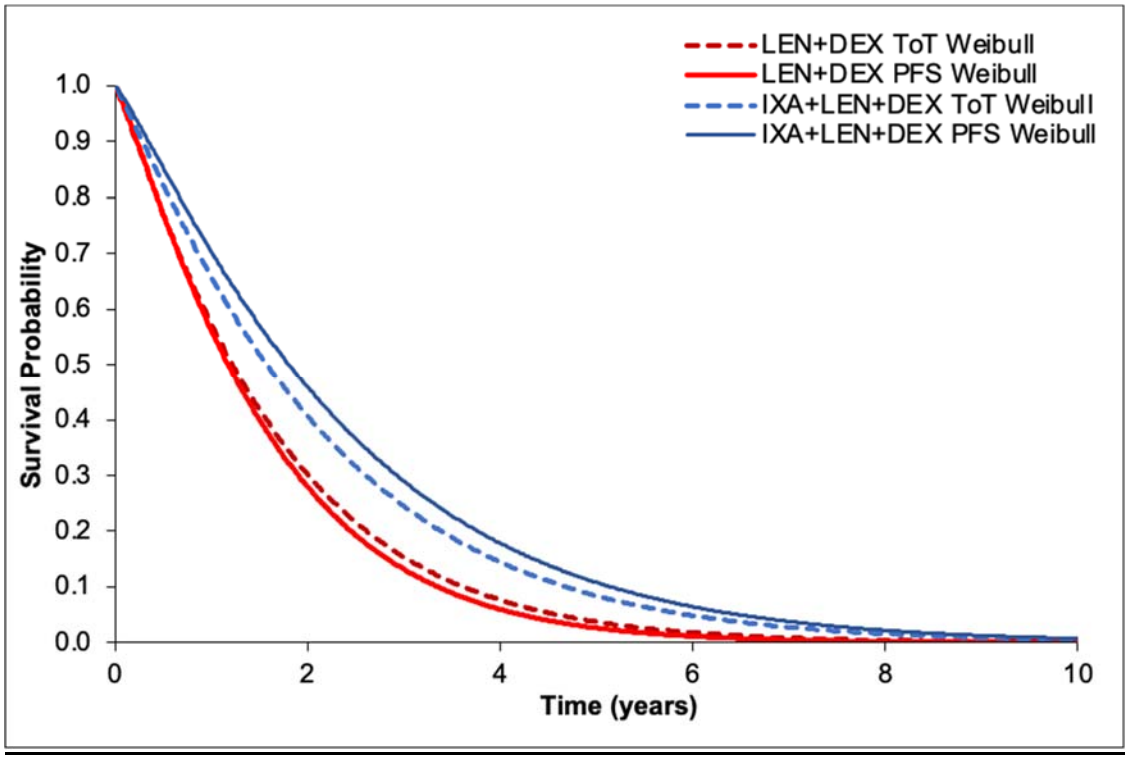

Figure 10: Weibull models for PFS (solid) and ToT (dashed)

The company's analysis of OS is based on the final data cut-off with observation extended to approximately eight years. The company are concerned that subsequent treatments received after progression between arms will confound naïve estimates of OS. The company have submitted results from methods that might mitigate these difficulties. In consequence the company has submitted a completely new analyses of OS (see 3.1.2).

- The company's favoured analysis is that based on a new two-stage adjustment with re-censoring designed to correct for confounding from unequal use of subsequent treatments unavailable in UK practice. This new analysis delivers less added benefit from IXA+LEN+DEX over LEN+DEX than in all previous submissions and is a major driver of the cost-effectiveness analysis that in the base-case delivers an incremental gain of 1.08 LYs (after discounting).

    - Since randomisation could not be stratified by the post-progression treatments received the proposed results cannot be considered to represent a randomised comparison of treatments.
    - Although the ERG agrees that adjustment for post-progression treatments is ideally desirable the company has adopted a two-stage method not specified in the trial protocol. The method used represents a post hoc adoption and in the opinion of the ERG this could potentially lead to implausible outcomes. Results from two types of adjustment were presented: from two-stage adjustment with re-censoring and from adjustment by IPCW; other adjustment methods may have been considered but additional results not reported.
    - The results from the two adjustment methods differed markedly from each other and also to some degree from the unadjusted OS data. Results from IPCW were judged clinically implausible by clinicians at an advisory board conducted by the company in March 2021. Over eight years observation, the two-stage adjustment with re-censoring generated poorer survival for both arms (relative to no adjustment) while generating an improved adjusted HR (0.713; 95%CI 0.535, 0.952). This result appears substantial in the context of CS Document Table 11 (page 26) which lists the numbers of patients in each arm whose survival times were adjusted.

- The company have used generalised gamma parametric modelling to generate TSE-OS curves (see Section 3.2). Alternative parametrics are made available within the economic model. Weibull and generalised gamma models are almost identical but deliver different ICERs indicating considerable sensitivity of to small changes in

modelling of TSE-OS. On the basis of evidence available to the ERG, the ERG favours the choice of Weibull over generalised gamma models.

- The company have provided a scenario analysis that modifies waning of treatment continuation for approximately 1% LEN+DEX and approximately 5% of IXA+LEN+DEX patients respectively. As described in Section 3.3, the ERG believes waning of retention in treatment is a separate issue to waning of a treatment's effect. The time elapsed between ceasing treatment and end of observation was approximately two years and approximately one third of IXA+LEN+DEX patients remained alive at end of observation. The ERG suggests it is unlikely that two years of observation after cessation of treatment would be sufficient to fully capture waning of ixazomib's treatment effect.
    - The company modelling extrapolates OS for approximately 35% of IXA+LEN+DEX patients under the assumption that full effectiveness of ixazomib seen at end of observation is maintained for a further 18 years; the ERG judges this unlikely.

4.1.6 Health related quality of life

The company used updated EQ-5D data from the TMM1, using the data from the population with 2 or 3 prior lines of therapy, as per committee preferred assumptions (see terms of engagement, Table 12).

- The HRQoL data were analysed in line with the methods presented in the original NICE submission (i.e., regression analyses have been performed which account for multiple observations per patient and a potential list of covariates).

Utility regression included: response assessment, age, hospitalisations, and death within 3 months. The company stated that "*grade 3/4 adverse events, gender and race were shown not to be significant drivers of HRQL in the backwards stepwise selection process with the updated data. Therefore, these were not included in the final regression model. However, to ensure no HRQL impact is being missed in relation to adverse events, the decrement assumed in the original NICE submission is applied in the base case (CS Document, Table 16 page 45).*" In response to the ERG clarification question B4 (April submission), the company has suggested that since line of treatment was not found to be a significant

predictor of HRQoL, these were not included in the final regression model. The ERG accepts these justifications.

The absolute utility values were lower when the final analysis was used compared to IA2. The company has stated that *"This is largely driven by the inclusion of baseline EQ-5D-3L (0.658) as a covariate; further exploration of the data and feedback from clinicians indicated that this should be adjusted for (CS Document, Section A.7.5 page 41)."* The ERG agrees with this statement and accepts that the utilities estimated from the final analysis better align with the literature and, also, better reflect patients' HRQoL with RRMM.

4.1.7 Resources and costs

Please see Sections 2.3 (Table 12), 3.1.2, and 3.1.6 for a detailed ERG critique regarding subsequent therapy assumptions made in the CS.

The final analysis of the TMM1 trial the company provides updated follow-up on the adverse events (AE), hospitalisations, and concomitant medications in the IXA+LEN+DEX and LEN+DEX arms.

- These have been updated within the economic model. The AEs, hospitalisations, and concomitant medications were accounted for using the same methodology as in the original STA appraisal (ID TA505). All costs within the economic model were updated by the company to reflect the 2018/2019 cost year – the original NICE submission was based on the 2014/2015 cost year.

Following guidance from NICE, the company conducted all analyses in the CS using the list price of ixazomib. Arising from the initial discussions with NHS England, the company have applied to reinstate a discount PAS which combines the existing [redacted] and the [redacted] offered through the commercial access agreement (CAA) in the CDF, thus offering a [redacted]% straight discount to the NHS list price (a net price of £[redacted] per capsule).

- At the time of writing, the ERG recognise that this is not the final commercial arrangement for ixazomib. The company presented the cost-effectiveness results including the proposed PAS for ixazomib in Appendix F rather than in the main CS document. During the clarification telephone conference with NICE and the company (Thursday 29th April 2021, 15:00), the ERG was advised, by the Associate Director, to conduct base-case and scenario analyses using the proposed PAS for ixazomib. Therefore, this is presented in the ERG report.

In the CS document (page 43) the company has stated that: "*It is assumed that lenalidomide will be available as a generic medicine from* [redacted]*. To reflect this, the cost of lenalidomide is based on the list price of the branded product (Revlimid®) for* [redacted] *(assuming a FAD for this CDF review is published in* [redacted]*) before then being replaced by an estimated generic cost. Therefore, the model assumes* [redacted] *of branded lenalidomide (Revlimid®) costs before applying an assumed generic price for lenalidomide. The generic lenalidomide cost has been estimated by assuming* [redacted] *(i.e., one cycle of generic lenalidomide is assumed* [redacted] *– equivalent to a* [redacted] *discount from the list price of branded lenalidomide).*"

As per the CDF methods guide,[6, 7] Section 5.5.2 statement on price reductions, the ERG note that "*analyses based on price reductions for the NHS will only be considered when the reduced prices are transparent and consistently available across the NHS, and if the period for which the specified price is available is guaranteed*." Therefore, the ERG considers that the lenalidomide price reduction presented in the CS is forthcoming, not a reflection of current NHS practice.

At the 'Kick Off meeting' for this CDF appraisal (5th March 2021, 11.30) attended by the ERG, NICE and the company, the company were requested to not include price changes to generics in their submission. When asked to explain this during the first clarification stage (question B13) the company responded;

"[redacted]"

Acknowledging the response above, the ERG suggest that the company should use the list price throughout for the base-case analysis. (The ERG appreciate that price reductions are included as scenarios in the CS).

- The ERG will explore results with the cost of lenalidomide based on the list price of the branded product (Revlimid®) throughout the model time horizon and

assumptions regarding the inclusion of generic lenalidomide costs will be explored as scenarios.

5 COST-EFFECTIVENESS RESULTS

The company reports deterministic base-case and probabilistic results, as well as sensitivity analysis results for the comparison between IXA+LEN+DEX and LEN+DEX. Outcomes are reported in terms of LYG and QALYs, and the results reported in the form of an ICER expressed as cost per QALY. We present the results (deterministic, probabilistic and sensitivity analysis as presented by the company using the ixazomib list price and approved PAS.

5.1 Company's cost-effectiveness results (deterministic)

The CS company base-case model, using list prices for ixazomib, produces an ICER of [redacted] when IXA+LEN+DEX is compared to LEN+DEX.

This result means that IXA+LEN+DEX compared to LEN+DEX accrues an additional 0.71 QALYs at an additional cost of [redacted]. This is achieved when the model is updated to incorporate the updated clinical evidence from the final analysis of TMM1 relating to: OS (two-stage re-censoring novel therapies) with parametric model fitted and extrapolated using generalised gamma, subsequent therapies, time-on-treatment, HRQoL, adverse events, hospitalisations, concomitant medications, uprated costs, ixazomib costs and lenalidomide costs.

The new base-case also reflects the 2018/2019 cost year, list price for ixazomib and the list price for branded lenalidomide for [redacted]. Results are also presented based on the proposed [redacted] ([redacted] off the NHS list price).

Table 17 summarises the total costs, total life year gained (LYG), total quality-adjusted life years (QALYs) and associated ICERs, for the original STA appraisal (ID TA505) based on IA2 data from TMM1 and the new company base-case based on the final analysis of TMM1.

Table 17. Summary of cost-effectiveness results for the original NICE submission (ID TA505) based on IA2; and the new company base-case based on the final analysis of TMM1

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry (including the original CDF CAA for ixazomib) (CS Table 17)							
LEN+DEX	[redacted]	3.58	2.70	[redacted]	-	-	-
IXA+LEN+DEX	[redacted]	4.85	3.68	[redacted]	1.2675	0.97	£31,691
Cost-effectiveness results from the original NICE submission based on IA2 (deterministic), Based on list price for ixazomib (CS Table 17)							
LEN+DEX	[redacted]	3.58	2.70	[redacted]	-	-	-
IXA+LEN+DEX	[redacted]	4.85	3.68	[redacted]	1.2675	0.97	[redacted]
Cost-effectiveness results from the new company base-case based on the final analysis of TMM1 (deterministic): based on list price for ixazomib (CS Table 18)							
LEN+DEX	[redacted]	3.78	2.47	[redacted]	-	-	[redacted]
IXA+LEN+DEX	[redacted]	4.86	3.18	[redacted]	1.08	0.71	[redacted]
Cost-effectiveness results from the new company base-case based on the final analysis of TMM1 (deterministic): including proposed ixazomib PAS (Appendix F Table 27)							
LEN+DEX	[redacted]	3.78	2.47	[redacted]	-	-	-
IXA+LEN+DEX	[redacted]	4.86	3.18	[redacted]	1.08	0.71	£65,703

CAA, Commercial Access Agreement; CDF, Cancer Drug Fund; DEX, dexamethasone; IA2, interim analysis two; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; LYG, life-year gained; OS, overall survival; PAS, patient access scheme; QALY, quality adjusted life-year; ToT, time-on-treatment

5.2 Company's sensitivity analyses

5.2.1 Company's probabilistic results (list price)

The scatterplot and cost-effectiveness acceptability curve (CEAC) generated by the company PSA results are shown in Figure 11 and Figure 12, respectively. The company's

PSA based on the list price for ixazomib produced an ICER of [redacted], which is similar to the deterministic ICER.

Figure 11: Incremental cost-effectiveness plane of probabilistic results (based on list price for ixazomib)

Figure 12: Cost-effectiveness acceptability curve (list price for Ixazomib)

It can be seen in Figure 12 that using the list price for ixazomib, treatment with IXA+LEN+DEX compared to LEN+DEX is [redacted] at these willingness-to-pay thresholds.

5.2.2 Company's probabilistic results (PAS)

The company's PSA results based on the proposed PAS for ixazomib produced an ICER of approximately £65,900, which is in line with the deterministic ICER.

The scatterplot and CEAC generated by the company PSA results are shown in Figure 13 and Figure 14, respectively.

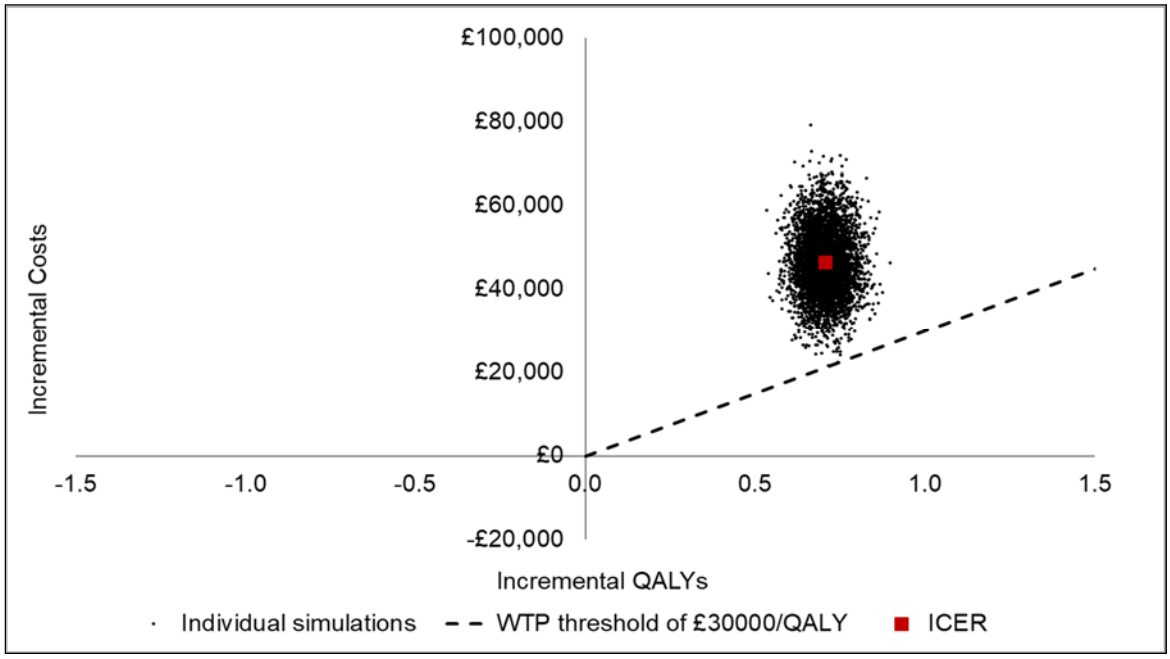

Figure 13: Incremental cost-effectiveness acceptability curve (based on proposed PAS)

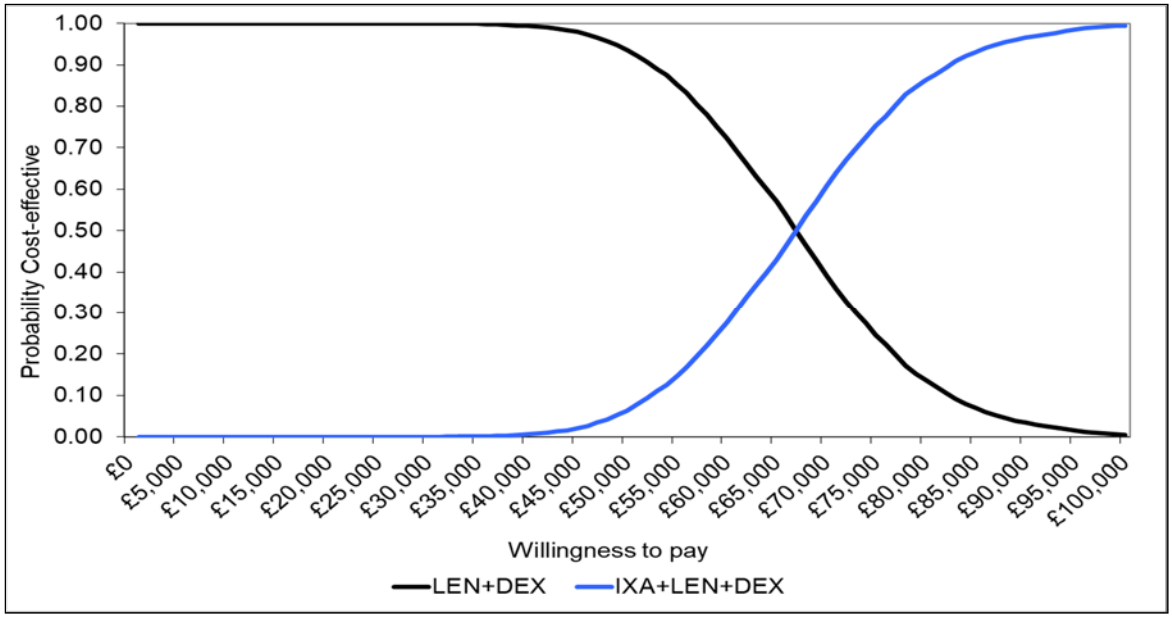

Figure 14:Cost-effectiveness acceptability curve (based on proposed PAS)

Figure 14 shows the CEAC based on the PAS for ixazomib. These results show that there is a zero probability that treatment with IXA+LEN+DEX is cost-effective compared to LEN+DEX at a willingness to pay threshold of £30,000 per QALY.

The ERG identified several concerns in the company's PSA, which may impact on the PSA results.

- the choice of distribution for to reflect uncertainty around costs. At the clarification stage, the company provided justification about their choice of the normal distribution. There was no functionality in the model to easily select other distributions.

- the ERG found that for several input parameters for the rate of AEs their base-values were not within the upper/lower bounds, which the company later clarified that the parameters for distributions used for these adverse event inputs were incorrectly calculated.

5.3 One-way sensitivity analysis

One-way sensitivity analyses were conducted using the list price and proposed PAS for ixazomib to explore the robustness of ICER to individual changes to inputs.

- The parameters with the greatest impact on model outcomes were coefficients relating to the estimation of utility (age and intercept).

- To a lesser extent, the proportion of patients receiving specific types of subsequent therapy were shown to impact the ICER.

The ERG found that the upper and lower bounds were in reverse order for the coefficient associated with age. The company acknowledged there was an error and provided an updated tornado diagram based on a re-run of the one-way sensitivity analyses using the list price (see Figure 15) and proposed PAS (see Figure 16) for ixazomib.

[redacted]

Figure 15: Updated tornado diagram for the comparison between IXA+LEN+DEX and LEN+DEX (based on list price for ixazomib)

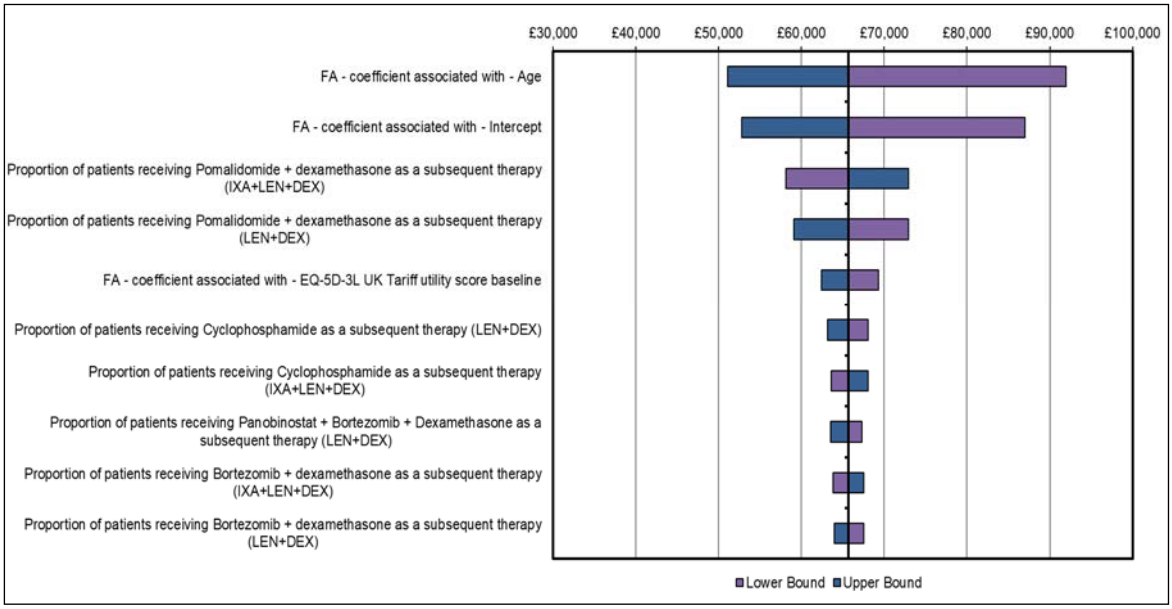

Figure 16: Updated tornado diagram for the comparison between IXA+LEN+DEX and LEN+DEX (based on proposed PAS for ixazomib)

5.4 Company's scenario analyses

The company undertook several scenario analyses using the list and PAS prices for ixazomib. The company undertook the following scenario analyses (*see* CS Document Table 20 and Appendix F Table 29 for further information):

- Unadjusted TMM1 OS data: Use TMM1 OS data unadjusted for subsequent therapies
- Adjusted OS (using the two-stage methods with re-censoring).
    - Adjusted OS using the two-stage methods without recensoring.
    - Adjusted OS (IPCW): Adjusted OS using the IPCW treatment switching analyses.
- Treatment waning: include adjustment for treatment waning effect in both treatment arms
- Generic lenalidomide costing: Assume a generic LEN cost at a [redacted], [redacted], and [redacted] discount of the list price
- Ixazomib costing: [redacted] for ixazomib

5.4.1 Using list price for ixazomib:

- Using the updated model, with an [redacted] had the greatest impact on the ICER, decreasing the ICER by approximately [redacted].

- Including adjustment for a treatment waning effect in both treatment arms resulted in a [redacted] to the base-case ICER.

- The base-case assumes the list price for lenalidomide for [redacted] followed by an estimate of the generic cost. The generic cost of lenalidomide was informed based on a [redacted] discount applied to lenalidomide. Given the uncertainty the company undertook several scenario analyses for the generic lenalidomide costs. Assuming a generic lenalidomide cost at [redacted] discount of the list price increased the ICER by [redacted] and reductions to the ICER by [redacted] and [redacted], respectively.

5.4.2 Including proposed ixazomib PAS:

- Using the updated model, with an [redacted] had the greatest impact on the ICER, decreasing the ICER to approximately £38,200.

- Including adjustment for a treatment waning effect in both treatment arms resulted in a -£4 decrease to the base-case ICER.

- The base-case assumes the list price for lenalidomide for [redacted] followed by an estimate of the generic cost. The generic cost of lenalidomide was informed based on [redacted] discount applied to lenalidomide. Given the uncertainty the company undertook several scenario analyses for the generic lenalidomide costs. Assuming a generic lenalidomide cost at [redacted] discount of the list price increased the ICER by [redacted] and reductions to the ICER by [redacted] and [redacted], respectively.

5.5 Model validation and face validity check

The ERG conducted a face validity check of the model submitted by the company and found that the company have adhered to the majority of the Appraisal Committee's preferred assumptions from the ToE. However, there are some key deviations which are summarised and critiqued by the ERG in Section 2.3 and are also listed in Table 12.

- The ERG opinion is that the face validity of the model is questionable.
- The partitioning of LY gain and QALY gain appears uncertain and adds to the uncertainty of economic modelling. (detailed in ERG section 3.1.6).

The ERG has examined the plausibility of disaggregated LYs by health state. Using the two-stage adjustment method provides discounted results as shown in Table 18.

Table 18. Model comparison

Model name	Effect	Therapy	Median OS months	Median OS year	HR (95% CI)	Total LYs	LYs	
							Pre-Progr.	*Post-Progr.*
Unadjusted	Presumed "positive" effect of novel therapies = INCLUDED	IXA+LEN+DEX	53	4.42	0.845 (0.642, 1.114)	4.89	*2.25*	*2.65*
		LEN+DEX	43	3.58		4.08	*1.50*	*2.59*
		Incremental	10	0.83		0.81	0.75	0.06
TSE (re-censored* + adjust for baseline characteristics†)	Presumed "positive" effect of novel therapies = EXCLUDED	IXA+LEN+DEX	51.4	4.28	0.713 (0.535, 0.952)	4.86	*2.25*	*2.62*
		LEN+DEX	41.5	3.46		3.78	*1.50*	*2.29*
		Incremental	9.9	0.83		1.08	0.75	0.33
CI, confidence interval; HR, hazard ratio; LY, life-year; OS, overall survival								

The ERG considers that results in Table 18 suggest that;

- The treatment switching adjustment has a more substantial impact on the LEN+DEX arm, as post-progression LY drops from 2.59 to 2.29 years, which represents 0.3 year (3.6 months).

- Conversely, using the same method there is an almost identical post-progression LY in the IXA+LEN+DEX arm between the unadjusted an adjusted analyses respectively, i.e., 2.65 years versus 2.62 years, representing a difference of 0.03 years (approximately 11 days) which appears to be negligible and/or insignificant.

- When asked to comment on this result at first round clarification stage (question B1), the company replied that "*the ERG's analysis demonstrates that OS reduces for both treatment arms when subsequent therapies which are not routinely funded or available in UK practice are adjusted for*", then explained that "*the observed difference in LY adjustment on removal of novel therapies between the two treatment arms is due to the differences in subsequent therapies received by these patients*" taking several examples such as the proportion of patients who received subsequent therapy based on daratumumab, elotuzumab, and autologous stem-cell transplant.

- The ERG view is that the company's response is unsatisfactory. Indeed, the ERG's analysis has precisely emphasised that the effect of adjustment appears to be negligible on the IXA+LEN+DEX arm. Secondly, as stated in section 3.1.6.2, the ERG questioned the impact that small differences in subsequent therapies may have on OS (daratumumab received by 31/149=21% in LEN+DEX as opposed to 19/148=13% in IXA+LEN+DEX, elotuzumab [7/149=5% versus 3/148=2%, respectively] and autologous stem-cell transplant [9/149=6% versus 1/148=0.7%, respectively]. It is possible that the company's model has over-adjusted OS analyses.

- While in the section 3.1.6.2 the ERG highlighted that the impact of adjustment was apparently minimal when examining incremental median OS estimate (median OS dropped by approximately 1.5 months in both arms), however, it appears not plausible to the ERG that post-progression LY before/after adjustment for subsequent therapies only drops by 11 days in the IXA+LEN+DEX arm and by 3.6 months in the LEX+DEX arm.

- The ERG view is that the reduction in post-progression LY after adjustment should have been higher in the IXA+LEN+DEX arm and/or lower in the LEN+DEX arm.

- The ERG believes this concern to be of importance. After adjustment, the post-progression LY gain, as obtained from the company's model, represents 0.33/1.08 = 30.5% of total LY gain which is considerable.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

During the clarification telephone conference with NICE and the company (Thursday 29th April 2021, 15:00), the ERG was advised by the Associate Director to undertake the ERG base-case and scenario analyses using the proposed PAS for ixazomib. Therefore, results are presented using the discounted price for ixazomib.

6.1 Exploratory analysis undertaken based on the company's base-case

In view of the ERG's concerns, we have undertaken the following additional exploratory analysis using the company model:

A. Based on the company's economic model and Weibull parametric model for adjusted OS: 2-stage re-censoring (novel therapies)

In Table 19 we present deterministic results of the exploratory analysis undertaken by using the Weibull parametric model to model OS. These results show that the ICER increases to approximately £71,100 per QALY.

Table 19. Deterministic results using the Weibull model for overall survival (using the proposed PAS for ixazomib)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER £/QALY
LEN+DEX	[redacted]	2.43	[redacted]	-	-
IXA+LEN+DEX	[redacted]	3.08	[redacted]	0.65	£71,093
ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year					

B. Using the branded cost of lenalidomide throughout model

Table 20 shows the deterministic results using the branded cost of lenalidomide throughout the model. These results show that the ICER increased to approximately £91,293 per QALY.

Table 20. Deterministic results using the branded cost of lenalidomide throughout model (using the proposed PAS for ixazomib)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER £/QALY
LEN+DEX	[redacted]	2.47	[redacted]	-	-
IXA+LEN+DEX	[redacted]	3.18	[redacted]	0.71	£91,293
ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year					

C. Using the company's estimate of the generic cost of lenalidomide throughout model

In Table 21 we present the results based on the company's estimate of the generic costs of lenalidomide used throughout the model. These results show that ICER decreased to £65,594 per QALY.

Table 21. Deterministic results using the company's estimate of the generic cost of lenalidomide throughout model (using the proposed PAS for ixazomib)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER £/QALY
LEN+DEX	[redacted]	2.47	[redacted]	-	-
IXA+LEN+DEX	[redacted]	3.18	[redacted]	0.71	£65,594
ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year					

D. Treatment waning

The results in Table 22 shows that applying waning to the benefits of treatment after treatment itself has stopped, led to an increase to the company's ICER.

Table 22. Waning of the treatment effect (using the proposed PAS for ixazomib)

Scenario	Section in main ERG report	LEN+DEX		IXA+LEN+DEX		Cost per QALY
		Costs	QALYs	Costs	QALYs	
Waning takes 18 years to complete (generalised gamma model for OS)	Section 3.3	[redacted]	2.47	[redacted]	3.14	£69,497
Waning takes 5 years to complete (generalised gamma model for OS)		[redacted]	2.47	[redacted]	3.03	£85,100
Waning takes 7.5 years to complete (generalised gamma model for OS)		[redacted]	2.47	[redacted]	3.06	£79,822
Waning takes 18 years to complete (Weibull model for OS)		[redacted]	3.71	[redacted]	3.05	£74,026
ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year						

6.2 ERG's preferred assumptions and additional analysis

Based on the ERG's concerns, we have made changes to the company model to form the ERG's base-case.

In Table 23, we present the changes with justification and the results of each change, then present the results for making all changes simultaneously forming the ERG base-case. Based on the individual changes, results show that using the list price for lenalidomide had the greatest impact to the company's base-case ICER.

Table 23. ERG's preferred model assumptions (using the proposed PAS for ixazomib)

ERG preferred assumption	**Scenario detail**	**Brief rationale and section in ERG report**	**Results (Impact to base-case ICER)**
Company base-case			**£65,703**
Use of Weibull model for OS	In this scenario, the ERG selected 'Weibull' from the 'Main Settings' worksheet.	The ERG considers that the company's 2-stage adjusted KM plots of overall survival and the Weibull models are plausible to extrapolate overall survival. (see Section 4.1.5)	£71,093 (+£5,390)
Use the list price for branded lenalidomide throughout the model	The ERG preferred assumption is to not assume a generic lenalidomide cost (the company base case submission included a list price for branded lenalidomide for [redacted].	The ERG considers that the lenalidomide price reduction presented in the CS is forthcoming, not a reflection of current NHS practice (see Section 4.1.7).	£91,293 (+25,590)
ERG base-case: use the Weibull model for OS and	The ERG's base-case analysis comprises making these changes simultaneously.	The ERG implemented these changes simultaneousl	£98,811 (+33,108)

use the list price for branded lenalidomide		y to assess the cost-effectiveness of IXA+LEN+DEX compared to LEN+DEX for treating relapsed or refractory multiple myeloma based on the ERG's preferred assumptions.	
CS, company submission; ERG, Evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival			

6.3 ERG deterministic base-case results

Under the ERG's preferred assumptions, the results show that treatment with IXA+LEN+DEX is approximately [redacted] more costly than treatment with LEN+DEX, and expected to yield an additional 0.65 QALYs, equating to an ICER of approximately £98,800 per QALY (see Table 24).

Table 24. ERG deterministic results based on cost per QALY gained (using the proposed PAS for ixazomib)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER £/QALY
LEN+DEX	[redacted]	2.43	[redacted]	-	-
IXA+LEN+DEX	[redacted]	3.08	[redacted]	0.65	£98,811
ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year					

6.4 Results of the sensitivity analyses and scenario analyses undertaken by the ERG

6.4.1 Probabilistic sensitivity analysis

The mean results of the probabilistic sensitivity analyses are presented in Table 25. The ERG suggests that these results are in good agreement with the deterministic results.

Table 25. Probabilistic sensitivity analysis results based on ERG's preferred assumptions (using the proposed PAS for ixazomib)

Technologies	Total costs	Incremental costs	Total QALYs	Incremental QALYs	Cost per QALY

LEN+DEX	[redacted]	[redacted]	2.42	-	-
IXA+LEN+DEX	[redacted]	[redacted]	3.08	0.65	£99,022
ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year					

Figure 17 shows the incremental cost-effectiveness plane with each iteration of the incremental costs and QALYs for the comparison between IXA+LEN+DEX versus LEN+DEX.

These results show that treatment with IXA+LEN+DEX is likely to yield modest benefits in terms QALYs. Based on the iterations, there is little uncertainty around the incremental QALYs but more variability around the incremental costs.

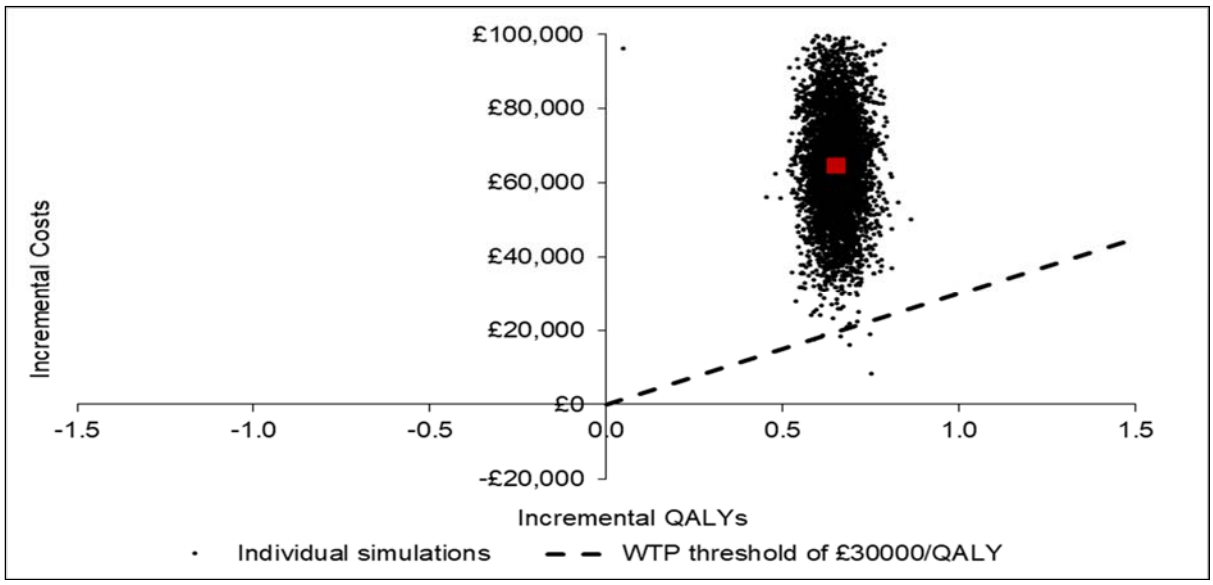

Figure 17: Incremental cost-effectiveness scatterplot for the comparison between IXA+LEN+DEX versus LEN+DEX (using the proposed PAS for ixazomib)

Figure 18 shows the results of the probabilistic sensitivity analysis in the form of a CEAC for both treatment options. The curves show the proportion of iterations in which treatments are cost-effective at different willingness-to-pay thresholds for a QALY. These results show that at a willingness-to-pay threshold of £30,000 per QALY, treatment with IXA+LEN+DEX has a zero probability of being cost-effective.

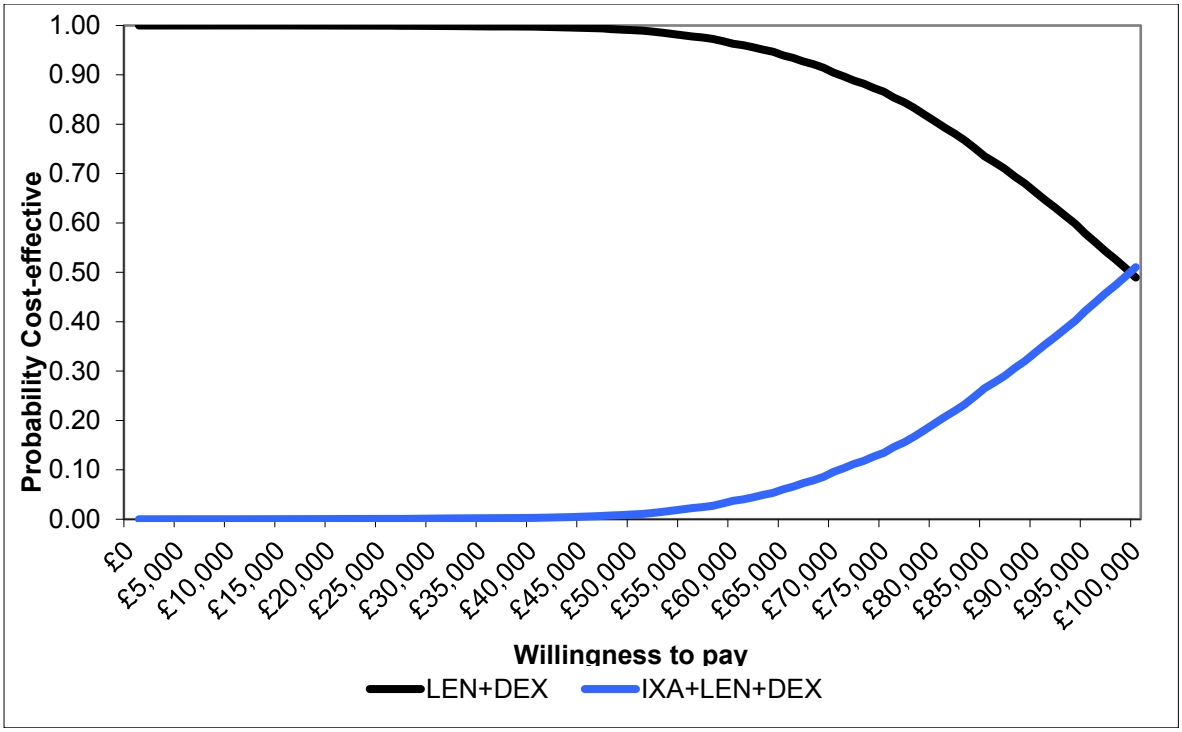

Figure 18: Cost-effectiveness acceptability curves for LEN+DEX and IXA+LEN+DEX (using the proposed PAS for ixazomib)

6.4.2 One-way sensitivity analysis

In Figure 19 we report the deterministic one-way sensitivity analysis results based on the ERG's base-case. These results show that the coefficients associated with age and the intercept had the greatest impact to the ICERs.

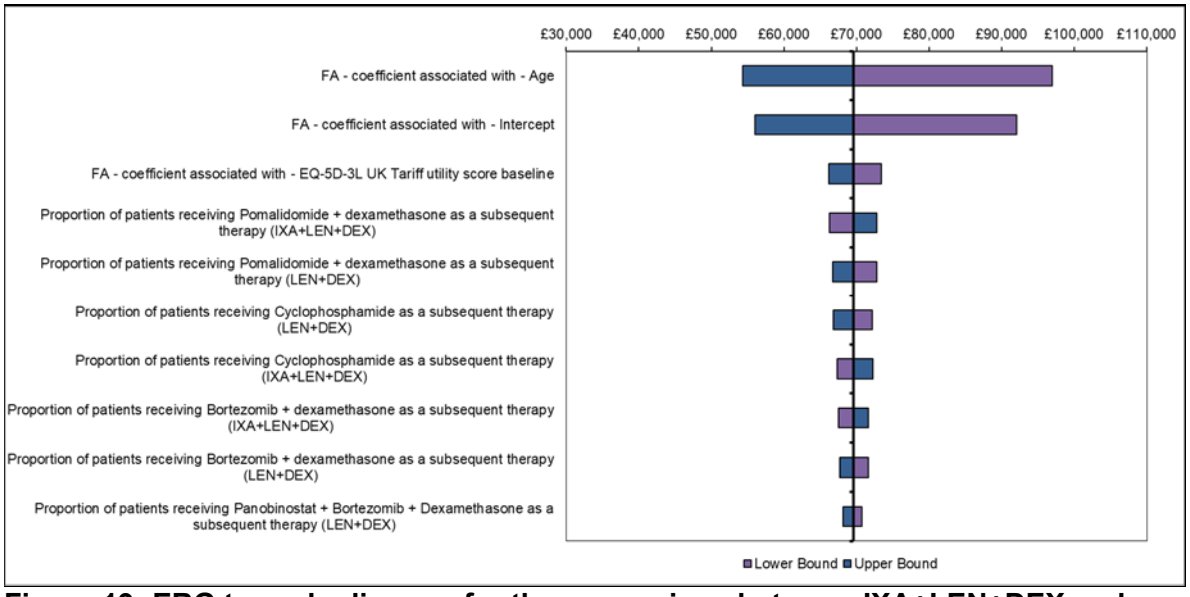

Figure 19: ERG tornado diagram for the comparison between IXA+LEN+DEX and LEN+DEX (based on proposed PAS for ixazomib)

6.4.3 ERG scenario analyses

The ERG undertook several scenario analyses to explore the impact to the ERG's base-case results, with the results reported in Table 26. Under different waning scenarios increased the ICER from approximately £102,800 to £115,800 per QALY.

Table 26. Exploratory analyses based on the ERG's base-case results (based on the proposed PAS for ixazomib)

Scenario	LEN+DEX		IXA+LEN+DEX		Cost per QALY
	Costs	QALYs	Costs	QALYs	
ERG base-case	[redacted]	2.43	[redacted]	3.08	£98,811
Waning takes 18 years to complete (Weibull model for OS)	[redacted]	2.43	[redacted]	3.05	£102,832
Waning takes 5 years to complete (Weibull model for OS)	[redacted]	2.43	[redacted]	2.99	£115,788
Waning takes 7.5 years to complete (Weibull model for OS)	[redacted]	2.43	[redacted]	3.03	£107,348
ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year					

6.5 Conclusions of the cost-effectiveness section

Adhering to the majority of the ToE, the company have presented the most recent data from the 30 September, 2020 data cut of the phase-3 randomised controlled trial named TMM1. This was the source of new evidence to support the safety, clinical effectiveness, and cost-effectiveness of IXA+LEN+DEX compared with LEN+DEX for treatment of adults with relapsed or refractory multiple myeloma who have received 2 or 3 prior lines of therapy. The company submission included the final analysis of updated OS and cost-effectiveness data collected in TMM1 trial at a median follow-up time of 85-months.

- The company have made significant changes since their original CS by adopting the majority of the Appraisal Committee's key assumptions as outlined in the ToE. However, there are some key deviations which are summarised and critiqued by the ERG in Section 1.1 and are also listed in Table 12 Section 2.3.

- Substantial uncertainty remains around the reliability of the cost-effectiveness evidence submitted. In particular, the ERG believes the adjustments to OS data (for both study arms: IXA+LEN+DEX and LEN+DEX), using the final analysis of TMM1

study were not adequately justified by the company and may have led to an artificially overestimated OS HR in favour of the ixazomib arm.

- The company's chosen two-stage adjustment based on final cut off data when used in conjunction with AI-2 cut-off PFS may introduce untestable anomalies such that the face validity of the analysis is threatened and its suitability for use in a partitioned survival model questionable.

    - In the presence of such unexaminable anomalies the company's selection of generalised gamma modelling for OS with the only justification that it offered clinically plausible extrapolations adds to the uncertainty in the economic modelling.

    - The company Weibull models for OS are almost indistinguishable from the generalised gamma and as valid on grounds of clinical plausibility. The ERG additional analysis suggests that Weibull modelling provided superior fit to the reconstructed IPD than does generalised gamma and in consequence is a more justified selection for extrapolating OS.

- The company's updated submission is based on an economic analysis of IXA+LEN+DEX compared to LEN+DEX. While the model captures the key features for people undergoing treatment for relapse/refractory multiple myeloma, under the company's assumptions the base-case results are likely to higher than that presented.

- Changes to the some of the company's assumptions resulted in an increase to the ICER. The company's updated base-case (including the proposed PAS for ixazomib) yielded a gain of 0.71 QALYs costing an additional [redacted], resulting in an ICER of £65,703 whereas the ERG base-case yielded a gain of 0.65 costing an additional [redacted], resulting in an ICER of £98,811. This difference is achieved through a change in two assumptions.

    - First, the choice of the Weibull parametric to model overall survival using the 2-stage re-censoring (novel therapies).

    - Second, the using the list price for the branded lenalidomide. Results from the PSA showed that treatment with IXA+LEN+DEX compared to LEN+DEX is not likely to be cost-effective at current willingness-to-pay thresholds.

7 END OF LIFE

The ERG agrees that ixazomib does not meet the end-of-life criteria as stated in the terms of engagement shown in Table 12.

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9 Appendix

9.1 Appendix 1

In the Appendix Figure 1, we present the adjusted OS using the two-stage re-censoring (novel therapies) KM plots for IXA+LEN+DEX and LEN+DEX from the information obtained from the economic model.

Appendix Figure 1: Detail of the adjusted OS: 2-stage re-censoring (novel therapies) for each arm

9.2 Appendix 2

9.2.1 ERG reconstructed IPD

The ERG undertook exploratory analysis based on the company's base-case model, by using the ERG's Weibull parametric model fitted to reconstructed IPD for overall survival. In Appendix Table 1, the results show that the ICER increased to approximately £75,500 per QALY.

Appendix Table 1. Exploratory analysis, using the ERG's reconstructed IPD and Weibull models for adjusted OS: 2-stage re-censoring (based on proposed PAS for ixazomib)

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
LEN+DEX	[redacted]	2.60	[redacted]	-	-
IXA+LEN+DEX	[redacted]	3.22	[redacted]	0.62	£75,471

ICER, incremental cost-effectiveness ratio; IPD, individual patient data; QALY, quality adjusted life-year

9.3 Appendix 3

9.3.1 Additional clarification question

Clarification request A1 submitted to the company (September 27) asked:

'A.1 For each of the four Kaplan-Meier plots shown in Figure 7 (Two stage adjustment with re-censoring), CS Document, pg. 33. Please supply data in the form shown in the Table 25. It would be appreciated if this information could be supplied in Microsoft Excel.'

Patient-level information

Timepoint	Number at risk	Event	Censored	Survival(t)
T=0	N=???	0	0	100%
T=???	N=???	N=???	N=???	???
T=???	N=???	N=???	N=???	???
Etc…	Etc…	Etc…	Etc…	Etc…

The implicit purpose of this request was to obtain the IPD underlying the development of the company's OS models, particularly the TSE-OS based models. This is a standard request that has made by the ERG for numerous previous assessments and has been almost universally responded to by companies and has allowed ERG to cross check the company modelling.

The response provided by the company (October 7) did not provide the information sought by the ERG and appeared to be incomplete for TSE-OS data. The ERG therefore asked NICE to request additional clarification and this was responded to by the company October 13. This response provided information regarding how the data provided the first time (October 7) was obtained. In particular this response mentioned:

This has no impact within the base case economic model, as these Kaplan–Meier curves are not implemented in the model calculations.

And

The Stata commands used by the company (as summarised below).

The data used for the first command is thus far unavailable to the ERG. Consequently, the ERG has no way to validate the company's TSE-OS outputs or their parametric modelling.

In short, the company have so far been unable to provide data relevant to the ERG conducting independent analysis of the validity of the company's modelling. This may be due to misinterpretation of the intent of the original ERG request.

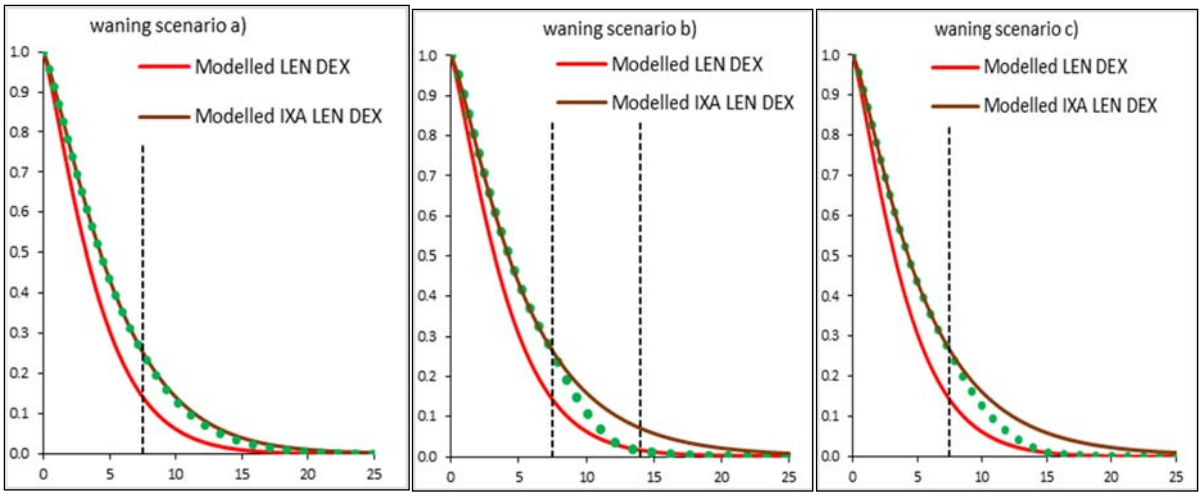
AND

the maximum time we have Kaplan–Meier data for IXA+LEN+DEX is 401 weeks for the unadjusted OS analysis and 324 weeks for the adjusted OS analysis.

This would appear to correspond to the pale green plot (adjusted IXA+LEN+DEX) in CS Figure 7; unfortunately, this graph too compressed for easy interpretation.

9.4 Appendix 4

9.4.1 Waning of ixazomib treatment effect



Appendix Figure 2: Scenarios of waning of ixazomib treatment effect: the dotted lines represent the waned Weibull model of TSE-OS

Title: *Multiple myeloma (relapsed, refractory) - Ixazomib (with lenalidomide and dexamethasone) (CDF Review of TA505) Appraisal 1635.* ***Addendum***

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Declared competing interests of the authors
None.

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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 Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Please note that: *Sections highlighted in* [redacted] *are* [redacted]. *Sections highlighted in* [redacted].

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List of Tables

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Content of addendum

In this addendum, all analyses will be based on the ERG's preferred assumption of using the Weibull parametric model of the adjusted overall survival: 2-stage re-censoring (novel therapies) and using the company's estimate of the discounted price for lenalidomide throughout the model time horizon, as advised by NICE.

This addendum includes the following:

- Re-run of the ERG's base-case by using the company's assumed level of discount for lenalidomide throughout the model
- Sensitivity analyses (one-way and probabilistic)
- Re-run of our scenario analyses

1.1 ERG's preferred base-case and sensitivity analyses

In this section we report the ERG's deterministic results for the comparison between IXA+LEN+DEX and LEN+DEX in *"Adults with relapsed or refractory multiple myeloma, who have had 2 or 3 lines of prior therapy, which is a subgroup of patients of final TMM1 study data"*. Additionally, we report the one-way and probabilistic sensitivity analyses results.

1.1.1 ERG's base-case deterministic results

Based on our critique of the company's economic model, the ERG suggested amendments are as follows:

- Using the Weibull parametric to model adjusted overall survival: 2-stage re-censoring (novel therapies)

Under the ERG's preferred assumptions, and the company's assumed level of discount for lenalidomide throughout the model, the base-case results in Table 1 generate an ICER of approximately £71,000.

Table 1 Cost-effectiveness results (deterministic), using the ERG's assumptions (based on the proposed PAS for ixazomib)

Technologies	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
LEN+DEX	[redacted]	2.43	[redacted]	-	-
IXA+LEN+DEX	[redacted]	3.08	[redacted]	0.65	£70,975

ICER, Incremental cost-effectiveness ratio; QALY, Quality adjusted life years

1.1.2 ERG's one-way sensitivity analysis results

In Figure 1, we report the one-way sensitivity analyses in the form of a tornado diagram based on the ICERs for the comparison between IXA+LEN+DEX and LEN+DEX. The parameters with the greatest impact on model outcomes were coefficients relating to the estimation of utility.

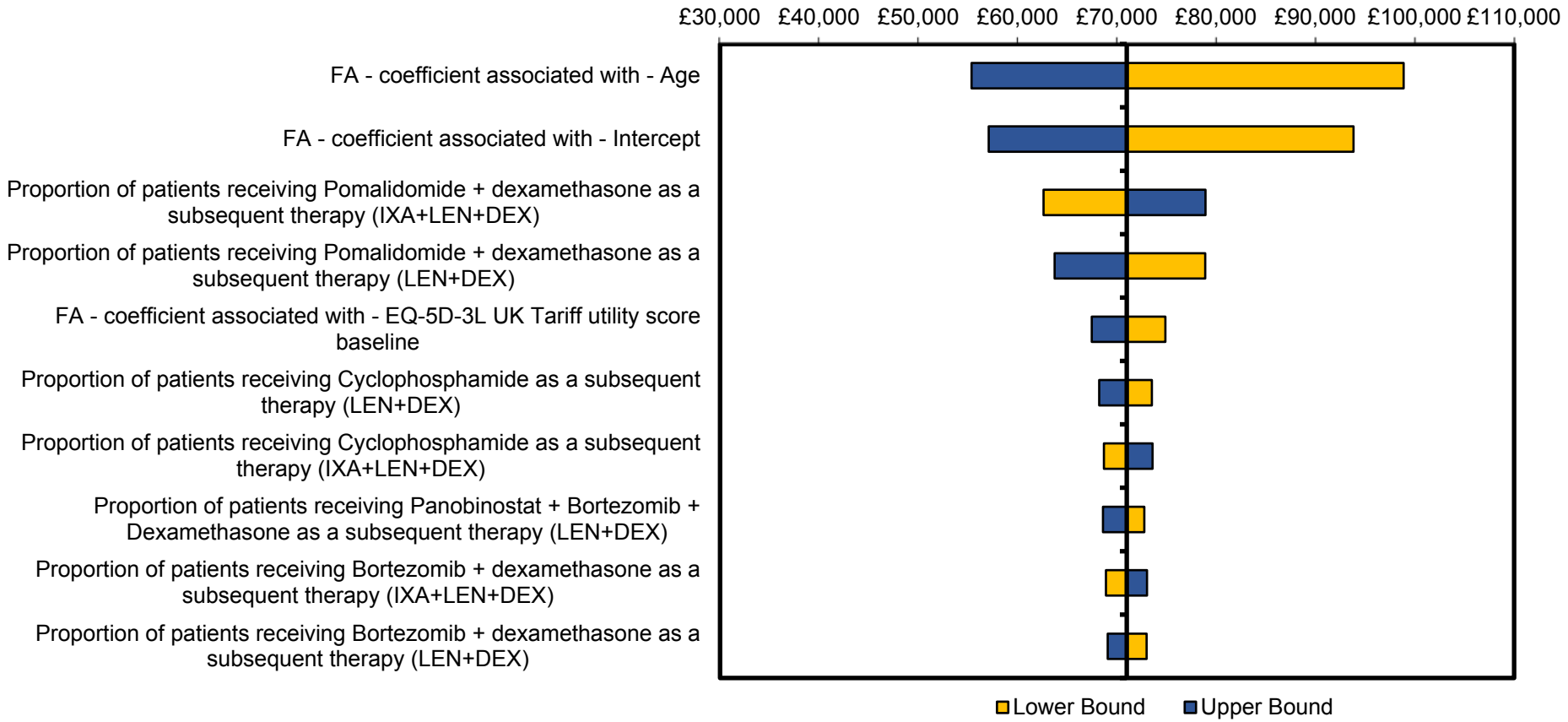

Figure 1 Tornado plot of deterministic sensitivity analysis: impact on ICER results (ERG) (based on the proposed PAS for ixazomib)
Abbreviations: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; FA, final analysis.

1.1.3 ERG's probabilistic sensitivity analysis results

We present the probabilistic sensitivity analysis results in Table 2. The results produced an ICER of approximately £71,100, which is similar to the deterministic ICER.

Table 2 Probabilistic sensitivity analysis results for ERG's base-case (based on proposed PAS for ixazomib)

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
LEN+DEX	[redacted]	2.42	[redacted]	-	-
IXA+LEN+DEX	[redacted]	3.07	[redacted]	0.65	£71,095
ICER, Incremental cost-effectiveness ratio; QALY, Quality adjusted life years					

In Figure *2* and Figure 3, we report the results on a scatterplot and CEAC, respectively. The results in Figure 3 show that at a willingness-to-pay threshold of £30,000 per QALY, treatment with IXA+LEN+DEX has a zero probability of being cost-effective.

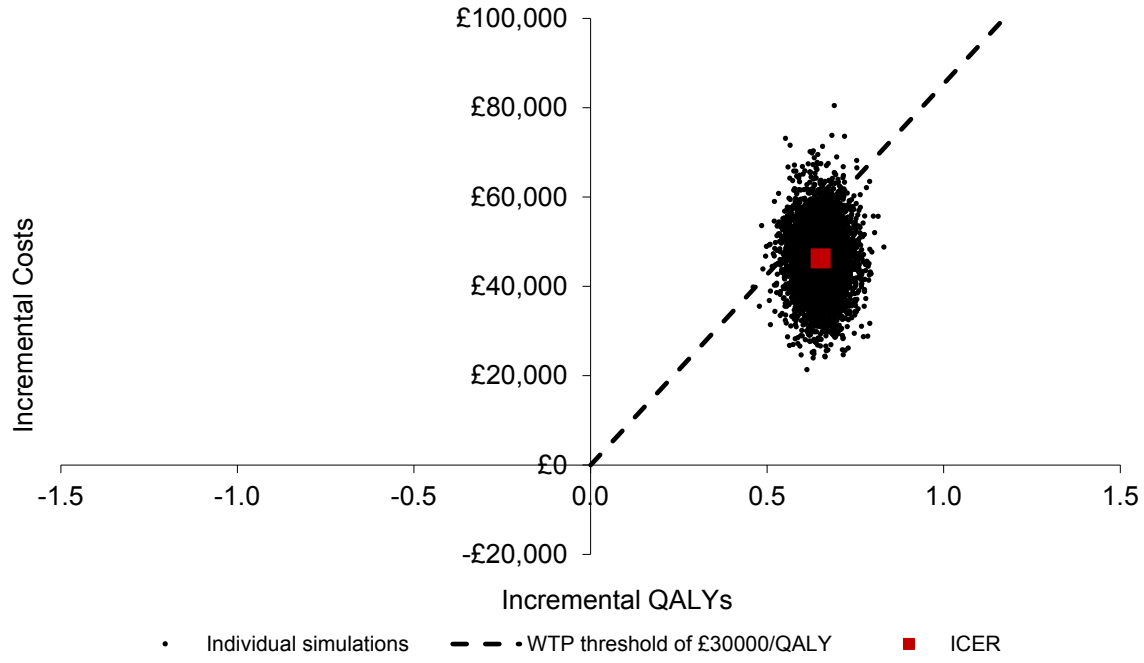

Figure 2 Incremental cost-effectiveness scatterplot for the comparison between LEN+DEX versus IXA+LEN+DEX (ERG) (based on the proposed PAS for ixazomib)

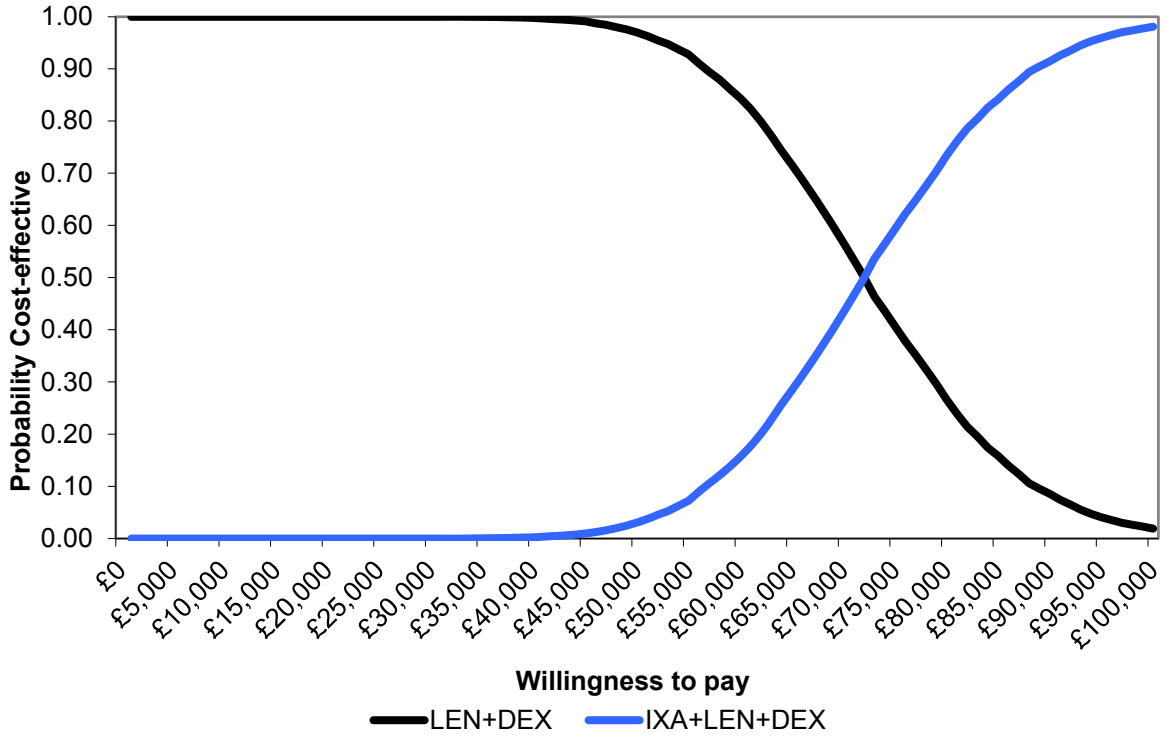

Figure 3 Cost-effectiveness acceptability curves for LEN+DEX and IXA+LEN+DEX (ERG) (based on the proposed PAS for ixazomib)

1.1.4 ERG scenario analyses

The ERG undertook several scenario analyses to explore the impact to the ERG's base-case results, with the results reported in Table 3. Under different waning scenarios increased the ICER from approximately £73,900 to £83,400 per QALY.

Table 3 Exploratory analyses based on the ERG's base-case results (based on the proposed PAS for ixazomib)

Scenario	LEN+DEX		IXA+LEN+DEX		Cost per QALY
	Costs	QALYs	Costs	QALYs	
ERG base-case	[redacted]	2.43	[redacted]	3.08	£70,975
Waning takes 18 years to complete (Weibull model for OS)	[redacted]	2.43	[redacted]	3.05	£73,903
Waning takes 5 years to complete (Weibull model for OS)	[redacted]	2.43	[redacted]	2.99	£83,393
Waning takes 7.5 years to complete (Weibull model for OS)	[redacted]	2.43	[redacted]	3.03	£77,247

ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

ERG Summary

Using the ERG's preferred assumptions simultaneously and the discount agreement for ixazomib, these results generated an ICER of approximately £71,000 per QALY. One-way sensitivity analysis results continued to show that the parameters with the greatest impact on model outcomes were coefficients relating to the estimation of utility. The ERG's PSA results showed that at a willingness-to-pay threshold of £30,000 per QALY, treatment with IXA+LEN+DEX has a zero probability of being cost-effective.

Title: **Multiple myeloma (relapsed, refractory) - Ixazomib (with lenalidomide and dexamethasone) (CDF Review of TA505) Appraisal 1635.**

Produced by **Warwick Evidence**

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Declared competing interests of the authors.None.

This erratum page replaces page 27 of the ERG report and corrects a factual accuracy

- statistically significantly improved OS experience in patients receiving IXA+LEN+DEX compared to those receiving LEN+DEX (HR=0.713, 95%CI: 0.535, 0.952).

- The Rank Preserving Structural Failure Time (RPSFT) methods were also considered to adjust for bias due to switching to subsequent treatments. However, in MM-1, as it was multicentre trial, the common treatment effect assumption has been shown to be invalid across multiple trials. This was confirmed by UK clinical experts who noted the relative efficacy of different treatment regimens varies depending on the line of therapy. Therefore, these methods were discounted from further analysis. (CS Document, Section A.7.1, pages 26-29).

- The median OS, (as provided in the second round of clarification responses), and HR for both unadjusted and adjusted analyses are presented in Table 1.

Table 1. Median OS time and HR (unadjusted and adjusted for switching to subsequent treatments)

Endpoint Parameter	**IA2 [median follow-up of 23-months]**		**Final analysis [median follow-up time of 85-months]**	
	IXA+LEN+DEX	**LEN+DEX**	**IXA+LEN+DEX**	**LEN+DEX**
Unadjusted for treatment switching HR (95% CI)	0.645 (0.409, 1.017) Median OS (in months)		0.845 (0.642, 1.114) Median OS (in months)	
	not estimable	not estimable	53.0	43.0
Naïve – censor at switch	N/A		0.712 (0.507, 0.999) Median OS (in months)	
			70.7	44.7
Naïve – 'per protocol'‡			0.699 (0.493, 0.990) Median OS (in months)	
			34.5	25.9
TSE (no re-censoring + adjust for baseline characteristics†)			0.785 (0.596, 1.035) Median OS (in months)	
			52.5	43.4
TSE (re-censored* + adjust for baseline characteristics†)			0.713 (0.535, 0.952) Median OS (in months)	
			51.4	41.5
IPCW (stabilised weights + adjust for baseline characteristics†)			0.674 (0.465, 0.979) Median OS (in months)	
			54.6[α]	38.6[α]

HR, hazard ratio; IA2, second interim analysis; IPCW, inverse probability of censoring weights; N/A, not applicable; NR=not reported; OS, overall survival

† Adjusts for high risk, age>65, ISS stage at screening, and history of bone lesions.

‡ Excludes all patients who switched from the analysis.

[α]Median estimates for ICPW do not adjust for baseline covariates

*Counterfactual survival times are re-censored for all patients at the minimum of the administrative censoring time of the study (28th September 2020;C_i) and $C_i\psi_2$where $\psi_2$is the adjustment factor associated with group 2 membership. This represents the earliest possible censoring time

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (CDF review of TA505) [ID1635]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 25 October 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Treatment waning

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 7 – "While the ERG acknowledges that waning of treatment (during the treatment itself) has almost completely been captured within the observed time of the trial, we consider that the prolonged sustained effect of the treatment (after treatment has finished) that is currently included in the company models should be considered separately." There are multiple occurrences throughout the report in relation to an assumed **sustained treatment effect of ixazomib** for the full model time horizon. We are concerned that this could be misinterpreted as the treatment effect relating to treatment with ixazomib is assumed for the model time horizon.	The treatment effect on OS from the TOURMALINE-MM1 clinical trial is no longer an isolated effect of IXA+LEN+DEX vs. LEN+DEX. Rather it is the differential effect on survival from the beginning of the trial until the end of follow-up between the two arms, including an extended period where patients have discontinued IXA+LEN+DEX or LEN+DEX and may be receiving other therapies. In the base case, we have extrapolated the treatment effect of the IXA+LEN+DEX arm over the model time horizon. However, we have not extrapolated the treatment effect specifically for patients on-treatment with ixazomib over the model time horizon. We believe this distinction is important when discussing a topic which is already very complex. Where a sustained effect is discussed, reference should be made to the effect on OS observed in the IXA+LEN+DEX arm (including the off-ixazomib treatment window) rather than specifically to the ixazomib treatment.	It is important to distinguish between the treatment effect of ixazomib directly and the treatment effect of the IXA+LEN+DEX arm of the TOURMALINE-MM1 trial of which a large proportion of follow-up captures outcomes after treatment with IXA+LEN+DEX has ended.	Not a factual error. Consideration of waning of treatment effect in the ERG report represents an expression of ERG opinion and is therefore not a factual error. The ERG finds the company's description of this problem difficult to follow and believe that the ERG opinion on waning of treatment effect is clearly explained in the ERG report and contains no factual error.

Issue 2 Type of PAS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 53 – *"…the company have applied to reinstate a* [redacted]	The word "[redacted]" should be deleted from the following locations: page 14, page 53 (x2),	To remove confidential information from the report	The ERG has deleted the word "[redacted]" throughout the report.

discount PAS…" The type of PAS (i.e. "[redacted]") is CIC and should be deleted from all sections of the ERG report, consistent with the latest CS and Appendices.	page 54, page 65 and page 72		

Issue 3 Differentiation between list price and with PAS analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17 – *"Results from the PSA showed that at a willingness-to-pay threshold of £30,000 per QALY, IXA+LEN+DEX has a [redacted] probability of being cost-effective"* Throughout the report the ERG presents multiple analyses of ixazomib cost-effectiveness, using either the list price or the proposed ixazomib PAS. In many cases, in both text and figure/table captions, it is unclear whether the values presented are based on the list price or the proposed PAS. This should be clarified throughout the report, and particularly for the sentence shown above which suggests that IXA+LEN+DEX would not be cost-effective at any discount.	The Company requests that the ERG clarifies the commercial assumptions used to calculate cost-effectiveness results each time they are presented. This should, at a minimum, mean that "list price" and "with proposed PAS" appear at each point that these data are presented. The Company would also request the ERG checks the redaction for the report. In some cases, the Company is unable to confirm whether data have been highlighted correctly as it is not clear whether analyses refer to list price or with proposed PAS assumptions.	To ensure accurate interpretation of figures presented by the ERG and ensure that redaction is done appropriately to protect all CIC information.	The ERG has differentiated analyses undertaken using the list price and with the proposed PAS throughout the report.

Issue 4 Inclusion of *de novo* ITT analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 32, 33 – The ERG has independently "*reviewed the final OS analyses of the TMM1 trial beyond the scope of the CDF review, i.e. including the ITT TMM1 population (RRMM with 1+prior therapy) and based on the original analyses planned in the TMM1 SAP.*" While it may be of interest to the ERG to explore the switching methodology on a larger sample size, we believe it is inappropriate to do so for a patient population that is beyond the scope of this CDF review. The data presented by the ERG is based on a different patient population to that under consideration in this review, and subsequent therapies across these populations differed. It is wholly inappropriate to extrapolate from one population to the other. The Company requests that this analysis is removed from the report.	The text relating to these *de novo* analyses should be removed in their entirety from the report	To remove data and analysis from the report that is beyond the scope of the current CDF review	Not a factual error. The ERG considers the TMM1 trial data as presented in the 2021 paper in NEJM not only of interest but also of direct relevance to any consideration of clinical effectiveness of IXA+LEN+DEX versus LEN+DEX in any identified subgroups.

Issue 5 Rationale for treatment switching analysis (1/2)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 31 – *"The company's adjusted analyses accounted for the use of novel therapies in the TMM1 trial which are neither reimbursed nor routinely available for use in clinical practice in the UK although this is not recommended by the CDF (CS Document page 24)."* The last part of the statement as written is both not consistent with the CS, and not consistent with the NICE Position Statement on consideration/exclusion of CDF therapies in appraisals. On page 24 of the CS, we state "As per the NICE Position Statement,[10] medicines available only via the CDF and not via routine commissioning should not be included as a comparator or subsequent therapy." The statement implies that this methodology is not endorsed by the CDF when, in fact, it is consistent with published NICE methods.	Delete the following text. "…although this is not recommended by the CDF"	To correct a statement that is neither consistent with the CS, or with the NICE Position Statement	We have removed the following text,*'…although this is not recommended by the CDF'*

Issue 6 Rationale for treatment switching analysis (2/2)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51 – *"The company are concerned that subsequent treatments received after progression and differing distribution of prognostic factors between arms will confound naïve estimates of OS."* and *"The company's favoured analysis is that based on a new two-stage adjustment with re-censoring designed to correct for confounding from unequal use of subsequent treatments unavailable in UK practice and for imbalance in prognostic factors."* The CS does not state that the adjustment has been conducted to adjust for imbalances in prognostic factors. As stated in the CS (page 24), "[the submission] presents the extensive statistical analyses and clinical validation undertaken to derive the OS data that would have been expected had the subsequent therapy profile in TMM1 aligned with UK clinical practice (termed the "adjusted	The sentences should read. "The company are concerned that subsequent treatments received after progression between arms will confound naïve estimates of OS." and "The company's favoured analysis is that based on a new two-stage adjustment with re-censoring designed to correct for confounding from unequal use of subsequent treatments unavailable in UK practice" Any further references to adjusting for differences in prognostic factors due to imbalances between treatment arms should also be removed/amended	To correct incorrect statements on the rationale for the treatment switching analysis	We have amended these sentences to: "The company are concerned that subsequent treatments received after progression between arms will confound naive estimates of OS." and "The company's favoured analysis is that based on a new two-stage adjustment with re-censoring designed to correct for confounding from unequal use of subsequent treatments unavailable in UK practice"

OS" data)." While the Company has adjusted for prognostic factors in its analysis, the rationale for doing so it that is a requirement of the TSE methods.			

Issue 7 Impact of subsequent therapies on median OS estimates

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 32 – *"The apparent minimal effect of adjustment on median OS estimates contrasts with the statement made by the company regarding the effect of subsequent therapies."* The Company requests that the ERG clarifies the statement to which it is referring.	No specific change can be suggested	To correct a potentially misleading ERG interpretation of the Company's position on subsequent therapies	There is no factual error or inaccuracy.

Issue 8 Lack of progression free survival data in the final analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12 – *"The ERG recognises that data on PFS were not collected beyond the second interim analysis (IA2) of TMM1. Therefore, there are no updates to PFS available."* The Company would also	The sentence on page 12 should read. "The ERG recognises that collection of further data on PFS – beyond IA2 – was not included in the CDF Data Collection Agreement for ixazomib, and is beyond the scope of this appraisal. Moreover, data on PFS were not collected beyond the second interim analysis	To ensure readers are clear on the scope of the review and to correct misleading wording that suggests lack of PFS data is an oversight by the Company	Not a factual error. The ERG does not accept that this misleads readers into believing that lack of post AI2 PFS data is an oversight of the company. The ERG clearly states that PFS data were not

highlight that further collection of PFS data was not included in the ixazomib Data Collection Agreement for CDF funding. It is therefore beyond the scope of the current review process. At a minimum, the Company requests the report to be amended to state this fact. Our preference would be for "Additional Issue 1" to be removed from the report This issue recurs on page 25 – "The ERG considers that updated PFS would have been beneficial for the CDF review, as PFS is not affected by the post-progression treatment switching that leads to confounding. However, the ERG acknowledge that it was not in the statistical analysis plan."	(IA2) of TMM1, as the primary study endpoint had already been met. Therefore, there are no updates to PFS available" The sentence on page 25 should read. "The ERG considers that updated PFS would have been beneficial for the CDF review, as PFS is not affected by the post-progression treatment switching that leads to confounding. However, the ERG acknowledge that it was neither in the T-MM1 statistical analysis plan, nor in the ixazomib Data Collection Agreement for CDF entry agreed with NHS England."		collected beyond the second interim analysis (IA2) of TMM1. Therefore, there are no updates to PFS available.

Issue 9 PFS data maturity

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 50 – *"The company submitted the same PFS analysis as submitted in response to ACD following original STA appraisal (ID TA505); this is based on data up to interim analysis IA2 and is therefore less mature than data now submitted for ToT and for*	Delete "IA2 and is therefore less mature than data now submitted for ToT and for OS, each of which correspond to the final data cut" and also delete "It should be borne in mind that the PFS KM are based on AI2 and are less mature than other KMs."	To correct an inaccurate interpretation of PFS data maturity by the ERG	We have changed the 'less mature' to 'less extended follow-up'.

OS, each of which correspond to the final data cut." It is not correct to say that the data are "less mature". The primary endpoint of T-MM1, PFS, was reached at the first interim analysis (IA1) which occurred after a median follow-up of 15 months. A second non-inferential assessment of the PFS was conducted at IA2 (median follow-up of 23 months). Due to longer follow-up, IA2 was the preferred data cut by the NICE Committee, but the primary endpoint was reached at IA1. All PFS events have been captured for the T-MM1 population, and the analysis is mature. This issue recurs on page 40, "It should be borne in mind that the PFS KM are based on AI2 and are less mature than other KMs."			

Issue 10 Progression-free survival benefit for IXA+LEN+DEX vs. LEN+DEX

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 18 – "*In its recommendations, the Committee noted that in the TOURMALINE*	The sentence should read. "In its recommendations, the Committee noted	To correct an inaccurate statement around the PFS benefit of IXA+LEN+DEX vs LEN+DEX for	The ERG has amended the statement.

MM-1 trial,[1] ixazomib (plus LEN and DEX [IXA-LEN-DEX]) appeared to improve progression-free survival (PFS) and that there was potential for ixazomib to be cost-effective" The statement that IXA+LEN+DEX *"appeared"* to improve PFS is inaccurate. T-MM1 met its primary endpoint in statistically improving PFS at IA1, and the NICE committee – after reviewing the PFS data at both IA1 and IA2 – agreed. In the Final Appraisal Determination for TA505 (Section 3.9, page 10), the NICE "*committee concluded that ixazomib improves progression-free survival in people who have had 2 or 3 lines of therapy."* The statement in the ERG report should be corrected to replace "*appeared to improve*" with *"improves"*	that in the TOURMALINE MM-1 trial,[1] ixazomib (plus LEN and DEX [IXA-LEN-DEX]) improves progression-free survival (PFS) and that there was potential for ixazomib to be cost-effective."	patients with 2–3 prior therapies	

Issue 11 Clinical expert opinion

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 42 – *"The ERG thinks there is so little difference in predicted survival between generalised gamma (dashed lines) and Weibull (dotted lines) that clinical experts*	The sentence should read. "The ERG thinks there is so little difference in predicted survival between generalised gamma (dashed lines) and Weibull (dotted lines) that	To make clear that this an opinion of the ERG.	Not a factual error. This is what the ERG opinion, no change needed.

would be unable to distinguish one from the other and therefore on this basis the ERG thinks the Weibull based ICER is as equally valid as the generalised gamma-based ICER" It is inappropriate for the ERG to suggest what clinical experts would, or would not, be able to distinguish. In the March advisory board conducted to inform this appraisal, clinical experts were agreed in selecting the generalised gamma curve over the Weibull, predominantly on the basis of the landmark survival figures/percentages, rather than the visual representation of the curves. The ERG should clarify throughout the report that it is their opinion that the curves cannot be distinguished, not clinical expert opinion (unless this has been specifically sought on this point and documented by the ERG) This issue recurs on page 47	the Weibull based ICER is as equally valid as the generalised gamma-based ICER" There may be other instances in the report where similar changes are required		

Issue 12 ERG justification for implausible results for two-stage method

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51 – *"Although the ERG agrees that adjustment for post-*	The ERG should either justify this point – describing the implausible outcomes it is	To amend what we regard as unsupported comments.	Not a factual error. It is an expression of the

progression treatments is ideally desirable the company has adopted a two-stage method not specified in the trial protocol. The method used represents a post hoc adoption and in the opinion of the ERG this could potentially lead to implausible outcomes." The ERG provides no rationale or justification for suggesting that the two-stage method could lead to implausible outcomes. There are numerous references to implausibility in the report. It is unclear in many cases on what evidence these statements are based, or whose opinion they are (ERG, or clinical expert advisors). As currently written, the ERG report implies that these statements are facts when they are likely opinions or judgements. This should be stated.	anticipated the method will provide, and the reasons – or remove the relevant text. More generally, the Company requests that the ERG clarifies who has proposed that the approach is implausible (i.e. ERG opinion or clinical expert advice) and the rationale for these statements. For example a statement may read 'in the ERG's opinion, this result is implausible' so that it is clear which statements are judgement vs factual.	In the CS, the Company was clear on the derivation of its assumptions around plausibility, citing advice received from clinical advisors at an advisory board conducted in March 2021. To aid interpretation of the ERG report, and provide the Committee with information on what is/isn't clinical opinion, it is important to clarify: 1. what is ERG opinion, 2. what is based on clinical expert advice, and 3. for both, what is the justification for the statement This is currently inconsistent in the report.	ERG's opinion.

Issue 13 Considerations for the RPSFT models methodology

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 27 – *"The company also considered the Rank Preserving Structural Failure Time (RPSFT) Models method to adjust for bias due to switching to subsequent treatments, but because the*	The sentence should read. "*The company also considered the Rank Preserving Structural Failure Time (RPSFT) Models method to adjust for bias due to switching to subsequent treatments. The*	To correct an incorrect statement on the rationale for not using RPSFT methods	Not a factual error. The ERG has found it difficult to identify a factual error. Although the company states in

TMM1 trial was multicentre, the common treatment effect assumption across multiple trials was not deemed to be valid (CS Document, Section A.7.1, pages 26-29).” It is not correct to say that the RPSFT was not selected because T-MM1 was multicentre. In the CS (Section A.7.1, page 29), we state “The RPSFTM methods were also considered. However, in MM, the common treatment effect assumption has been shown to be invalid across multiple trials. This was confirmed by UK clinical experts who noted the relative efficacy of different treatment regimens varies depending on the line of therapy. Therefore, these methods were discounted from further analysis.”	*Company stated that in MM, the common treatment effect assumption has been shown to be invalid across multiple trials, and that this was confirmed by UK clinical experts who noted the relative efficacy of different treatment regimens varies depending on the line of therapy. The Company therefore discounted these methods from further analysis.*”		Section A.7.1, pages 26-29 that RPSFT has been “shown” to be invalid across multiple trials no accompanying reference was offered to support this statement. Therefore the ERG could not validate this claim.

Issue 14 Misrepresentation of IPCW implausibility

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51 – *“Results from IPCW were judged clinically implausible by the company”* Results from the IPCW were judged clinically implausible by the clinicians at the March advisory board, not by the	The sentence should read. “Results from IPCW were judged clinically implausible by clinicians at an advisory board conducted by the Company in March 2021”	To correct misleading wording of text.	We have amended the wording to *“Results from IPCW were judged clinically implausible by clinicians at an advisory board conducted by the Company in March 2021”*

Company. This point should be corrected.			

Issue 15 PSA HRQL coefficients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59 – *"Coefficients associated with HRQoL regression analysis were not considered in the PSA. The coefficients associated with age and intercept were key drivers of the economic model (see Figure 15 and Figure 16)."* This is incorrect. The coefficients were varied using Multinorminv distribution in the HRQL sheet in the model	The sentence should be deleted	To correct an incorrect statement on the PSA analysis	The ERG is now clear that the coefficients associated with HRQoL was considered in the PSA. We have now deleted that sentence on page 59.

Issue 16 Kaplan–Meier plot tails

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 36 – *"The KM for TSE-OS, copied from the submitted economic model, implies that the TSE-OS KMs extend to approximately [redacted], corresponding to the depiction in CS Figure 8, page 35 (see also ERG Section 9.1) but not corresponding to Figure 7 page 33. The ERG cannot explain these differences.* *The unadjusted OS KM plots (CS Figure 1) extend to about [redacted] months approximately [redacted] (unfortunately time axis tick marks are lacking in this and other CS figures). The ERG is unsure why OS extends [redacted] but believe this maybe an error in view of IPD data supplied to the ERG by the company during the second round of clarifications (received October 7 2021: document ID1635 ixazomib Takeda clarification questions A3_A4 05102021CM noACIC). This indicates that for the two-stage adjusted OS, the first death event or censoring time occurred at [redacted] and the last death event or censoring time occurred at [redacted].*	No specific amendment can be suggested. The Company requests that the report is updated the reflect the responses already provided by the company to the ERG's Clarification Questions.	To remove an implication for a model error that was addressed during clarification questions	Not a factual error. The company additional clarification response was unhelpful in clarifying this matter. The ERG received KM data in a different form to that received in previous clarifications of ixazomib submissions and unfortunately, the ERG remains unsure what data the company used to prepare its parametric models and remains unable to check these. The clarification referred to here by the company was received very late relative to the ERG deadline for report submission.

The relevant part of the CS clarification document is shown Table 14. The [redacted] for last death or censoring was also shown for the LEN+DEX arm." This issue was addressed in the Company responses to the Additional ERG Clarification Questions (document *ID1635 Company response to additional ERG clarifications [CIC]).* As stated on page 5 of this document, *"the maximum time we have Kaplan–Meier data for IXA+LEN+DEX is 401 weeks for the unadjusted OS analysis and 324 weeks for the adjusted OS analysis – see the screenshots below from the response to A3 from the Clarification Questions. When the adjusted OS data are selected there is no Dynamic Chart function set up in the model. Therefore, the tail of the Kaplan–Meier curve is defaulting to the last survival estimate until 401 weeks; from week 324 to week 401 the same survival estimate is used resulting in a longer flat tail. This has no impact on any of the model calculations and did not influence the parametric curve selected in the base case."*			

The ERG report does not appear to incorporate the Company's responses to the latest round of clarification questions.			

Issue 17 Clarification of number of patients still receiving treatment at the end of the observation period in T-MM1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 8 – *"For the continued treatment effect assumption, the ERG note that for a small sample of patients still receiving treatment at the end of observation in TMM1 study (4% versus 1% in the respective study arms) the effect of treatment waning has not been fully captured."* The report does not specify which T-MM1 treatment arms the 4% and 1% figures refer to. This should be amended. This issue recurs on pages 29 and 52	The sentence should read. "For the continued treatment effect assumption, the ERG note that for a small sample of patients still receiving treatment at the end of observation in TMM1 study (4%, IXA+LEN+DEX arm versus 1%, LEN+DEX arm) the effect of treatment waning has not been fully captured."	To ensure the report is clear as to the proportion of patients in each treatment group who had completed study treatment at the end of the T-MM1 observation period	We have now amened to *"For the continued treatment effect assumption, the ERG notes that for a small sample of patients still receiving treatment at the end of observation in TMM1 study (4%, IXA+LEN+DEX arm versus 1%, LEN+DEX arm) the effect of treatment waning has not been fully captured."*

Issue 18 Updating the PSA at clarification question stage

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59 – *"The ERG was unclear if the PSA was re-run by making the appropriate changes."*	Delete the following text. "The ERG was unclear if the PSA was re-run by making the appropriate changes."	To ensure the report reflects corrections made at clarification stage.	We have now deleted the text on page 59.

As detailed in the response to ERG Clarification Question B.5, the upper and lower bounds of the four adverse event rate parameters (Anaemia, Nausea, Neutropenia and Pneumonia) were updated. This would only impact results of the OWSA. However, as seen in the updated tornado plots provided by the Company, the rates of adverse events are not key drivers of the model and so this error does not impact OWSA results. This will have no impact on the PSA as the upper and lower bounds do not feed into this analysis. Therefore, the PSA was not rerun.			

Issue 19 Typo, page 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10 – *"After adjustment, the post-progression LY gain, as obtained from the company's model, represents* [redacted] *of total LY gain which is considerable."* The percentage value should be [redacted].	The sentence should read. "After adjustment, the post-progression LY gain, as obtained from the company's model, represents [redacted] of total LY gain which is considerable."	To correct a typo	As far as the ERG is aware, the calculation is correct. Hence, there is no typo here.

Issue 20 Typo, page 27

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 13, Page 27 – "[α]*Median estimates for ICPW do not adjust for baseline covariates*" The table footnote above does not appear to refer to anywhere in the table. The following footnote from the CS is also missing. *"*Counterfactual survival times are re-censored for all patients at the minimum of the administrative censoring time of the study (28th September 2020; C_i) and $C_i\psi_2$, where ψ_2 is the adjustment factor associated with group 2 membership. This represents the earliest possible censoring time."*	Clarify in the table where the footnote refers to. Include the following footnote. "*Counterfactual survival times are re-censored for all patients at the minimum of the administrative censoring time of the study (28th September 2020; C_i) and $C_i\psi_2$, where ψ_2 is the adjustment factor associated with group 2 membership. This represents the earliest possible censoring time."	To correct typos	We have included this footnote.

Issue 21 Typo, page 28

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 28 – "Meaningful comparisons of updated median ToT duration and median OS time were hindered by notable differences in the duration of median follow-up between the TMM1 study (85-months) and the	The sentence should read. "Meaningful comparisons of updated median ToT duration and median OS time were hindered by notable differences in the duration of median follow-up between the TMM1 study (85-months) and the SACT datasets (8.3	To correct typos	We have amended the sentence.

SACT datasets (8.3 months) and in the distribution of important patient characteristics independently associated with ToT and OS (e.g., age, co-morbidities, prior SCT).*"* Given that this sentence refers to both ToT and OS, the Company requests that the ERG clarifies the SACT follow-up lengths as 8.3 months and 15 months for ToT and OS, respectively	months for ToT and 15 months for OS) and in the distribution of important patient characteristics independently associated with ToT and OS (e.g., age, co-morbidities, prior SCT)."		

Issue 22 Typo, page 37

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 37 – *"…while approximately [redacted] remain alive at end of observation according and have discontinued ixazomib and at some stage have received various subsequent treatments that have been adjusted for in the TSA procedure…"* TSA should read TSE	The text should read "while approximately [redacted] remain alive at end of observation according and have discontinued ixazomib and at some stage have received various subsequent treatments that have been adjusted for in the TSE procedure"	To correct a typo	We have corrected this typo.

Issue 23 Typo, page 38

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 38 – *"…based on the*	The text should read	To correct a typo	We have made these changes.

company's AI2 analysis …" For consistency, this time point should be referred to as IA2. This issue recurs on pages 40 and 71	Page 38 | "based on the company's IA2 analysis" Page 40 | "It should be borne in mind that the PFS KM are based on IA2 and are less mature than other KMs" Page 71 | "conjunction with IA2 cut-off PFS"		

Issue 24 Typo, page 38

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 38 – "*The two-stage adjustment with censoring undertaken by the company…"* This should read "re-censoring"	The text should read "The two-stage adjustment with re-censoring undertaken by the company""	To correct a typo	We have corrected this typo.

Issue 25 Typo, page 38

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 38 – *"The final analysis of the TMM1 trial pertains to the population of interest for this appraisal, namely patients with RRM who have had at least two prior therapies and, the intention-to-treat population of the trial, namely patients with RRMM who had at least one prior therapy. …"* Typo for RRMM	The text should read "The final analysis of the TMM1 trial pertains to the population of interest for this appraisal, namely patients with RRMM who have had at least two prior therapies and, the intention-to-treat population of the trial, namely patients with RRMM who had at least one prior therapy."	To correct a typo	The ERG corrected this typo on page 25.

Issue 26 Typo, page 43

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 43, Table 15 – Some values for the proportion of patients alive at 10 and 15 years using the Weibull curves are incorrect.	Replace values as follows. [redacted]	To correct typos	We have corrected these typos.

Issue 27 Typo, page 61

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61 – decreasing the ICER to approximately [redacted].*"* The ICER decreased "by", not "to" this value.	The sentence should either read "decreasing the ICER by approximately [redacted]" or "decreasing the ICER to approximately [redacted]"	To correct a typo	We have corrected this typo.

Issue 28 Typo, page 61

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61 – *"…had the greatest increase to the ICER…"* This phrase appears twice on page 61. It should read "impact on", as the ICER do not always increase for the sentences in which the phrase is used.	Replace "increase to" with "impact on" in both locations	To correct typos	We have amended this sentence.

Issue 29 Typo, page 66

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 66 – *"These results show that ICER decreased to approximately [redacted] per QALY"* The ICER decreased to exactly [redacted] *per QALY*.	Delete "approximately"	To correct a typo	We have amended this sentence.

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
ID1635 ixazomib ERG report, pages 26, 32, and 63	"Three examples of imbalance in these therapies were highlighted by the Company: daratumumab (received by [redacted] in LEN+DEX as opposed to only 19/148=13% in IXA+LEN+DEX), elotuzumab ([redacted], respectively) and autologous stem-cell transplant ([redacted], respectively)."	These data are no longer AIC. All highlighting can be removed	We have removed confidentiality markings.
ID1635 ixazomib ERG report, page 26	"Overall, [redacted] patients ([redacted] in the IXA+LEN+DEX arm and [redacted] patients in the LEN+DEX arm) required adjustment for receipt of agents not routinely available in the UK"	These data are no longer AIC. All highlighting can be removed	We have removed confidentiality markings.
ID1635 ixazomib ERG report, page 35	"Faster waning [redacted] the ICER beyond a [redacted] increase."	Please mark "[redacted]" as CIC	We have marked this as CIC.
ID1635 ixazomib ERG report, page 56, Table 17	[redacted]"	This can be unhighlighted. It presents the with PAS ICER. With PAS ICERs can be unredacted throughout the report	We have removed the confidential markings for analyses using the PAS for ixazomib.
ID1635 ixazomib ERG report, page 62, Table 18	Columns 4 and 5. The Company is not aware of a reason that these data need to be marked AIC	Highlighting can be removed	We have removed the confidential markings for columns 4 and 5.

Public Health England

Protecting and improving the nation's health

Ixazomib with lenalidomide and dexamethasone – data review

Commissioned by NHS England and NHS Improvement

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing and reduce health inequalities. We do this through world-leading science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. We are an executive agency of the Department of Health and Social Care, and a distinct delivery organisation with operational autonomy. We provide government, local government, the NHS, Parliament, industry and the public with evidence-based professional, scientific and delivery expertise and support.

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Contents

Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of ixazomib with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma. The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) and duration of treatment in the evidence submission. As a result, they recommended commissioning of ixazomib with lenalidomide and dexamethasone through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England and NHS Improvement commissioned Public Health England (PHE) to evaluate the real-world treatment effectiveness of ixazomib with lenalidomide and dexamethasone in the CDF population, during the managed access period. This report presents the results of the use of ixazomib with lenalidomide and dexamethasone in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHS Improvement and PHE partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 97% of patients and 86% of patient outcomes reported in the SACT dataset. PHE and NHS England and NHS Improvement are committed to providing world first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England and NHS Improvement's Blueteq® system was used to provide a reference list of all patients with an application for ixazomib with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma in the CDF. Patient NHS numbers were used to link Blueteq applications to PHE's routinely collected SACT data to provide SACT treatment history.

Between 19 December 2017 and 18 June 2020, 2,769 applications for ixazomib with lenalidomide and dexamethasone were identified in NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 2,460 unique patients, who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

2,460 (97%) unique patients with CDF applications were reported in the SACT dataset and were included in the final cohort.

Median treatment duration was 11.5 months [95% CI: 10.5,12.2] (350 days). 67% [95% CI: 65%,69%] of patients were receiving treatment at 6 months,48% [95% CI: 46%, 50%] of patients were receiving treatment at 12 months and 38% of patients were still receiving treatment at 18 months [95% CI: 36%, 40%].

At data cut off, 59% (N=1,444) of patients were identified as no longer being on treatment. Of these 1,444 patients, 42% (N=604) of patients stopped treatment due to disease progression, 13% (N=187) of patients stopped treatment due to acute toxicity, 5% (N=73) of patients chose to end their treatment, 17% (N=248) of patients died not on treatment, 14% (N=195) of patients died on treatment, 4% (N=53) of patients completed treatment as prescribed and 6% (N=84) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

The median OS was 30 months[a] (913 days). OS at 6 months was 84% [95% CI: 82%, 85%], OS at 12 months was 73% [95% CI: 71%,74%] and OS at 18 months was 63% [95% CI: 61%, 65%].

A sensitivity analysis was conducted for a cohort with at least 6 months' data follow-up in the SACT dataset. Results for treatment duration and survival were consistent with the full analysis cohort.

Conclusion

This report analysed SACT real world data for patients treated with ixazomib with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma in the CDF. It evaluates treatment duration, OS, treatment outcomes for all patients treated with ixazomib with lenalidomide and dexamethasone for this indication.

[a] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

Introduction

Multiple Myeloma (C90) accounts for 2% of all cancer diagnoses in England. In 2017, 5,034 patients were diagnosed with myeloma (males 2,931, females 2,103)[2].

Ixazomib, with lenalidomide and dexamethasone, is recommended for use within the Cancer Drugs Fund as an option for treating multiple myeloma in adults only if:

- they have already had 2 or 3 lines of therapy; and
- the conditions in the managed access agreement for ixazomib are followed[3].

Background to this report

The Public Health England and NHS England and NHS Improvement partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England and NHS Improvement and Public Health England's (PHE's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the PHE and NHS England and NHS Improvement partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by PHE. This includes NHS England and NHS Improvement commissioning PHE to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England[4]. From 29 July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical effectiveness. During this period of managed access, ongoing data collection is used to answer the clinical uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

PHE analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of PHE.

NICE Appraisal Committee review of ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [TA505].

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of ixazomib with lenalidomide and dexamethasone (Takeda) in treating relapsed or refractory multiple myeloma [TA505] and published guidance for this indication in February 2018[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended commissioning of ixazomib with lenalidomide and dexamethasone through the CDF for a period of 32 months, from December 2017 to October 2020.

During the CDF funding period, results from an ongoing clinical trial (TOURMALINE MM-1[7]) evaluating ixazomib with lenalidomide and dexamethasone in the licensed indication is likely to answer the main clinical uncertainties raised by the NICE committee. Data collected from the TOURMALINE MM-1 clinical trial are the primary source of data collection.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for ixazomib with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma in England, during the CDF funding period. This acts as a secondary source of information alongside the results of the TOURMALINE MM-1 trial[7].

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection;

- **treatment duration** for the use of ixazomib with lenalidomide and dexamethasone; and
- **overall survival** from the start of a patient's first treatment with ixazomib with lenalidomide and dexamethasone.

Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, PHE and the company (Takeda) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of ixazomib with lenalidomide and dexamethasone. It also detailed the eligibility criteria for patient access to ixazomib with lenalidomide and dexamethasone through the CDF and CDF entry and exit dates.

This report includes patients with approved CDF applications for ixazomib with lenalidomide and dexamethasone, approved through Blueteq® and followed-up in the SACT dataset collected by PHE.

Methods

CDF applications - identification of the cohort of interest

NHS England and NHS Improvement collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving a CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. PHE has access to the Blueteq database and key data items such as NHS numbers, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the United Kingdom (UK) General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). The processing of special categories of personal data is also covered under article 9(2)(h) of UK GDPR (processing is necessary for the purposes of preventive or occupational medicine).
As NHS England and NHS Improvement do not have an exemption to the Common Law Duty of Confidentiality, NHS England and NHS Improvement cannot access the identifiable data directly. PHE, through the National Cancer Registration and Analysis Service have permission to process confidential patient information though Regulation 2 of The Health Service (Control of Patient Information) Regulations 2002.

PHE collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Ixazomib with lenalidomide and dexamethasone clinical treatment criteria

- Confirmed diagnosis of multiple myeloma
- Patient has previously received 2 or 3 prior lines of treatment (induction chemotherapy and stem cell transplant is considered to be 1 line of therapy). Note: Patients previously treated with 1 or >3 lines of treatment are not eligible for ixazomib
- Patient must not be refractory to previous proteasome inhibitor-based or lenalidomide-based treatment at any line of therapy (in this context, refractory disease is defined as disease progression on treatment or disease progression within 60 days of the last dose of a proteasome inhibitor or lenalidomide). Note: as lenalidomide is only commissioned by NHS England and NHS Improvement after 2 prior therapies, the only eligible patients who have had prior lenalidomide must have received it in the context of a clinical trial in an earlier line of therapy. Such patients must not be refractory to lenalidomide according to the above definition.
- Patient has either been refractory to 1 or more lines of therapy or has responded and relapsed after each line of therapy.
- Acknowledgement whether a patient has been treated with a previous autologous or allogenic stem cell transplant or not.
- Patient must be treatment-naïve to any therapy with ixazomib.
- Ixazomib is only to be used in combination with lenalidomide and dexamethasone.
- Ixazomib is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment, whichever is the sooner.
- Performance status of the patients must be 0 or 1 or 2.
- No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed. (Treatment breaks up to 6 weeks are allowed to let any toxicity of current therapy to settle or intercurrent comorbidities to improve.)
- Ixazomib to be otherwise used as set out in its Summary of Product Characteristics.

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

- If two trusts apply for ixazomib with lenalidomide and dexamethasone for the treatment of relapsed or refractory multiple myeloma for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

- If two trusts apply for ixazomib with lenalidomide and dexamethasone for the treatment of relapsed or refractory multiple myeloma for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

- If two applications are submitted for ixazomib with lenalidomide and dexamethasone for the treatment of relapsed or refractory multiple myeloma and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

Initial CDF cohorts

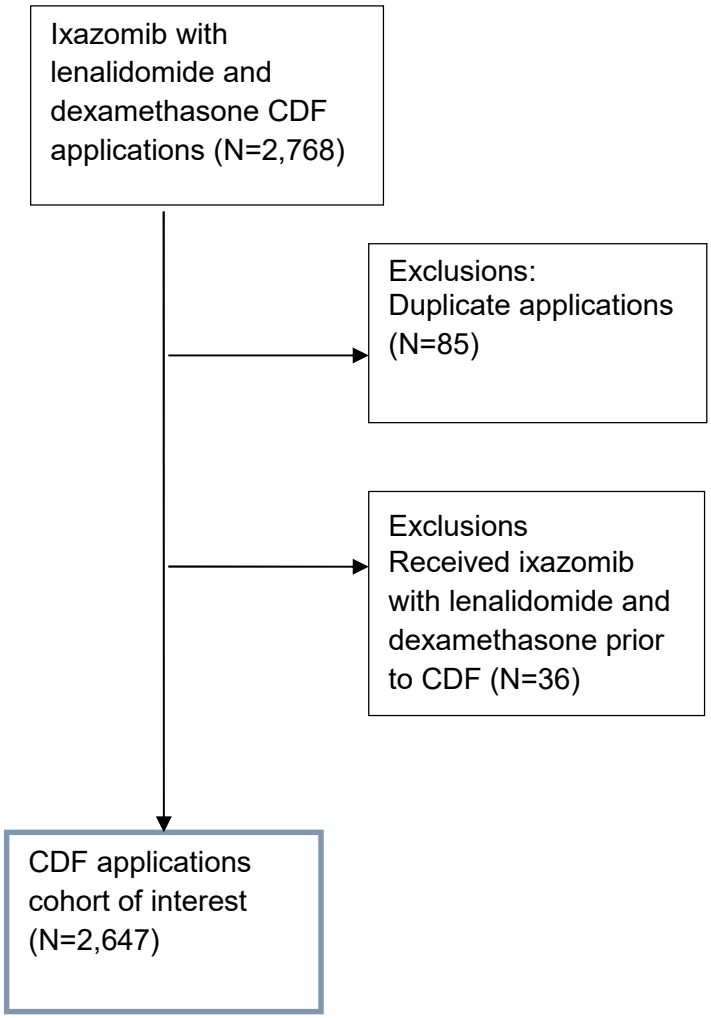
The analysis cohort is limited to the date ixazomib with lenalidomide and dexamethasone entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 19 December 2017 and 18 June 2020. A snapshot of SACT data was taken on 3 October 2020 and made available for analysis on 9 October 2020 and includes SACT activity up to the 30 June 2020. Tracing the patients' vital status was carried out on 25 November 2020 using the personal demographics service (PDS)[1].

There were 2,768 applications for CDF funding for ixazomib with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma between 19 December 2017 and 18 June 2020 in the NHS England and NHS Improvement Blueteq database. Following de-duplication this relates to 2,683 unique patients.

Thirty-six patients were excluded from these analyses as they appeared to have received ixazomib with lenalidomide and dexamethasone prior to the drug being available through the CDF.

Figure 1: Derivation of the cohort of interest from all CDF (Blueteq) applications made for ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma between 19 December 2017 and 18 June 2020



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for ixazomib with lenalidomide and dexamethasone in NHS England and NHS Improvement's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items[8] used to determine a patient's earliest treatment date are:

- Start date of regimen – SACT data item #22
- Start date of cycle – SACT data item #27
- Administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)[8] are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

Start date of regimen
A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle
A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date
An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length', which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Ixazomib with lenalidomide and dexamethasone is administered orally, treatment is generally prescribed in a healthcare facility and healthcare professionals are able to confirm that the prescribing of treatment has taken place on a specified date. A duration of 28-days has been added to final treatment date for all patients; this represents the duration from a patient's last cycle to their next[9]. Ixazomib with lenalidomide and dexamethasone is a 28-day cycle consisting of one administration.

Treatment duration is calculated for each patient as:
Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days). This date would be the patients censored date, unless a patient dies in between their last treatment and the prescription length added, in this case, the censored date would be the patients date of death.

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died.
- the outcome summary, detailing the reason for stopping treatment has been completed:
    - SACT v2.0 data item #41
    - SACT v3.0 data item #58 - #61.
- there is no further SACT records for the patient following a three-month period.

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead/alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) – treatment start date

The patient is flagged as either:

Dead (event):
At the date of death recorded on the PDS.

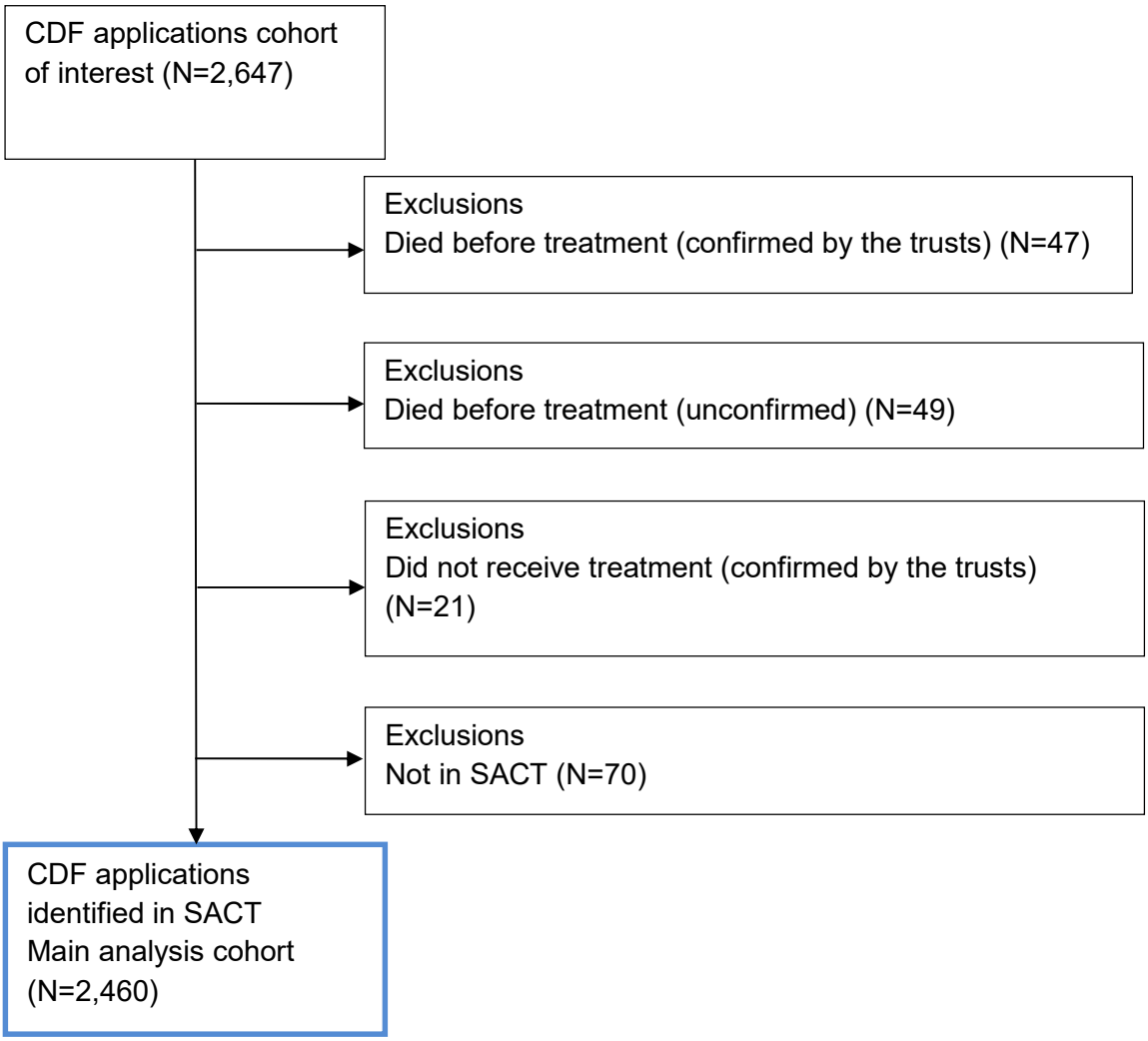
Alive (censored):
At the date patients were traced for their vital status as patients are confirmed as alive on this date.

Results

Cohort of interest

Of the 2,647 new applications for CDF funding for ixazomib with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma, 21 patients did not receive treatment, 96 patients died before treatment and 70 patients were missing from SACT[b] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma between 19 December 2017 and 18 June 2020



[b] The 21 patients that did not receive treatment, all were confirmed by the relevant trust by the PHE data liaison team. Of the 96 that died before treatment, 47 have been confirmed by the relevant trusts by the PHE data liaison team, 49 patients were followed up by the data liaison team but the relevant trust did not confirm if the patient died before treatment.

A maximum of 2,530 ixazomib with lenalidomide and dexamethasone records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 97% (2,460/2,530) of these applicants for CDF funding have a treatment record in SACT.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen is 77% complete.

Table 1: Completeness of key SACT data items for the ixazomib with lenalidomide and dexamethasone cohort (N=2,460)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Sex	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	77%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with ixazomib with lenalidomide and dexamethasone in at least three months. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 1,444. Of these, 1,246 (86%) have an outcome summary recorded in the SACT dataset.

Table 2: Completeness of outcome summary for patients that have ended treatment (N=1,444)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	86%

Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq. Completeness of prior lines, previous treatment outcomes and previous SCT is 100%. Completeness of previous lenalidomide is 36%.

Table 3: Completeness of key Blueteq data items (N=2,460)

Variable	Completeness (%)
Prior lines	100%
Previous treatment outcomes	100%
Previous SCT	100%
Previous lenalidomide[c]	36%

Patient characteristics

The median age of the 2,460 patients receiving ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma was 72 years. The median age in males and females was 71 and 72 years respectively.

Table 4: Patient characteristics (N=2,460)

Patient characteristics[d]		N	%
Sex	Male	1,425	58%
	Female	1,035	42%
Age	<40	10	<1%
	40-49	77	3%
	50-59	311	13%
	60-69	603	25%
	70-79	1,026	42%
	80+	433	18%
Performance status	0	590	24%
	1	953	39%
	2	318	13%
	3	29	1%
	4	6	<1%
	Missing	564	23%

c This data item was added to the Blueteq form at a later date so 100% completeness cannot be expected.
[d] Figures may not sum to 100% due to rounding.

Blueteq data items

Prior lines distribution

The distribution of prior lines in table 5 shows that 95% (N=2,340) of patients received two prior lines of therapy and 5% (N=120) of patients received three prior lines.

Table 5: Distribution of prior lines in Blueteq (N=2,460)

Prior lines	n	%
2	2,340	95%
3	120	5%
Total	**2,460**	**100%**

Previous treatment outcomes

The distribution of previous treatment outcomes in table 6 shows that 84% (N=2,057) of patients responded and relapsed but were not refractory to all prior therapies and 16% (N=403) of patients were refractory to at least 1st line therapy.

Table 6: Distribution of previous treatment outcomes in Blueteq (N=2,460)

Previous treatment outcomes	n	%
Responded and relapsed but not refractory to all prior therapies	2,057	84%
Refractory to at least 1 line of therapy	403	16%
Total	**2,460**	**100%**

Previous stem cell transplant

The distribution of previous stem cell transplant (SCT) in table 7 shows that 62% (N=1,513) of patients have not previously received a SCT and 38% (N=947) of patients previously received a SCT.

Table 7: Distribution of previous stem cell transplant in Blueteq (N=2,460)

Previous SCT	n	%
No	1,513	62%
Yes	947	38%
Total	**2,460**	**100%**

Previous lenalidomide

The distribution of previous lenalidomide in table 8 shows that 2% (N=46) of patients received lenalidomide as part of 1st line therapy, 1% (N=26) of patients received lenalidomide as part of 2nd line therapy and 33% (N=822) of patients were naïve to lenalidomide.

Table 8: Distribution of previous lenalidomide in Blueteq (N=2,460)

Previous lenalidomide	n	%
Received lenalidomide as part of 1st line therapy	46	2%
Received lenalidomide as part of 2nd line therapy	26	1%
Treatment naïve to lenalidomide	822	33%
Not captured	1,566	64%
Total	**2,460**	**100%**

Treatment duration

Of the 2,460 patients with CDF applications, 1,444 (59%) were identified as having completed treatment by 30 June 2020 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with ixazomib with lenalidomide and dexamethasone in at least three months (see Table 12). The median follow-up time in SACT was 8.3 months (252 days).

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of 30 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides a maximum follow-up period of 31 months. SACT follow-up ends 30 June 2020.

Table 9: Breakdown by patients' treatment status[e,f,g]

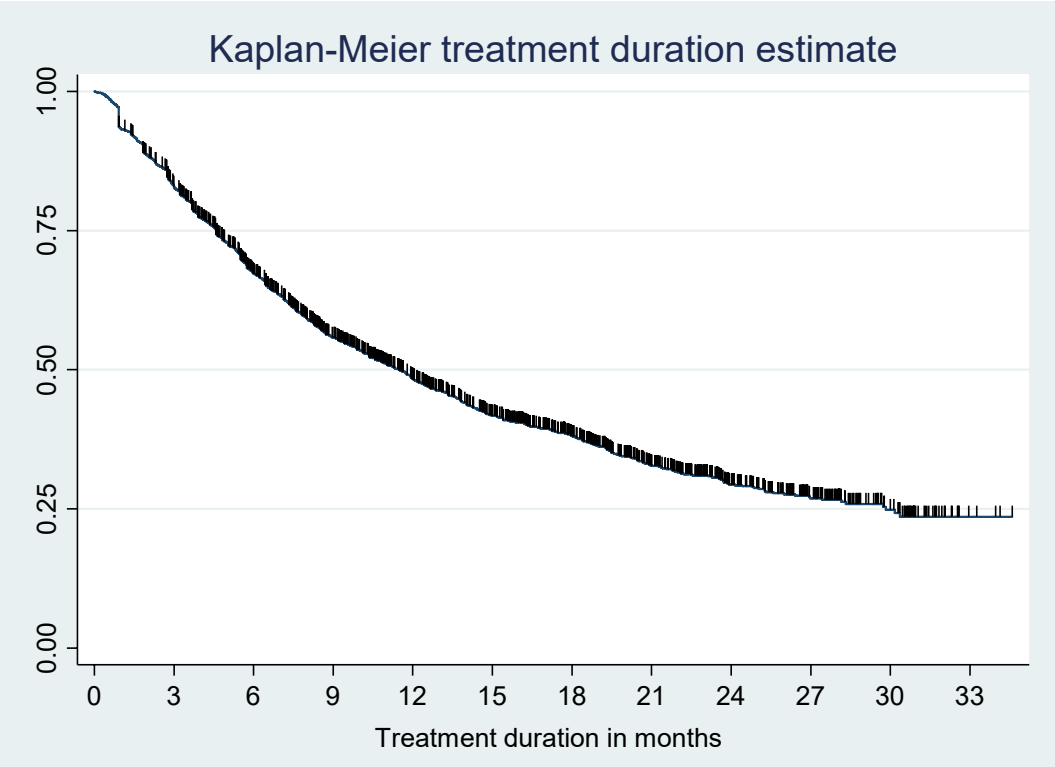
Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	770	31%
Patient died – on treatment	195	8%
Treatment stopped	479	19%
Treatment ongoing	1,016	41%
Total	**2,460**	**100%**

[e] Figures may not sum to 100% due to rounding.
[f] Table 12 presents the outcome summary data reported by trusts. This includes patients from Table 9 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[g] 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/.

The Kaplan-Meier curve for ongoing treatment is shown in figure 3. The median treatment duration for all patients was 11.5 months [95% CI: 10.5, 12.2] (350 days) (N=2,460).

67% of patients were still receiving treatment at 6 months [95% CI: 65%,69%], 48% of patients were still receiving treatment at 12 months [95% CI: 46%, 50%] and 38% of patients were still receiving treatment at 18 months [95% CI: 36%, 40%]

Figure 3: Kaplan-Meier treatment duration (N=2,460)



Tables 10 and 11 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 30 months (913 days). SACT contains more follow-up for some patients.

Table 10: Number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-31	3-31	6-31	9-31	12-31	15-31	18-31	21-31	23-31	25-31	28-31	31
Number at risk	2,460	1,998	1,520	1,143	862	649	488	318	185	110	44	4

Table 11 shows that for all patients who received treatment, 1,016 were still on treatment (censored) at the date of follow-up and 1,444 had ended treatment (events).

Table 11: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored).

Time intervals (months)	0-31	3-31	6-31	9-31	12-31	15-31	18-31	21-31	23-31	25-31	28-31	31
Censored	1,016	973	859	732	593	490	380	271	165	103	42	4
Events	1,444	1,025	661	411	269	159	108	47	20	7	2	0

Table 12 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 59% (N=1,444) of patients had ended treatment at 30 June 2020.

Table 12: Treatment outcomes for patients that have ended treatment (N=1,444)[h,i]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	604	42%
Stopped treatment – acute chemotherapy toxicity	187	13%
Stopped treatment – patient choice	73	5%
Stopped treatment – died not on treatment[j]	248	17%
Stopped treatment – died on treatment	195	14%
Stopped treatment – completed as prescribed	53	4%
Stopped treatment – no treatment in at least 3 months	84	6%
Total	**1,444**	**100%**

[h] Figures may not sum to 100% due to rounding.
[i] Table 12 presents the outcome summary data reported by trusts. This includes patients from Table 9 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[j] 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/.

Table 13: Treatment outcomes and treatment status for patients that have ended treatment (N=1,444)

Outcome[k]	Patient died [l] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – progression of disease	401	203	
Stopped treatment – acute chemotherapy toxicity	74	113	
Stopped treatment – patient choice	33	40	
Stopped treatment – completed as prescribed	14	39	
Stopped treatment – died not on treatment	248		
Stopped treatment – died on treatment			195
Stopped treatment – no treatment in at least 3 months		84	
Total	**770**	**479**	**195**

[k] Relates to outcomes submitted by the trust in table 12.

[l] Relates to treatment status in table 9 for those that have ended treatment.

Overall survival

Of the 2,460 patients with a treatment record in SACT, the minimum follow-up was five months (152 days) from the last CDF application. Patients were traced for their vital status on 25 November 2020. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT was 15 months (456 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Figure 4 provides the Kaplan-Meier curve for OS, censored at 25 November 2020. The median survival was 30 months[m], (913 days) (N=2,460).

Survival at 6 months was 84% [95% CI: 82%, 85%], 12 months survival was 73% [95% CI: 71%, 74%] and 18 months survival was 63% [95% CI: 61%, 65%].

Figure 4: Kaplan-Meier survival plot (N=2,460)

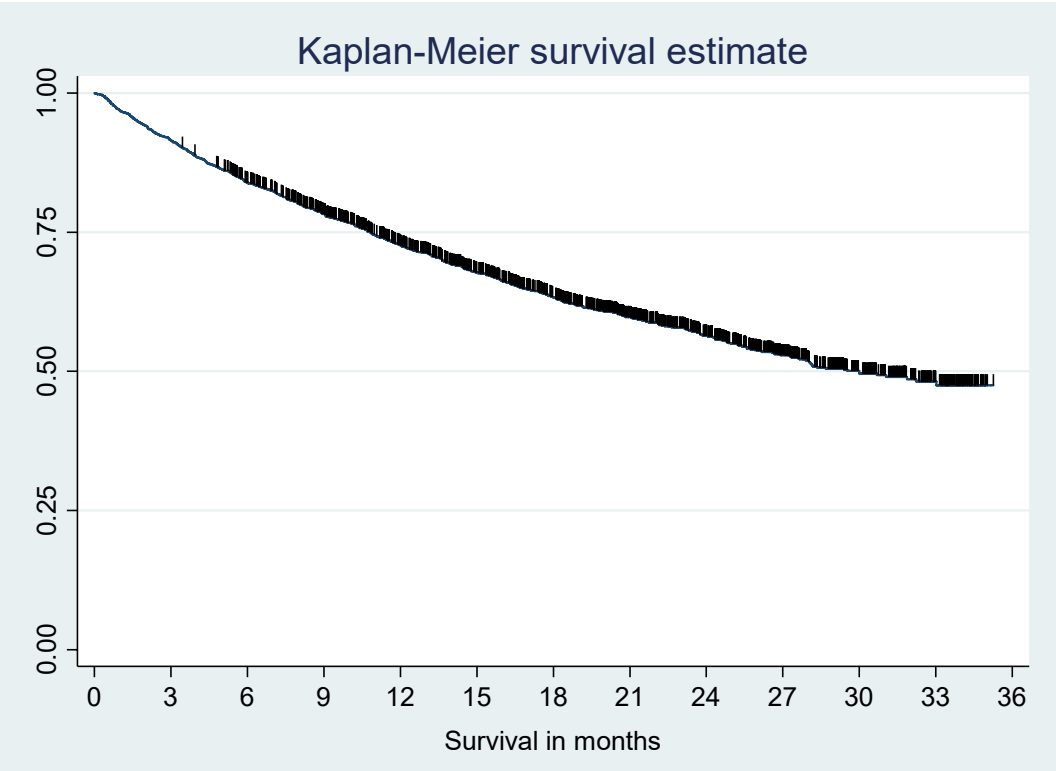


Table 14 and 15 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 35 months (1,065 days), all patients were traced on 25 November 2020.

[m] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

Table 14: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-33	3-33	6-33	9-33	12-33	15-33	18-33	21-33	24-33	27-33	30-33	33
Number at risk	2,460	2,251	2,025	1,776	1,492	1,230	1,004	772	570	373	214	75

Table 15 shows that for all patients who received treatment, 1,495 were still alive (censored) at the date of follow-up and 965 had died (events).

Table 15: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	0-33	3-33	6-33	9-33	12-33	15-33	18-33	21-33	24-33	27-33	30-33	33
Censored	1,495	1,495	1,454	1,339	1,175	1,009	859	679	515	349	209	74
Events	965	756	571	437	317	221	145	93	55	24	5	1

Sensitivity analyses

Cohort 1: 6-month SACT follow up

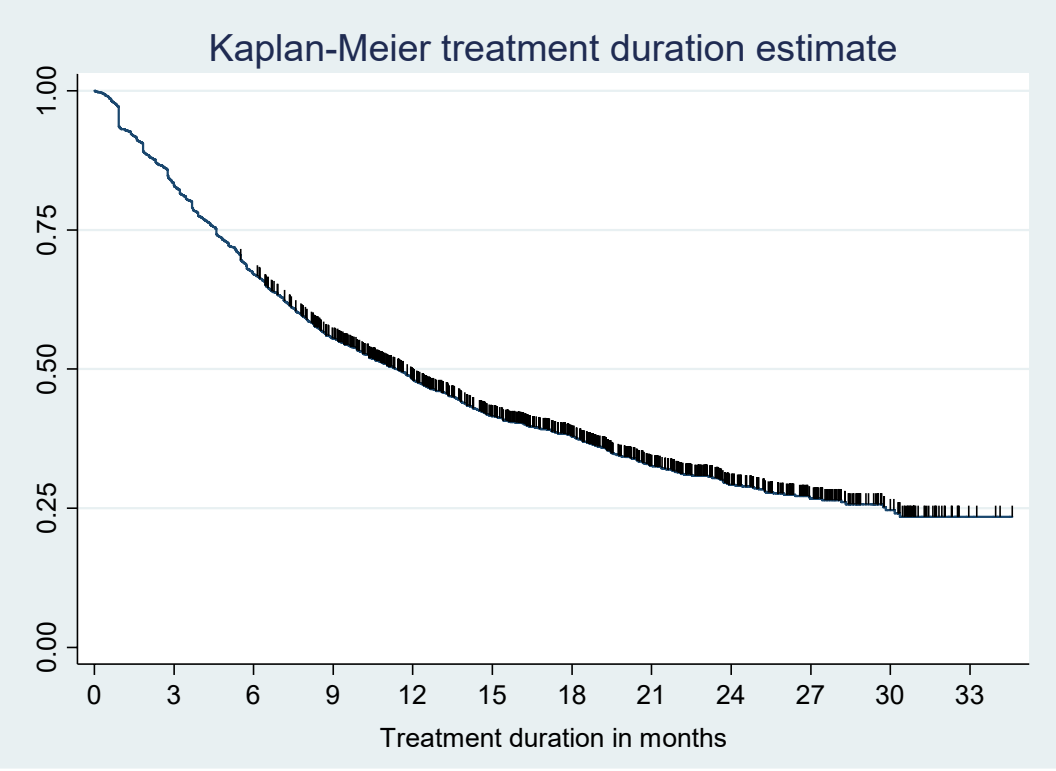
Treatment duration

Sensitivity analyses was carried out on a cohort with at least six months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 19 December 2017 to 30 December 2019 and SACT activity was followed up to the 30 June 2020.

Following the exclusions above, 2,125 patients (86%) were included in these analyses. The median follow-up time in SACT was 9.9 months (301 days)

The Kaplan-Meier curve for ongoing treatment is shown in figure 5. The median treatment duration for patients in this cohort was 11.4 months [95% CI: 10.3, 12.1] (346 days) (N=2,125).

Figure 5: Kaplan-Meier treatment duration plot (N=2,125)



Tables 16 and 17 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 30 months (913 days).

Table 16: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-31	3-31	6-31	9-31	12-31	15-31	18-31	21-31	23-31	25-31	28-31	31
Number at risk	2,125	1,765	1,425	1,133	859	648	487	317	184	109	44	4

Table 17 shows that for all patients who received treatment, 773 were still on treatment (censored) at the date of follow-up and 1,352 had ended treatment (events).

Table 17: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored).

Time intervals (months)	0-31	3-31	6-31	9-31	12-31	15-31	18-31	21-31	23-31	25-31	28-31	31
Censored	773	773	772	723	590	489	379	270	164	102	42	4
Events	1,352	992	653	410	269	159	108	47	20	7	2	0

Overall survival

Sensitivity analyses was also carried out for OS on a cohort with at least six months follow-up in SACT. To identify the cohort, CDF applications were limited from 19 December 2017 to 25 May 2020.

Following the exclusions above, 2,415 patients (98%) were included in these analyses. The median follow-up time in SACT was 15.4 months (468 days).

Figure 6 provides the Kaplan-Meier curve for overall survival, censored at 25 November 2020. The median survival was 30 months[n], (913 days) (N=2,415).

Figure 6: Kaplan-Meier survival plot (N=2,415)

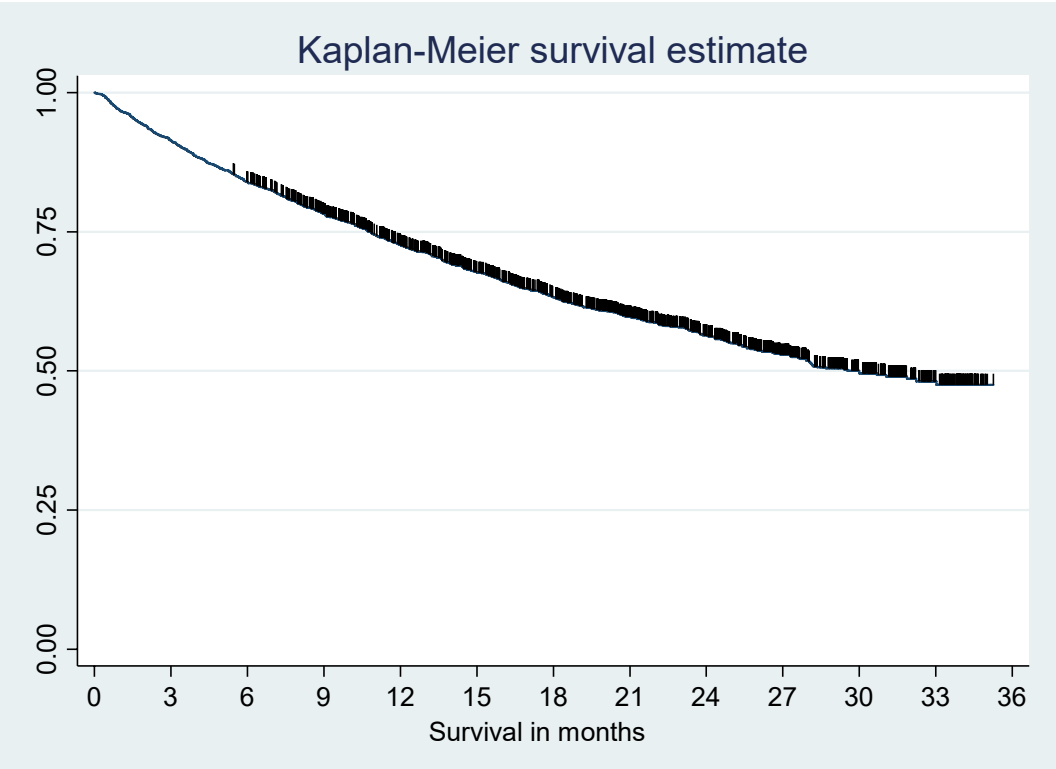


Table 18 and 19 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 35 months (1,065 days), all patients were traced on 25 November 2020.

[n] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

Table 18: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-33	3-33	6-33	9-33	12-33	15-33	18-33	21-33	24-33	27-33	30-33	33
Number at risk	2,415	2,207	2.024	1,776	1,492	1,230	1,004	772	570	373	214	75

Table 19 shows that for all patients who received treatment, 1,456 were still alive (censored) at the date of follow-up and 959 had died (events).

Table 19: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	0-33	3-33	6-33	9-33	12-33	15-33	18-33	21-33	24-33	27-33	30-33	33
Censored	1,456	1,456	1,453	1,339	1,175	1,009	859	679	515	349	209	74
Events	959	751	571	437	317	221	145	93	55	24	5	1

Table 20: Median treatment duration and OS, full cohort and sensitivity analysis.

Metric	Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort: treatment duration	Sensitivity analysis: 6 months follow-up cohort: OS
N	2,460	2,125	2,415
Median treatment duration	11.5 months (350 days)	11.4 months (346 days)	
OS[o]	30 months (913 days)		30 months (913 days)

[o] Confidence intervals could not be produced for OS as there was an insufficient number of events at the time this report was produced.

Conclusions

2,530 patients received ixazomib with lenalidomide and dexamethasone for the treatment of relapsed or refractory multiple myeloma [TA505] through the CDF in the reporting period (19 December 2017 and 18 June 2020). 2,460 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 97%. An additional 21 patients with a CDF application did not receive treatment and 96 patients died before treatment. Not all were confirmed by the trust responsible for the CDF application by the team at PHE.

Patient characteristics from the SACT dataset show that 58% (N=1,425) of patients that received ixazomib with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma were male, 42% (N=1,035) of patients were female. Most of the cohort was aged between 50 and 80+ years (96%, N=2,373) and 76% (N=1,861) of patients had a performance status between 0 and 2 at the start of their regimen.

At data cut off, 59% (N=1,444) of patients were identified as no longer being on treatment. Of these 1,444 patients, 42% (N=604) of patients stopped treatment due to progression, 13% (N=187) of patients stopped treatment due to acute toxicity, 5% (N=73) of patients chose to end their treatment, 17% (N=248) of patients died not on treatment, 14% (N=195) of patients died on treatment, 4% (N=53) of patients completed treatment as prescribed and 6% (N=84) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

Median treatment duration was 11.5 months [95% CI: 10.5, 12.2] (350 days). 67% [95% CI: 65%,69%] of patients were receiving treatment at 6 months, 48% [95% CI: 46%, 50%] of patients were receiving treatment at 12 months and 38% of patients were still receiving treatment at 18 months [95% CI: 36%, 40%].

The median OS was 30 months[p] (913 days). OS at 6 months was 84% [95% CI: 82%, 85%], OS at 12 months was 73% [95% CI: 71%, 74%] and OS at 18 months was 63% [95% CI: 61%, 65%].

Sensitivity analyses were carried out to evaluate a cohort for which all patients had a minimum follow-up of six months. Results for treatment duration showed a difference of 0.1 months but this was not statistically significant (full cohort = 11.5 months; sensitivity analysis cohort = 11.4 months). The median OS was the same in both the full and sensitivity analysis, 30 months.

[p] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (CDF review of TA505) [ID1635]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report, in section 1.1.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Tuesday 16 November 2021**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	**Takeda UK Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Generalised gamma modelling of the adjusted overall survival: 2-stage re-censoring (novel therapies).	No	The generalised gamma curve was selected, by myeloma clinical experts at an advisory board, as reflecting expected outcomes for IXA+LEN+DEX and outcomes observed in clinical practice for LEN+DEX in the 2+ prior lines population. The clinical experts selected the generalised gamma curve after having considered a range of different options.
Uncertainty around model selection for adjusted overall survival: 2-stage re-censoring (novel therapies).	No	Table 1 below (Table 18 in the ERG Technical Engagement report) compares the outcomes predicted using the unadjusted OS data with those predicted using the adjusted OS data (as per the Company's base case) – adjusted to remove the effect of subsequent therapies which are neither reimbursed nor routinely available for use in clinical practice in the UK, as per the NICE Position Statement.[1] The ERG conclude that these results "depart from clinical plausibility" in terms of LY gains (Key Issue 2 in the ERG report). The Company strongly disagrees with these statements. Firstly, it is unclear at multiple points throughout the report on what basis the ERG justifies its assertion that results are clinically implausible. Throughout the CS, appendices and post-submission engagement, the Company has been clear on its

		rationale and clinical support – from a UK advisory board in March 2021 – on the plausibility of the data presented. By contrast, the ERG – at multiple points in its report – provides an opinion on clinical implausibility without justification or reference to clinical expert opinion. This is a point that has been raised repeatedly by the Company and we are yet to receive clear justification from the ERG on the basis for its assertion. The Company wishes to reiterate its position – which has been validated with 12 consultant haematologists at a UK advisory board – that the treatment switching approach provides clinically plausible results. Taking the ERG's specific point around the life years accrued in the LEN+DEX and IXA+LEN+DEX arms. Adjustment using the two-stage estimator (TSE) methodology results in a reduction in the life years accrued in the LEN+DEX arm of 3.62 months. Whereas, a smaller reduction in the life years accrued in the IXA+LEN+DEX arm of 0.39 months is observed. These findings align with our interpretation of the confounding from subsequent therapies and align with the expectations from our outreach to clinical experts (as outlined above). Therefore, we disagree with the ERG's conclusion – and its assertion that the results are not consistent with the Company's position on the influence of subsequent therapies on OS – and believe that the results are clinically plausible. An in-depth rationale is provided below.

Table 1: Unadjusted OS data vs. adjusted OS data (Table 18 of ERG Report)

Model name	Effect	Therapy	Median OS months	Median OS year	HR (95% CI)	Total LYs	LYs	
							Pre-Progr.	*Post-Progr.*
Unadjusted	Presumed "positive" effect of novel therapies = INCLUDED	IXA+LEN+DEX	53	4.42	0.845 (0.642, 1.114)	4.89	*2.25*	*2.65*
		LEN+DEX	43	3.58		4.08	*1.50*	*2.59*
		Incremental	10	0.83		0.81	0.75	0.06
TSE (re-censored* + adjust for baseline characteristics†)	Presumed "positive" effect of novel therapies = EXCLUDED	IXA+LEN+DEX	51.4	4.28	0.713 (0.535, 0.952)	4.86	*2.25*	*2.62*
		LEN+DEX	41.5	3.46		3.78	*1.50*	*2.29*
		Incremental	9.9	0.83		1.08	0.75	0.33

CI, confidence interval; HR, hazard ratio; LY, life-year; OS, overall survival

In the TOURMALINE-MM1 (T-MM1) clinical trial, there was an imbalance in the type and number of subsequent therapies which are neither reimbursed nor routinely available across the IXA+LEN+DEX and LEN+DEX treatment arms. Patients in the LEN+DEX treatment arm received more novel therapies in subsequent lines and also received more subsequent lines in total when compared to the IXA+LEN+DEX arm. The effect of receiving novel therapies on survival is shown in Figure 1 (Figure 2 in the CS); patients who receive novel subsequent therapies are shown to have superior survival. This effect is more pronounced in the LEN+DEX arm compared with the IXA+LEN+DEX arm as shown in Figure 2 (Figure 3 of the CS). This difference is driven by the fact that more patients in the LEN+DEX arm than in the IXA+LEN+DEX arm received novel subsequent

		therapies which are known to have prognostic importance, for example: daratumumab (31/149=21% in LEN+DEX vs. 19/148=13% in IXA+LEN+DEX), elotuzumab (7/149=5% vs. 3/148=2%) and autologous stem-cell transplant (9/149=6% vs. 1/148=0.7%) – this information is presented clearly in Section A.6.1 and Appendix B of the CS. Additionally, patients in the LEN+DEX arm received a median of three lines of subsequent therapy (mean 3.3) vs. two in the IXA+LEN+DEX arm (mean 2.4). Figure 2 clearly demonstrates that the confounding is greater in the LEN+DEX arm. Therefore, any statistical adjustment to remove this confounding would be expected to have a greater impact in the LEN+DEX arm. Also in Figure 2, the difference in survival for patients receiving novel subsequent therapies vs. those who don't is smaller in the IXA+LEN+DEX arm and the curves move closer together at the end of follow-up. Based on this we would not expect as big a difference in the IXA+LEN+DEX arm. The methods used and results estimated from the statistical adjustment have been validated by clinical experts during an advisory board and in follow-up interviews. Clinicians considered that both the direction of change and the size of change were plausible given the subsequent therapies received in T-MM1. Therefore, we believe that the results are clinically valid and do reflect what would be expected in the absence of these novel subsequent therapies. Section A.6.1 and Section A.7.1 in the CS explain this in detail.

Figure 1: OS unadjusted Kaplan–Meier curves for patients identified as switchers vs. non-switchers (all patients)

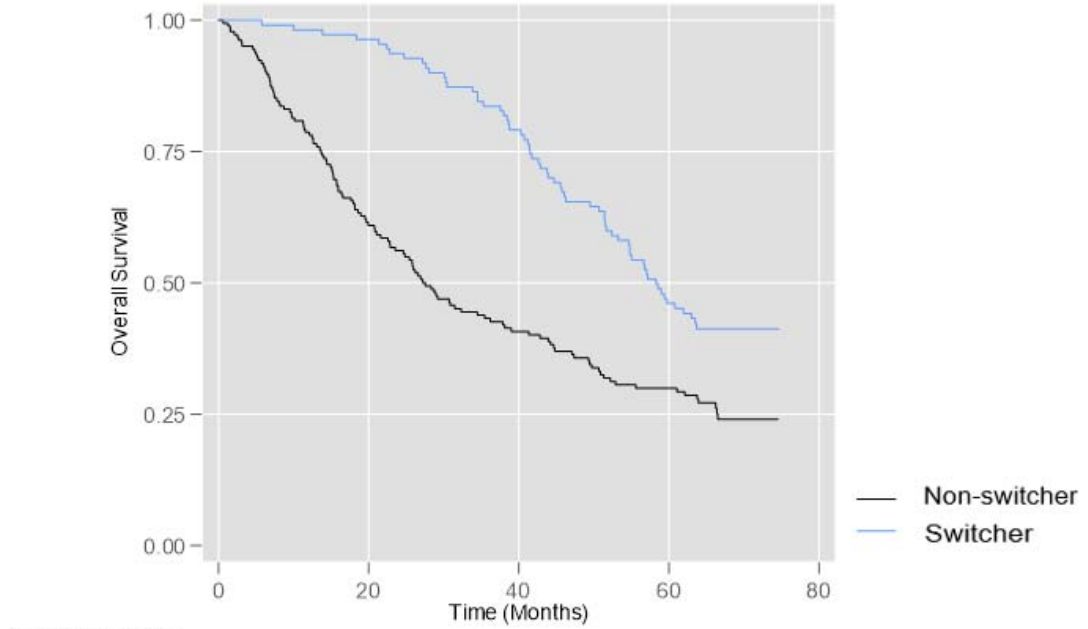
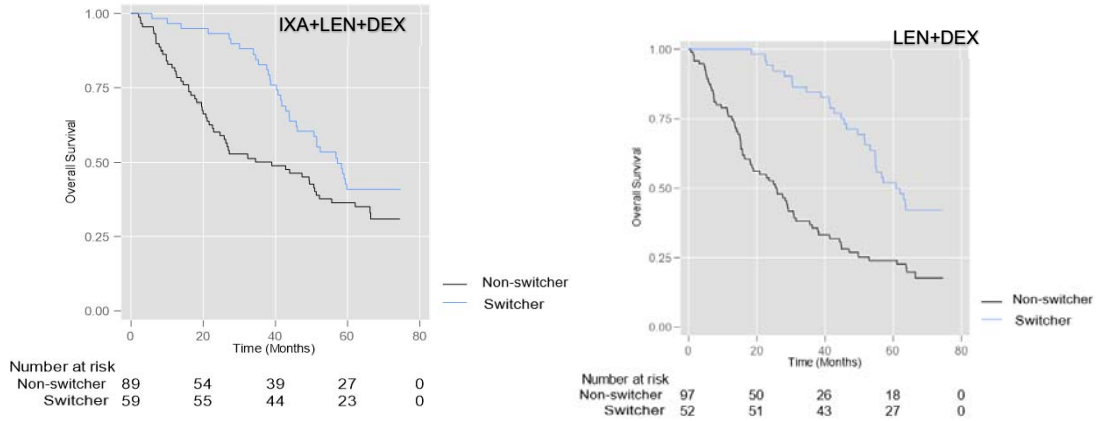


Figure 2: OS unadjusted Kaplan–Meier curves for patients identified as switchers vs. non-switchers (separated by treatment arms)



Abbreviations: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; OS, overall survival

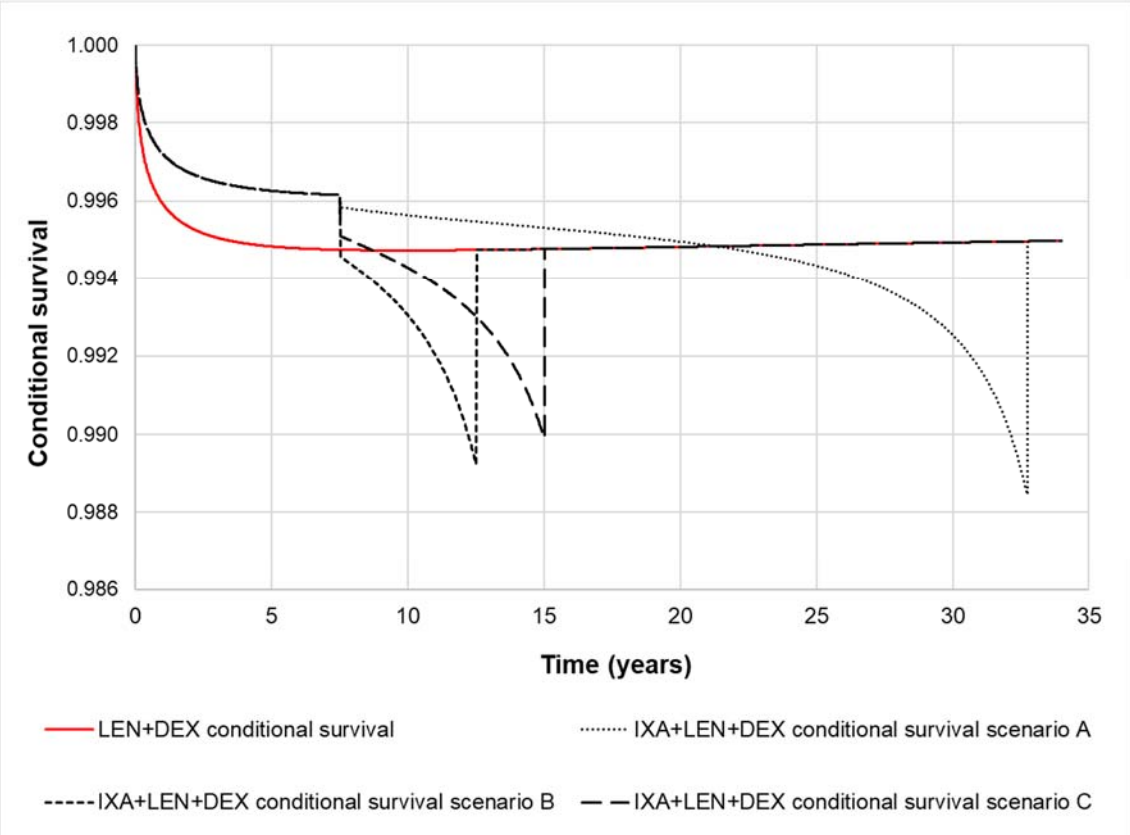
In addition, related to this issue, during Technical Engagement the ERG highlighted their concern that the impact of adjusting for novel subsequent therapies was greater in terms of the predicted hazard ratio compared with the median values. The effect of the adjustment reduces the hazard ratio from 0.845 (95% CI: 0.642 – 1.114; unadjusted) to 0.713 (95% CI: 0.535 – 0.952; adjusted) in the 2–3 prior therapies population. The corresponding median values (53 vs. 43; unadjusted and 51.4 vs. 41.5; adjusted, for IXA+LEN+DEX vs. LEN+DEX, respectively) provide a snapshot of the time at which 50% of the population are alive. The literature is clear that median values should be interpreted with caution and are not of statistical value; these reflect a single time point

		and do not account for the full duration of follow-up.[2] Reflecting the full duration of follow-up is particularly important in this setting where the potential for confounding is greater as the length of follow-up increases (i.e. in the latter part of the Kaplan–Meier plots). Consequently, we believe significantly more importance should be placed on the change in the HR (which is reflective of the entirety of the survival curves) rather than on the medians.
The sustained effect of treatment.	No	The ERG report explores treatment waning in exploratory scenarios. We fundamentally disagree with the ERG's approach to treatment waning, and we are concerned by some of the language used by the ERG to describe this within their report. We consider the methods used within the ERG's exploratory scenarios to be clinically implausible. Firstly, we want to emphasise that we now have a median follow-up of 85-months (over 7-years) from the T-MM1 clinical trial. Patients received treatment with IXA+LEN+DEX and LEN+DEX for a median of 18.2-months and 13.4-months, respectively. This leaves a window of 66.8 months (5.6-years) and 71.6 months (6.0-years) where patients are **not** receiving the **study treatments**. The mean time on treatment within the trial was 25.8 and 20.0, respectively. Using these values this leaves a window of 59.2-months (4.9-years) and 65-months (5.4-years) where patients are **not** receiving the **study treatments**. Therefore, we believe that the follow-up time post-discontinuation within the trial is sufficient to reflect any treatment waning.

		We are concerned by the wording in the ERG report around the "sustained effect of ixazomib after treatment has ended" and how this could be misinterpreted. We do not assume a sustained effect of ixazomib. We use the treatment effect estimated across the whole trial follow-up, including the effect of ixazomib **and** subsequent therapies relevant to UK clinical practice (in the base case). Therefore, in terms of OS, the hazard ratio or treatment effect in the IXA+LEN+DEX arm is no longer the isolated effect of treatment with IXA+LEN+DEX, but a composite measure reflecting a pathway of treatments. We have no evidence of a sustained effect of IXA+LEN+DEX and do not claim – and have never claimed – this within the CS. This point was already flagged as part of the Company's factual accuracy check of the ERG report. Another concern around the wording is in relation to the ERG's proposed approach to explore treatment waning: "The ERG's alternative approach would be to apply a waning of the post treatment continuing effect to the generalised gamma" (page 11 of the ERG report). None of the scenarios the ERG explore relate to the treatment effect within the model. The scenarios work by forcing the overall survival curves (not the treatment effect) to equal each other at specific time points. This is achieved by changing the overall survival probabilities and it results in a higher probability of dying in the IXA+LEN+DEX arm compared to the LEN+DEX arm, until such time as the curves are equal. We see no biological or pharmacological justification for this and it is an approach we consider to be completely clinically implausible. It is unclear what clinical expert validation (if any) the ERG has sought on this important point. **We consider it essential that NICE seeks**

		clinical expert opinion on this issue, ideally in advance of the Appraisal Committee Meeting scheduled for December 15th. We are also concerned about all reference to waning of the effect within the report as this implies a hazard ratio trending to 1.0 over time – this is not what the ERG has implemented. Further detail is provided below. The ERG considers three scenarios: Scenario A ("slow waning over 18-years"), Scenario B ("fast waning over 5-years") and Scenario C ("waning over 7.5-years"). Figure 3 presents the probability of dying each cycle within the model (i.e. the conditional survival). For example, if the conditional survival is 0.98 this means that 98% of the patients that are still alive in cycle x will survive to cycle x+1. This plot demonstrates that all three of the scenarios which the ERG explores results in a higher probability of dying in the IXA+LEN+DEX arm compared to the LEN+DEX arm. This increased risk of dying is maintained until the curves become equal, at which point the probability of dying immediately improves to equal the LEN+DEX arm. As above, we do not think that any evidence exists to support these scenarios and we do not consider them to be clinically plausible. We repeat our earlier call for NICE to seek clinical expert opinion on these ERG scenarios and the whole concept of treatment waning in relation to this CDF Review of ixazomib.

Figure 3: Conditional survival derived from the ERG's waning scenarios



As explained in our CS (see Section A.7.2), the updated OS data from the T-MM1 trial reflects survival outcomes for >96% of patients who have discontinued treatment with

		IXA+LEN+DEX and for >99% of patients who have discontinued treatment with LEN+DEX. Therefore, we believe any treatment effect waning is already reflected within these updated OS data. For illustrative purposes, in our CS we included a scenario analysis which explored waning the treatment effect for both the IXA+LEN+DEX and LEN+DEX treatment arms from the end of the trial follow-up over a 5-year time period for the 4% and 1% of patients, respectively, still on these treatments in the trial. As shown in Table 20 of the CS and Table 29 of the Appendices to the CS, this had a negligible impact on the ICER (ICER reduced by [redacted] and £4 respectively compared to the base case). This supports our position that treatment waning is not relevant to this CDF Review of ixazomib. This is consistent with the position reached by the Appraisal Committee at the conclusion of the original ixazomib appraisal (TA505) where the Committee's preferred base case for decision-making purposes did not include treatment waning (see Section 3.14 of TA505).[3]

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Lack of progression-free survival (PFS) data in the final analysis of the pivotal trial (TOURMALINE MM-1).	Sections 1.1, and 1.3	No	On page 8 (and elsewhere), the ERG states that it "recognises that data on PFS were not collected beyond the second interim analysis (IA2) of T-MM1. Therefore, there are no updates to PFS available." The ERG further states on page 25 that "[it considers] that updated PFS would have been beneficial for the CDF review, as PFS is not affected by the post-progression treatment switching that leads to confounding. However, the ERG acknowledge that it was not in the statistical analysis plan." The Company has repeatedly made the following points during the CDF review process. 1. As stated on page 4 of the CS, during the original ixazomib appraisal (TA505) the Committee used data from the second interim analysis (IA2) of the T-MM1 study – with a median follow-up of 23-months – to

			assess the cost-effectiveness of IXA+LEN+DEX.[3,4] At IA2, PFS data were **mature**, and demonstrated a significant 9-month median PFS advantage for IXA+LEN+DEX vs. LEN+DEX (hazard ratio [HR] = 0.617, 95% confidence interval [CI] 0.445–0.855; p=0.033) in patients who have had 2 or 3 prior lines of therapy.[5] 2. As PFS data at IA2 were considered mature, collection of further PFS data was not included in the CDF Data Collection Agreement that was agreed with NHS England. PFS was not considered by the Committee to be a key uncertainty in the original ixazomib appraisal (TA505). 3. Consistent with the points above, submission of new PFS data was not included in the Terms of Engagement provided by NICE for this appraisal. 4. As the ERG correctly states, as specified in the T-MM1 Statistical Analysis Plan (SAP), data on PFS were not collected beyond IA2 of T-MM1. However, to imply that updated PFS are not presented solely due to the T-MM1 SAP is both incorrect, and inconsistent with the CDF Data Collection Agreement and the NICE Terms of Engagement. We are disappointed to note that a request made by the Company in relation to this issue during its factual accuracy check of the ERG report was not actioned by the ERG. Furthermore, on page 50 of the report, the ERG states *"The company submitted the same PFS analysis as submitted in response to ACD following original STA appraisal (ID TA505); this is based on data up to interim analysis*

			IA2 and is therefore less mature than data now submitted for ToT and for OS, each of which correspond to the final data cut." It is not correct to say that the data are "less mature". The primary endpoint of T-MM1, PFS, was actually reached at the first interim analysis (IA1) which occurred after a median follow-up of 15 months. A second non-inferential assessment of the PFS was conducted at IA2 (median follow-up of 23 months). Due to longer follow-up, IA2 was the data cut preferred by the NICE Committee, but the primary endpoint was reached (and therefore should be considered mature) at IA1. This issue recurs on page 40, "It should be borne in mind that the PFS KM are based on AI2 and are less mature than other KMs." It is the Company's position that additional PFS data are clearly beyond the agreed scope for this CDF Review of ixazomib.
Inclusion of inappropriate ITT analysis in the ERG report, beyond the scope of the current CDF Review	Section 3.1.6 (pages 32 and 33)	No	Despite stating on page 31 of the report that "The ERG agrees with the company in not using the ITT analysis or per-protocol censoring and exclusion of switchers post-progression", on pages 32–33 the ERG conducts de novo analysis of published (non-patient-level data) for the T-MM1 ITT dataset. They state that they have "*reviewed the final OS analyses of the T-MM1 trial beyond the scope of the CDF review, i.e. including the ITT T-MM1 population (RRMM with 1+prior therapy) and based on the original analyses planned in the T-MM1 SAP."* We believe that this analysis is not relevant to the current decision problem for a number of reasons:

			1. The analysis presented in the report is based on a broader patient population than that under consideration in this CDF Review. Patient populations differed in a number of key parameters that affect prognosis, including number of prior therapies received, and subsequent therapies received. 2. The 1 prior therapy subpopulation from T-MM1 was excluded from the initial appraisal for ixazomib, after substantial discussion between the Company and the NICE Committee 3. Extrapolating results from one patient population to another, based on a dataset that includes patients outside of the scope for this CDF Review is therefore wholly inappropriate It is unclear to the Company what value this analysis adds to the decision-making process beyond perhaps an attempt to discredit the treatment switching methodology and results – which are based on methods recommended by NICE in TSD 16 – utilised in the CS. This point was raised by the Company during its factual accuracy check of the ERG Report. The Company maintains that this analysis is not relevant to the current decision problem.
Lack of clarity in the ERG report on what constitutes ERG opinion vs clinical expert opinion	Throughout the report, and specifically Section 3.2.2	No	Throughout this review process, the Company has been clear and transparent about its assumptions, and the clinical rationale that supports them. An advisory board with 12 Consultant Haematologists was conducted in March 2021, and the consensus from these myeloma clinical experts was used to inform the economic model. Given the extensive clinical validation conducted by the Company, it is disappointing to read phrases such as *"The ERG thinks*

	(pages 42 and 47)		*there is so little difference in predicted survival between generalised gamma (dashed lines) and Weibull (dotted lines) that clinical experts would be unable to distinguish one from the other and therefore on this basis the ERG thinks the Weibull based ICER is as equally valid as the generalised gamma-based ICER"* We would question whether it is appropriate for the ERG to suggest what clinical experts would, or would not, be able to distinguish. In the March advisory board conducted to help inform this review, clinical experts noted the similarity of the curves, but ultimately selected the generalised gamma over the Weibull. Multiple requests were made by the Company to the ERG to clarify in their report what is ERG opinion, what has been validated with myeloma clinical experts, and the justification for the positions taken by the ERG. Despite the Company's requests, the technical engagement report does not provide these clarifications, and there are numerous references to "implausible outcomes" without rationale or justification to support such assertions. As currently written, the ERG report implies that these statements are facts when they are likely opinions or judgements. The Company would like to put on record that it requested clarification in the report on:

			1. what is ERG opinion, 2. what is based on clinical expert advice, and 3. for both, what is the justification for the position taken by the ERG The aim of this was to provide the Committee with information on what is/is not clinical expert opinion, and to enable the Company to explore further if clinical experts thought that any of the results were clinically implausible. To date, the Company has received no response from the ERG to these requests and we remain unclear what clinical validation (if any) has been undertaken by the ERG. Therefore, we would suggest that all references to "clinical implausibility" within the ERG report should be interpreted with caution.
Rationale for excluding RPSFT method to adjust for treatment switching.	Section 3.1.2 (page 27)	No	The ERG states that *"The company also considered the Rank Preserving Structural Failure Time (RPSFT) Models method to adjust for bias due to switching to subsequent treatments, but because the T-MM1 trial was multicentre, the common treatment effect assumption across multiple trials was not deemed to be valid (CS Document, Section A.7.1, pages 26-29)."* As already highlighted in the Company's factual accuracy check, it is incorrect to say that the RPSFT method was not selected because T-MM1 was multicentre. In the CS (Section A.7.1, page 29), we clearly state that "The RPSFTM methods were also considered. However, in MM, the common treatment effect assumption has been shown to be invalid across multiple trials. This was confirmed by UK clinical experts who noted the relative efficacy of different treatment regimens varies depending on the line of therapy. Therefore, these methods were discounted from further analysis."

			The ERG statement is inaccurate, it misrepresents the Company's position and is not consistent with the information submitted by the Company to NICE. This was highlighted by the Company during the factual accuracy check of the ERG report, but has not been amended by the ERG.
ERG misrepresentation of NICE methods	Section 3.1.1 (pages 25–26)	No	In its report the ERG correctly states that *"the company adjusted the updated OS HR estimates to account for the impact of subsequent therapies which are not routinely funded in the UK (i.e., not available, or only funded via the CDF)."* However, it goes on to state that *"The company (and company's clinical advisors) propose an expected "UK clinical practice" pathway for subsequent line(s) of treatment (CS Document, page 8). As far as the ERG can ascertain, no guidelines exist describing this pathway; even if the proposed expected UK pathway is accurate, it is unlikely to remain unchanged in the near future as more research is published regarding the clinical effectiveness of new treatments beyond three or four lines. However, the company survival analysis assumes that their expected pathway will continue to operate for a further 26 years (from approximately 8 to 34 years) beyond the trial final cut."* In the Company's view, the ERG fundamentally misrepresents our approach, and also deviates from the scope and approved methods for NICE appraisals. In no section of the submission documents does the Company state that the therapies included in the switching analysis comprise the only therapies that will be used in routine practice in the NHS for the model time horizon. As the ERG is no doubt aware, therapies currently funded via the CDF are used by

			UK clinicians, and treatment pathways are subject to change as new, efficacious therapies are approved. However, the Company has adhered consistently to the remit and scope for this CDF Review, namely:[6] 1. That "the scope for re-consideration will remain the same as the final scope used for the published guidance" i.e. the treatment pathway and comparators as they were during the original appraisal, and 2. Consistent with NICE's Position Statement, medicines available only via the CDF and not via routine commissioning should not be included as a comparator or subsequent therapy.[1] The adjustments to the OS data conducted by the Company address both of these considerations, are consistent with methods used for previous appraisals in RRMM,[7] and the Company maintains that its approach to treatment switching are wholly consistent with approved NICE methods.
Residual ERG critiques that the Company addressed fully during clarification questions (1/2)	Section 3.1.6.3 (page 34–35), and Section 3.2.1 (page 36)	No	The ERG states on page 36 that *"The KM for TSE-OS, copied from the submitted economic model, implies that the TSE-OS KMs extend to approximately 7.8 years, corresponding to the depiction in CS Figure 8, page 35 (see also ERG Section 9.1) but not corresponding to Figure 7 page 33. The ERG cannot explain these differences.* *The unadjusted OS KM plots (CS Figure 1) extend to about 90 months approximately 7.5 years (unfortunately time axis tick marks are lacking in this and other CS figures). The ERG is unsure why OS extends beyond ToT but believe this may be an error in view of IPD data supplied to the ERG by the*

			company during the second round of clarifications (received October 7 2021: document ID1635 ixazomib Takeda clarification questions A3_A4 05102021CM noACIC). This indicates that for the two-stage adjusted OS, the first death event or censoring time occurred at 10 weeks and the last death event or censoring time occurred at 324 weeks (6.21 years). The relevant part of the CS clarification document is shown Table 14. The same time of 324 weeks for last death or censoring was also shown for the LEN+DEX arm." On page 34, the ERG also states that it *"had difficulties interpreting and validating the properties of the TSE-OS models presented in the CS because there were apparent contradictions within the CS (KM depictions in Figures 7 and Figure 8), and between the information supplied in clarification document (round two clarification) ID1635 ixazomib Takeda clarification questions A3_A4 05102021CM noACIC and information provided within the economic model."* This issue was addressed in the Company responses to the Additional ERG Clarification Questions (document *ID1635 Company response to additional ERG clarifications [CIC]).* As stated on page 5 of this document, *"the maximum time we have Kaplan–Meier data for IXA+LEN+DEX is 401 weeks for the unadjusted OS analysis and 324 weeks for the adjusted OS analysis – see the screenshots below from the response to A3 from the Clarification Questions. When the adjusted OS data are selected there is no Dynamic Chart function set up in the model. Therefore, the tail of the Kaplan–Meier curve is defaulting to the last survival estimate until 401 weeks; from week 324 to week 401 the same survival*

			estimate is used resulting in a longer flat tail. This has no impact on any of the model calculations and did not influence the parametric curve selected in the base case." The ERG report does not incorporate the Company's responses to the latest round of clarification questions, despite the Company submitting its responses prior to receiving the draft version of this report. The Company has addressed the ERG's criticism and it is disappointing to find the same critique in the published report, particularly given the implied – but incorrect – suggestion that the Company submitted inconsistent data and used the data incorrectly in the statistical analyses.
Residual ERG critiques that the Company addressed fully during clarification questions (2/2)	Section 3.1.7 (page 35)	No	In the referenced section, the ERG states that *"ToT and PFS correlated well for the LEN+DEX arm. However, for the IXA+LEN+DEX arm, there was a mismatch as discontinuation preceded progression. Although these comparisons are based on rather unsatisfactory data (in that PFS analysis was only available to IA2 cut off) the mismatch in one arm, but not the other, suggests there may be bias in the costing of treatments that may favour the IXA+LEN+DEX arm."* In the original NICE submission [TA505], the relationship between ToT and PFS was discussed at length. In the Committee Papers it is stated: *"During the second committee meeting, the Committee accepted that ToT can be and generally is less than PFS and that the gap is larger for the IXA+LEN+DEX arm within the T-MM1 observed period (in part due to the depth of response achieved by a triplet compared to a doublet regimen as was described within the consultation submissions).*

			However, the Committee questioned the magnitude of the difference between PFS and ToT, particularly within the modelled period. The ERG commented within their addendum that assuming a Weibull distribution for ToT as well as PFS negated this issue."[8] As part of the Clarification Response for this original appraisal, Takeda provided a detailed rationale and evidence supporting the link between response and PFS which supported the extended PFS beyond treatment discontinuation in the IXA+LEN+DEX arm. For more information, please refer to the original Committee Papers.[8] We do not think that this discussion needs to be re-visited, particularly as: 1. the rationale for PFS extending beyond treatment discontinuation in the IXA+LEN+DEX arm remains the same as in the original appraisal, 2. the PFS data have not been updated in this CDF Review and a Weibull curve has been applied to extrapolate outcomes (in line with the original NICE submission and ToE), 3. the ToT data have been updated and are almost complete and as such there is substantially reduced uncertainty associated with these data, in addition a Weibull curve has been applied to extrapolate outcomes (in line with the original NICE submission and ToE), and 4. this was not specified as an uncertainty for which more data was required as part of the CDF terms from the original submission.

Request by the ERG for confidential patient-level data	Section 9.3.1 (relating to ERG request for IPD) and Sections 1.3, 1.4, 3.22 and 6.5 (relating to IPD reconstruction by the ERG)	No	During clarification questions (September 27) the ERG requested patient-level information (QA.1). The Company responded to this request as best it was able within the limitations of being unable to provide confidential patient-level study data to outside organisations. In its report (pages 76–77), the ERG implies that the Company misunderstood the request, and that requests of this nature are routine for NICE technology appraisals. To the Company's knowledge this is not correct, and the Company does provide individual patient-level data to outside parties. However, in response to the ERG's request, we provided the Kaplan–Meier data as a separate Excel document – note these were also available within the economic model. The Company also notes that the ERG has reconstructed an approximation of the IPD for a number of its analyses. The Company would advise treating with caution any conclusions drawn from reconstructed IPD.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
NA. Changes to the Company's base-case ICER are due to the implementation of an updated Simple PAS for ixazomib. No changes have been made to the Company base-case beyond inclusion of the updated Simple PAS.	NA	NA	The new base-case ICER, including the updated Simple PAS, is £37,519, a reduction of £28,184 from the company's original base-case ICER (£65,703). **Full details and additional scenarios are presented in Appendix A.**

Sensitivity analyses around revised base case
See Appendix A.

Additional scenario analyses
As described to NICE in the New Evidence Submission form submitted by the Company on November 10th, three appendices are included in this response document: Appendix A, Appendix B and Appendix C.

Appendix A presents the Cost-effectiveness results and scenarios, including the updated Simple PAS for Ixazomib.

Appendix B presents additional scenarios exploring the impact of differing discount levels for generic lenalidomide. These scenarios provide additional information on the ixazomib ICER (including the updated Simple PAS) at differing discount levels for generic lenalidomide.

Appendix C explores the impact of upcoming changes in the NICE Methods Guide. Given the timing of this CDF Review for ixazomib and its relevance to the management of myeloma patients in the future, we believe it is appropriate to consider how the outcome of the Methods Review, particularly in relation to the severity modifier proposal, could impact on NICE's decision making. Appendix C provides the predicted willingness-to-pay thresholds for ixazomib – based on T-MM1 QALYs – should the proposed NICE Methods changes be applied to ixazomib.

Appendices to Technical Engagement

Appendix A | Cost-effectiveness results including the updated Simple PAS for ixazomib

The inclusion of this Appendix A has been agreed with NICE. It includes an updated Simple PAS that the company would like to be used as the basis for the decision-making ICERs considered by the Appraisal Committee at the meeting scheduled for December 15th 2021. In structure and content this Appendix A is equivalent to Appendix F that was included with the CS, and it should be seen as a replacement for Appendix F to the CS.

In April 2021, Takeda applied successfully to NHS England to reinstate a Simple PAS to replace the existing Commercial Access Agreement (CAA) within the CDF. This initial Simple PAS offered a [redacted] discount on the NHS list price, yielding a confidential net price of [redacted] per capsule. Takeda has now received approval from PASLU/NHS England for an updated Simple PAS with a discount of [redacted] on the list price, equivalent to a confidential net price of [redacted] per capsule.

Following guidance from NICE's project team, all analyses in the main body of the CS were presented using the list price of ixazomib. This Appendix A presents the cost-effectiveness results including the updated Simple PAS for ixazomib. Please note these results and the assumptions underpinning these analyses correspond to the results and assumptions presented in the CS (the key difference being that the CS reflects the ixazomib list price).

A.1 Deterministic cost-effectiveness results (including updated Simple IXA PAS)

Table 2 presents the cost-effectiveness results for the new company base case with the updated Simple PAS applied to the ixazomib list price. The new base case incorporates the updated clinical evidence from the final analysis of T-MM1 relating to: OS (with two-stage adjustment with re-censoring), subsequent therapies, ToT, HRQoL, adverse events, hospitalisations and concomitant medications. The new

base case also reflects the 2018/2019 cost year and assumes that lenalidomide will be available as a generic medicine from [redacted]. To reflect this, the cost of lenalidomide is based on the list price of the branded product (Revlimid®) for [redacted] (assuming a Final Appraisal Document [FAD] for this CDF review is published in [redacted] before then being replaced by an estimated generic cost. The generic lenalidomide cost has been estimated [redacted] (i.e. one cycle of generic lenalidomide is assumed [redacted] – equivalent to a [redacted] discount from the list price of branded lenalidomide).

The updated base case results, including the updated Simple PAS for ixazomib, generate an ICER per QALY gained of £37,519.

Table 2 Deterministic cost-effectiveness results (including updated Simple IXA PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
IXA+LEN+DEX	[redacted]	4.86	3.18				
LEN+DEX	[redacted]	3.78	2.47	[redacted]	1.08	0.71	**£37,519**

A.2 Probabilistic sensitivity analysis (including updated Simple IXA PAS)

To characterise the uncertainty in the parameter inputs, a probabilistic sensitivity analysis (PSA) was performed for 5,000 iterations. All inputs were simultaneously varied based upon distributional information. Results were then recorded and used to estimate a mean probabilistic ICER.

The probabilistic results, including the updated Simple PAS for ixazomib, are summarised in Table 3 and depicted in a cost-effectiveness plane (CEP) in Figure 4. The CEP illustrates the simulated estimates of expected incremental costs and QALYs of IXA+LEN+DEX versus LEN+DEX in the PSA against a willingness-to-pay (WTP) threshold of £30,000 per QALY gained. The cost-effectiveness acceptability

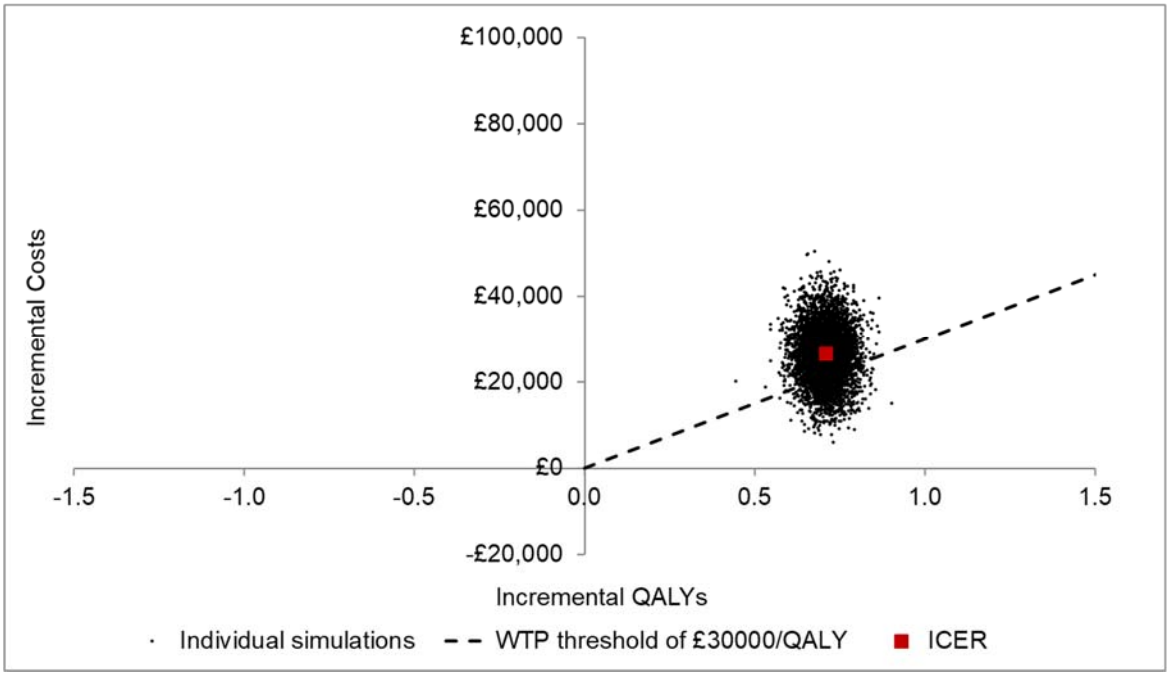
curve (CEAC) (Figure 6) shows the probability of IXA+LEN+DEX being cost-effectiveness versus LEN+DEX at varying WTP thresholds.

The PSA estimated mean incremental QALYs gained from IXA+LEN+DEX compared to LEN+DEX of 0.71 (95% CI: 0.62–0.80) and mean incremental costs of [redacted] (95% CI: [redacted]). Resulting in a probabilistic ICER of £37,607– based on the updated Simple PAS for ixazomib.

Table 3 Updated base-case results (probabilistic)

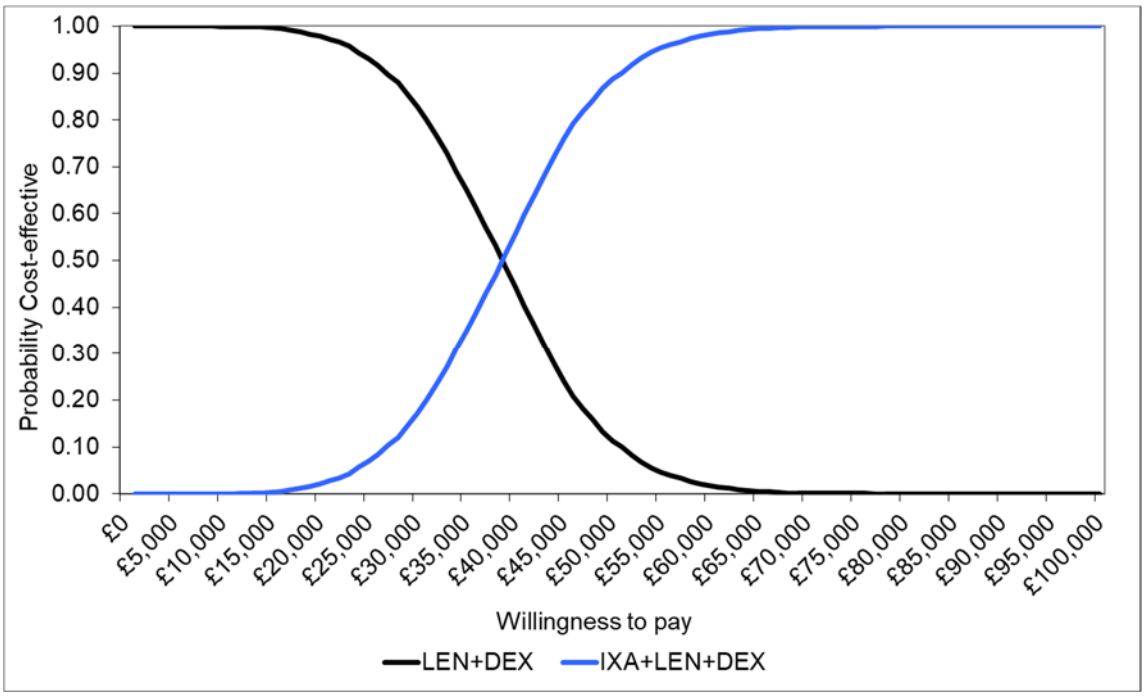
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
LEN+DEX	[redacted]	3.79	2.48				
IXA+LEN+DEX	[redacted]	4.87	3.18	[redacted]	1.08	0.71	**£37,607**

Figure 4: Cost-effectiveness plane of probabilistic results (with updated Simple IXA PAS)



Abbreviations: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; QALYs, quality adjusted life years; WTP, willingness-to-pay; ICER, incremental cost-effectiveness ratio

Figure 5: Cost-effectiveness acceptability curve (including updated Simple IXA PAS)



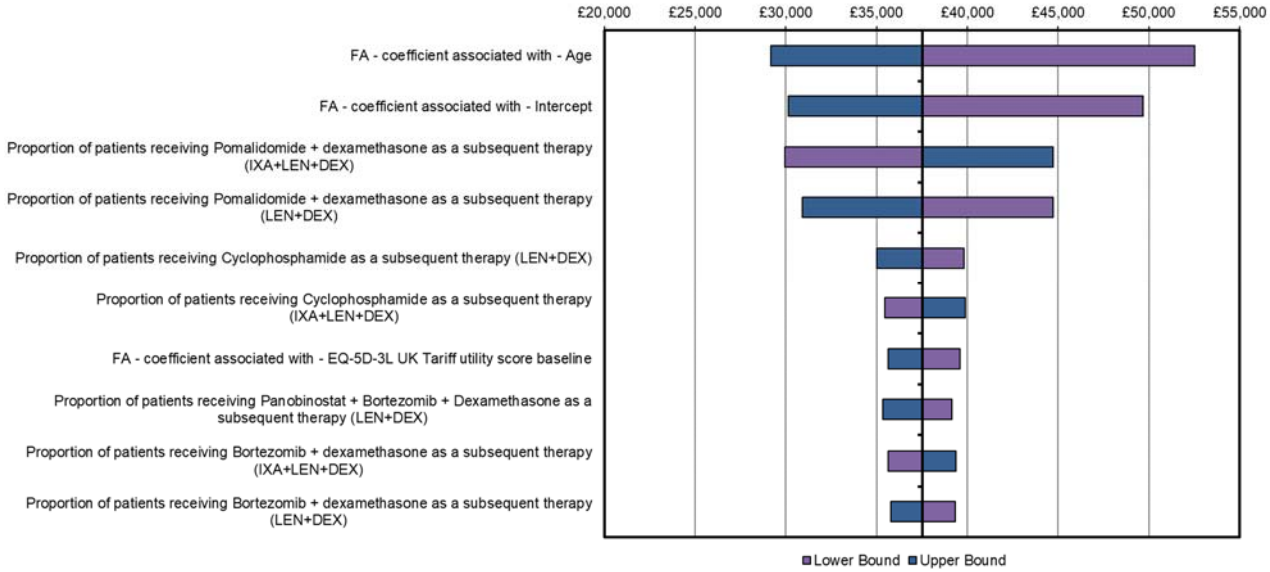
Abbreviations: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide.

A.3 Key sensitivity and scenario analyses (including updated Simple IXA PAS)

One-way sensitivity analyses were performed to evaluate the sensitivity of the modelled ICER to individual inputs. Inputs were varied in turn based on their lower and upper bound values. Results were then recorded to estimate the most influential parameters in descending order of ICER sensitivity.

Figure 6 depicts the results in a tornado diagram based on the updated Simple PAS for ixazomib; the parameters with the greatest impact on model outcomes were coefficients relating to the estimation of utility. This is to be expected as utility is a key driver of the total QALYs accrued by each treatment arm in the model, which directly impacts the ICER calculation. To a lesser extent, the proportion of patients receiving specific types of subsequent therapy was shown to impact the ICER.

Figure 6: Tornado diagram (including updated Simple ixazomib PAS)



Abbreviations: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; FA, final analysis.

Three key areas of uncertainty were explored in scenario analyses: (1) adjustments for subsequent therapy, (2) treatment waning, and (3) generic cost for lenalidomide.

Table 6 presents the results of these based on the updated Simple IXA PAS.

Firstly, the impact of using the unadjusted OS data from T-MM1 was considered. This scenario uses efficacy and applies subsequent therapy costs based on the T-MM1 trial. The ICER hardly changes (+£169) when the unadjusted OS data are used. This reflects two competing factors: firstly, a reduced relative treatment effect on OS outcomes for IXA+LEN+DEX vs. LEN+DEX compared to the adjusted OS data (i.e. a reduced LY and QALY gain); and secondly, the increased cost of more expensive subsequent therapies (especially daratumumab) used in the LEN+DEX arm when compared to the IXA+LEN+DEX arm (i.e. increased costs in the LEN+DEX arm leading to a lower incremental cost). The reduction in the health gain is offset by the reduction in the incremental costs so that overall the ICER remains almost unchanged – as shown in Table 4. It is important to note, that as the cost of ixazomib reduces, the effect of the treatment switching adjustment on efficacy is increasingly outweighed by the subsequent therapy costs – as shown in Table 5.

This is important, as with the original PAS the difference in ICERs estimated from the adjusted and unadjusted OS data were different (+£9,254 with the unadjusted data vs. the adjusted data). Whereas, with the updated Simple PAS there is a negligible difference between the ICERs (+£169 with the unadjusted data vs. the adjusted data).

We would reiterate that the unadjusted analysis is not reflective of the routinely funded treatment pathway in England and is not consistent with the NICE Position Statement regarding the inclusion of CDF medicines in a treatment sequence. [1] As such, the unadjusted analysis should not inform the base case. However, we do consider it notable that at the updated Simple PAS for ixazomib the resulting ICER is essentially the same whether one uses the adjusted or unadjusted OS analysis. This may provide reassurance to any Committee members who are uncertain regarding the treatment switching analyses and the resulting adjusted OS.

To further explore the impact of adjusting for subsequent therapies, the two-stage without re-censoring and the IPCW approaches are considered, alongside naïve comparisons of OS outcomes across switchers and non-switchers. The ICER worsens for IXA+LEN+DEX when the two-stage approach without re-censoring is used compared to the base case in which the two-stage with re-censoring approach is used. Re-censoring is an important component of the two-stage analysis as, without it, informative censoring can be introduced if there is an association between switching and prognosis – which is very likely to be the case in this context where the treatments defining a switcher are novel therapies with efficacious profiles. For this reason, it has been recommended that re-censoring should be applied in adjustment analyses and the results without re-censoring are presented as illustrative only. The IPCW method also worsens the ICER for IXA+LEN+DEX compared to the base case, and the predicted survival from this method does not align with clinical expectations (discussed in Section A.7.1).[9] Therefore, it is not used to inform the base case. However, both scenarios provide an exploration around the assumptions underpinning the treatment switching adjustments.

Table 4: Comparison of adjusted OS with unadjusted OS using the updated Simple PAS for ixazomib

	Total Costs £	Total LYs	Total QALYs	Incremental Costs vs Lowest Cost Therapy £	Incremental LYs vs Lowest Cost Therapy	Incremental QALYs vs Lowest Cost Therapy	Incremental Cost/QALY vs Lowest Cost Therapy £
Adjusted OS with subsequent therapies costed based on routine UK practice							
IXA+LEN+DEX	[redacted]	4.86	3.18				
LEN+DEX	[redacted]	3.78	2.47	[redacted]	1.08	0.71	**£37,519**
Unadjusted OS with subsequent therapies costed as in the TOURMALINE-MM1 clinical trial							
IXA+LEN+DEX	[redacted]	4.89	3.20				
LEN+DEX	[redacted]	4.08	2.67	[redacted]	0.81	0.53	**£37,688**

Table 5: Disaggregated costs comparison of adjusted OS with unadjusted OS using the updated Simple PAS for ixazomib

Adjusted OS with subsequent therapies costed based on routine UK practice						
Therapy	Drug costs and Therapy Specific Resource Use	Concomitant Therapy Use	TRAEs	Disease Management	Terminal Care costs	Total Costs
IXA+LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted OS with subsequent therapies costed as in the TOURMALINE-MM1 clinical trial						
Therapy	Drug costs and Therapy Specific Resource Use	Concomitant Therapy Use	TRAEs	Disease Management	Terminal Care costs	Total Costs
IXA+LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As discussed in Section A.7.2 in the CS, with any impact of waning on the treatment effect already captured for 96% and 99% of patients (in the IXA+LEN+DEX and LEN+DEX arms, respectively) in the observed data, treatment waning adjustments are not applied in addition to this in the base case. However, there is a small proportion of patients remaining on treatment in T-MM1 (4% and 1% of patients receiving IXA+LEN+DEX and LEN+DEX, respectively) for whom the effect of treatment waning has not been reflected. Therefore, a scenario explores the impact of waning for these patients. As expected, there is a negligible impact on the ICER due to most of the waning effect being implicitly captured within the observed data.

Although a confidential Simple PAS is currently in effect for branded lenalidomide, the base case assumes the list price of lenalidomide for [redacted] followed, by an estimated cost of generic lenalidomide. The rationale behind this assumption is that lenalidomide will be available as a generic medicine from [redacted] and therefore assuming a transition of IXA+LEN+DEX to routine commissioning in [redacted], branded lenalidomide would be commissioned for [redacted] before generics are available. The generic cost of lenalidomide has been assumed based on a comparison with [redacted]; this results in a [redacted] discount applied to the list price of branded lenalidomide. However, this is a key source of uncertainty which is explored in scenarios looking at a [redacted], [redacted] and [redacted] discount applied to the list price of lenalidomide to reflect potential generic pricing. Reducing the discount to [redacted] results in an increase in the ICER of £939. Whereas, [redacted] and [redacted] results in a decrease in the ICER of £2,583 and £6,104, respectively. Note: the absolute impact of changes to LEN prices are the same regardless of ixazomib pricing assumption.

Finally, the results presented in this Appendix apply the updated Simple PAS for ixazomib (a [redacted] from the list price of £2,112 per capsule to a net price of [redacted] per capsule).

Table 6 Scenario analyses (including updated Simple IXA PAS)

Scenario and cross reference	Scenario detail	Brief rationale	ICER (£/QALY)	Impact on base-case ICER
Base case			**£37,519**	
Unadjusted T-MM1 OS data [Section A.7.2]	Use T-MM1 OS data unadjusted for subsequent therapies	The base case includes an adjustment for subsequent therapies using the two-stage method. This scenario uses efficacy and applies subsequent therapy costs based on the T-MM1 setting (i.e., unadjusted). However, it is not considered reflective of the routinely funded treatment pathway in England, is not consistent with the NICE Position Statement re CDF medicines,[1] and was not considered reflective of UK treatment based on feedback from UK clinicians.	£37,688	+£169
Adjusted OS using two-stage methods with re-censoring [Section A.7.2]	Adjusted OS using the two-stage treatment switching analyses without re-censoring	The two-stage method with re-censoring is applied in the base case. To further explore the impact of adjusting for subsequent therapies, the two-stage method without re-censoring and the IPCW approaches are considered. However, as discussed in Section A.7.1 of the main dossier, the output from these methods do not align with the NICE Position Statement and the NICE TSD, or clinical expectations, respectively. They provide an exploration around the assumptions underpinning the treatment switching adjustments.	£48,377	+£10,858
	Adjusted OS using the IPCW treatment switching analyses		£38,950	+£1,432
Treatment waning [Section A.7.2]	Include adjustment for treatment waning effect in both treatment arms	The base case excludes treatment waning as the observed data reflects this effect for the majority of patients. However, there are a small proportion of patients remaining on treatment in T-MM1 (4% and 1% of patients receiving IXA+LEN+DEX and LEN+DEX, respectively). Therefore, a scenario explores the impact of waning for these patients.	£37,515	-£3

Generic LEN costing [Section A.7.9]	Assume a generic LEN cost at a [redacted] discount of the list price	The base case assumes list price of lenalidomide – although a confidential discount does exist for lenalidomide – for [redacted] followed by an estimate of the generic cost. The generic cost of lenalidomide has been informed based on a comparison [redacted] discount applied to the list price. However, this is a key source of uncertainty which is explored in scenarios looking at a [redacted], [redacted] and [redacted] discount applied to the list price of lenalidomide to reflect the generic pricing.	£38,458	+£939
	Assume a generic LEN cost at an [redacted] discount of the list price		£34,936	-£2,583
	Assume a generic LEN cost at a [redacted] discount of the list price		£31,415	-£6,104

Appendix B | Cost-effectiveness scenarios relating to generic lenalidomide pricing assumptions (including the updated Simple PAS for ixazomib)

Generic lenalidomide is scheduled to be launched in the UK from [redacted], but the price is as yet unknown to Takeda. As ixazomib is given in combination with lenalidomide (as IXA+LEN+DEX), the price of generic lenalidomide is one of the factors affecting the cost-effectiveness of ixazomib and is therefore worth exploring. Table 7 provides additional scenarios in relation to the impact of different generic lenalidomide pricing assumptions (all discounts shown are relative to the list price of the brand Revlimid). These scenarios assume that the discount applied to lenalidomide is applicable from the start of the model time horizon and assume the updated Simple PAS for ixazomib. Note: a discount of [redacted] applied to the list price of Revlimid® results in an ICER of under £30,000.

Table 7: Scenario analyses relating to the generic cost of lenalidomide

Lenalidomide discount (vs. Revlimid)	ICER including updated Simple PAS for ixazomib
[redacted] (base case)	£37,519
[redacted]	£37,410
[redacted]	£34,816
[redacted]	£34,462
[redacted]	£34,109
[redacted]	£33,755
[redacted]	£33,401
[redacted]	£33,048
[redacted]	£32,694
[redacted]	£32,340
[redacted]	£31,987
[redacted]	£31,633
[redacted]	£31,279
[redacted]	£30,926
[redacted]	£30,572
[redacted]	£30,218
[redacted]	£29,865
[redacted]	£29,511

Appendix C | Scenarios exploring impact of upcoming changes in the NICE Methods Guide

Whilst ixazomib does not meet the end-of-life criteria, it does meet the criteria for a higher willingness-to-pay threshold based on the severity modifiers which NICE have proposed will be used to replace the current end-of-life modifier from January 2022 as part of the ongoing NICE methods, processes and topic selection review (as of latest communication from NICE).[10]

As part of the consultation process for the NICE Methods Review, NICE have made available a document (the Methods Proposal Paper[11]) specifying the inputs and calculating the components of the two proposed approaches for a severity modifier (i.e. absolute and proportional QALY shortfall). The absolute shortfall in this case represents the difference between the QALYs in the LEN+DEX arm vs. the QALYs relating to a healthy individual, while the proportional shortfall is the ratio of absolute QALY shortfall to total QALY potential from a healthy individual.

Table 8 (copied from Table 2 in NICE's Methods Proposal Paper) presents the proposed weightings applied to the willingness-to-pay thresholds for different cut-offs of proportional and absolute shortfall.

Table 8: Severity modifier proposed options

Proportional shortfall	Absolute shortfall	Option 1 QALY weight	Option 2 QALY weight
<0.85	<12	1	1
≥0.85<0.95	≥12<18	x1.2	x1.25
≥0.95	≥18	x1.7	x1.5

Based on the median age of 67 years for the 2+ prior therapies subgroup in the T-MM1 clinical trial, the expected QALYs for a healthy individual are 15.3. The undiscounted QALYs in the LEN+DEX arm in the base case are 2.7. Therefore, the absolute QALY shortfall is 12.6 (i.e. 15.3 – 2.7). The proportional QALY shortfall is 0.82 (i.e. 12.6/15.3).

Based on this absolute QALY shortfall of 12.6, the two options for QALY weight proposed in the NICE Methods Review Consultation are x1.2 and x1.25, equivalent to willingness-to-pay thresholds of £36,000 and £37,500 per QALY gained, respectively.

Given the timing of this CDF Review for ixazomib and its relevance to the management of myeloma patients in the future, we believe it is appropriate to consider how the outcome of the Methods Review, particularly in relation to the severity modifier proposal, could impact on NICE's decision making.

As shown in Appendix A, the base-case results taking into account Takeda's updated Simple PAS for ixazomib generate an ICER of £37,519 per QALY gained. Depending on what exact assumptions are made in relation to the pricing and timing of generic lenalidomide, there is potential for the base-case ICER to be lower.

For example, discounts of [redacted] and [redacted] on the branded lenalidomide price would be required to meet the £37,500 and £36,000 willingness-to-pay thresholds, respectively (see Appendix B). Moreover, if the generic lenalidomide price is assumed to be an [redacted] or [redacted] discount on the branded price then the base-case ICER falls to either £34,936 or £31,415 respectively (see Appendix A). Both of these are well below the two willingness-to-pay thresholds of £36,000 and £37,500 that arise from the application of NICE's proposed severity modifier.

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NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (CDF review of TA505) [ID1635]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report in section 1.1. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Clinical expert statement

Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (CDF review of TA505)

Deadline for comments by **5pm** on **Tuesday 16 November 2021**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating relapsed or refractory multiple myeloma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Gordon Cook
2. Name of organisation	University of Leeds/Leeds Teaching Hospitals Trust
3. Job title or position	Professor of Haematology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with relapsed or refractory multiple myeloma? ☒ A specialist in the clinical evidence base for relapsed or refractory multiple myeloma or the technology ? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of the technology for relapsed or refractory multiple myeloma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	This technology is to improve disease response durability (PFS) and extend survivorship (OS) in patients with relapsed and refractory multiple myeloma.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Any clinical intervention that improves disease control, alleviates symptoms, improves quality of life and improves survivorship is to be considered a clinical benefit.
10. In your view, is there an unmet need for patients and healthcare professionals with relapsed or refractory multiple myeloma?	Yes. As an incurable disease where relapse is inevitable, having effective, safe and tolerated therapies to manage such relapses is key to improving QoL as well as quantity of life (survivorship). With each relapse, managing the disease can be more of a challenge for clinicians and patients alike. So effective and safe treatment options are very much required, hence the unmet need. IRD has proven to be effective at prolonging disease control, safe to administer and very much supported by clinicians and patients alike (as represented by the CDF uptake evidence).
11. How is relapsed or refractory multiple myeloma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would ixazomib with lenalidomide and dexamethasone have on the current pathway of care?	There is no commissioned pathway in England , rather a combined mixture of individually appraised HTAs that end up being inextricably linked, most often the newest replacing a previous or “re-shuffling” the order. Clinical guidelines regarding specific treatments are in place, generated by clinician who specialise in treating myeloma, but these guidelines cannot enforce funder to reimburse. Ixazomib, Revlimid and Dexamethasone (IRD) is a highly active and effective and all oral regime – it was and is widely used, but its use increased significantly over the pandemic period as part of emergency measures by the CDF. CDF usage data demonstrate how clinicians view the importance of this regime. Again, the popularity of the regime in this setting speaks to its ease of use, effectiveness, and the faith that the clinical community has in IRD as a highly effective myeloma therapy. Indeed, to withdraw this therapy now would be hugely disappointing, would cause significant distress amongst the myeloma

	community and would generate huge dismay by myeloma teams throughout the UK.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	IRD would continue to be used as it has been to date (with the exception of the COVID emergency changes) on the CDF. It is the standard of care third line therapy for patients who are not Revlimid refractory. Currently there is no other useful therapy available at the third line setting for patients with RRMM. This therapy is delivered through specialist clinics, and being an all oral combination, requires no need for specialised parenteral systemic anti-cancer therapy facilities, reducing patient footfall in comprehensive cancer centres. Consequentially, if this regimen is removed from standard of care clinical practice, then there will be an up-surge in patient footfall in anti-cancer therapy suites, resulting in increasing capacity pressures on already struggling services.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The therapy is effective and by controlling the disease, gives improvements in QoL for patients as well as improved disease control (PFS advantage) and prolongs survivorship (OS). As per the Myeloma UK survey and CDF usage, this technology is hugely appreciated by the clinical community and patients alike and forms an essential part of the treatment patient journey.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No, the technology has proven useful across all sub-groups of patients with myeloma, especially in those with genetic high risk disease. It is especially well tolerate in the older, frailer patient population, an important factor given the median age of presentation with myeloma is 74 in the UK.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?	The technology is all oral and there are no practical considerations for the introduction of this technology with no additional monitoring required, given it has become Standard of Care in third line so services are already set up to deliver the therapy.

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The rules and assessments for assessing the response of myeloma to therapy and assessing relapse are well established and follow standards procedures, tests and assessments and no additional testing would be required.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The importance of an all oral regime to patients is unlikely to be captured in a QALY calculation and the massive uptake of this regime during the COVID 19 pandemic speaks to the fact that this regime reduces time in hospital and on chemotherapy day units and greatly reduces the risk of nosocomial infection and patient anxiety around the pandemic.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, because its utility is not restricted by functionality (frail patients tolerate this therapy as well as Unfit and Fit patients alike) or genetic high risk (patients with standard risk and high risk disease respond equally well. This gives true equity of access and responsiveness across the myeloma patient population, which is well know for its patients and disease heterogeneity.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	This is clearly defined in the Myeloma UK submission documentation.

20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The pivotal study was a placebo controlled study, the treatment being used by the UK community reflects that used in the study. The populations are comparable. The main issue with a multi-national study is that post-trial care cannot be mandated so is highly variable across the jurisdictions of the study population. Whilst this does not impact on the primary end-point, it does impact on interpretation of the secondary end-point of OS. This does NOT mean the treatment cannot improve OS significantly (clearly shown in the Chinese cohort) rather that the exponential expansion of myeloma treatment options especially in clinical trials, can affect the patient pathway enough to skew a third line interventional study OS, especially in US and European jurisdictions. The study shows a significant improvement in response rates, PFS and OS for patients on the study arm. Yes No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	None
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA505?	Revlimid and dexamethasone as comparator treatment in particular has not be the subject of any recent publications of note in third line.
23. How do data on real-world experience compare with the trial data?	Several studies based on real world evidence have now been presented at international conferences and published in peer-reviewed journal. Two such studies, the INSIGHT Global patient registry and the European collaboration , have included significant (>300) patients form the Uk. Unlike many of these technologies where efficacy (trial -generated) and effectiveness (real world impact) have not been comparable, the IRD real world data shows distinctly comparable depth and durability of response, as well as OS advantage from

	using the technology. In addition, the tolerance (side effects, drug dose modifications and drug discontinuations) were actually better in the real world than in the reported trial results (TOURMALINE MM1).
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	Myeloma is twice as common in patients of Afro-Caribbean ancestry and so any adverse decision on IRD would impact this population disproportionately. However, all members of society have a right to access treatment regardless of race, religion or sexuality and therefore, a negative decisions here affects ALLL SOCIETY access and this should be considered before any such decision is taken.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Generalised gamma modelling of the adjusted overall survival: 2-stage re-censoring (novel therapies).	At a discussion with myeloma experts we all agreed the generalised gamma provided the most reasonable outcome estimation with Ixa, Len and Dex compared with len and Dex alone. It should be noted that both these models are looking to predict 20 year survival and beyond, which is somewhat fatuous. Most longitudinal studies of long-term survivorship, demonstrate the 20 year survival FROM DIAGNOSIS is les than 10%, yet these models used in this technology consideration are examining 20 year survival rate at third line.
Uncertainty around model selection for adjusted overall survival: 2-stage re-censoring (novel therapies).	The censoring for novel therapies was in line with therapies that are available elsewhere but not currently commissioned in England. These novel therapies would all have had a significant positive outcome, in terms of overall survival, on patients on these therapies. In other words patients in the England on current pathways do not have access to these therapies so this censoring is appropriate.

The sustained effect of treatment.	The “waning effect” frequently discussed in appraisal of therapy in myeloma is an anomaly. Waning effect, created in consideration of immunologically based biological therapies, is not founded in the sphere of sub-cellular targeted therapies, so adds very little to the discussion of such therapies and there place in clinical practice. This creates an unrealistic confusion and the assumptions generated add to the uncertainty rather than clarify. In the study being analysed, the prolonged follow gives confidence in long-term usage and post-treatment effect waning.
Lack of progression free survival data in the final analysis of the pivotal trial (TOURMALINE MM-1).	The trial has prolonged follow up and was analysed appropriately according to the statistical plan. The progression free survival was reported appropriately and after prolonged follow up. I am not sure what a further analysis of PFS would give us.
Are there any important issues that have been missed in ERG report?	None that I can see.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1: IRD is an effective well tolerated all oral regime that prolongs PFS and OS significantly.

2 The usage on the CDF shows how this regime is widely used and has been particularly vital during the COVID 19 PANDEMIC.

3 The myeloma UK survey shows patients with myeloma appreciate the availability of this technology and maintain their QOL despite the fact this is a triplet regime

4 It is effective across all risk groups including patients with the highest risk disease and older, frailer patients.

5 To remove IRD from the MM treatment pathway would be greeted with huge disappointment, concern and anxiety by the myeloma community but most particularly patients with myeloma who would find such an outcome extraordinarily distressing.

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The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (CDF review of TA505) [ID1635]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report in section 1.1. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Clinical expert statement

Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (CDF review of TA505)

NICE National Institute for Health and Care Excellence

Deadline for comments by **5pm** on **Tuesday 16 November 2021**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating relapsed or refractory multiple myeloma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Graham Jackson
2. Name of organisation	NHS/University of Newcastle Upon Tyne
3. Job title or position	Professor of Clinical Haematology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with relapsed or refractory multiple myeloma? ☒ A specialist in the clinical evidence base for relapsed or refractory multiple myeloma or the technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of the technology for relapsed or refractory multiple myeloma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The scope/aim of the technology is to extend the progression-free and overall survival of patients with relapsed/refractory multiple myeloma (RRMM).
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	I consider any therapy to be clinically significant if it increases the response rate, is well tolerated, and extends the progression free survival of patients with RRMM.
10. In your view, is there an unmet need for patients and healthcare professionals with relapsed or refractory multiple myeloma?	Yes, Myeloma is currently incurable and response rates and outcomes beyond third line therapies are very poor. IRD has proven to be hugely popular amongst physicians- see CDF use and patients – see UKMF submission.
11. How is relapsed or refractory multiple myeloma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would ixazomib with lenalidomide and dexamethasone have on the current pathway of care?	There are several guidelines regarding the treatment of RRMM but NICE and the SMC guide treatment at every stage of the treatment of RRMM. Ixazomib, Revlimid and Dexamethasone (IRD) is a highly active and effective and all oral regime – it is widely used as we see from the data from the CDF which demonstrate how clinicians view the importance of this regime, Also DURING THE COVID 19 pandemic the IRD regime has been widely used at first relapse providing an excellent but all oral regime that has reduced pressure on hospital out-patient and chemotherapy day units. Again, the popularity of the regime in this setting speaks to its ease of use, effectiveness, and the faith that the clinical community has in IRD as a highly effective myeloma therapy. Indeed, to withdraw this therapy now would be hugely disappointing, would cause significant distress amongst the myeloma community and would be greeted with huge dismay by myeloma teams throughout the UK. (See Myeloma UK document)
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	IRD would continue to be used as it has been via the CDF. It would be regarded as the key third line therapy for patients who are not Revlimid resistant. Currently

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	there is no other useful therapy available at the third line setting for patients with RRMM. The therapy would be delivered in secondary care and in a specialist clinic. As it is widely used and is an all-oral regime – there would be NO requirement for any investment to introduce the technology – indeed the opposite would be true – removing the technology would require significant investment as it would lead to increased use of IV and SC therapies and put considerable pressure on chemotherapy units which would be very difficult particularly at the moment given the problems thrown up by the COVID-19 pandemic.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, the technology significantly prolongs PFS and OS without any adverse impact on QoL. See Myeloma UK survey and CDF usage to appreciate how significant this technology is to the myeloma community.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No, the technology is equally effective across all sub-groups of RRMM patients, including patients with high-risk disease. It is also an effective regime that is well tolerated in older patients and saves them the inconvenience and issues around effective regimes that require parental therapy.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The technology is all oral and indeed is the only all oral triplet therapy for patients with myeloma. There are no practical considerations for the introduction of this technology with no additional monitoring required.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The rules and assessments for assessing the response of myeloma to therapy and assessing relapse are well established and follow standards procedures, tests and assessments and no additional testing would be required.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The importance of an all-oral regime to patients is unlikely to be captured in a QALY calculation and the massive uptake of this regime during the COVID 19 pandemic speaks to the fact that this regime reduces time in hospital and on chemotherapy day units and greatly reduces the risk of nosocomial infection and patient anxiety around the pandemic.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes Whilst all patients benefit from the technology it is unusual for patients with high-risk cytogenetics to do as well as patients with standard risk cytogenetics. Patients with high-risk disease would be particularly disadvantaged if the technology was not available.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Please see the myeloma UK submission.
20. Do the clinical trials on the technology reflect current UK clinical practice?	The study was well conducted and unusually was placebo controlled and with the caveats that the therapies available to patients coming off the study would be different in different territories.

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The study shows a significant improvement in response rates, PFS and OS for patients on the study arm. Yes No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	NO
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA505?	NO
23. How do data on real-world experience compare with the trial data?	There are several real-world studies looking at the applicability of this technology to populations outside of clinical trials. These real-world studies all show the technology performs similarly in a real world population to patients undergoing therapy within the clinical trial.
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	Myeloma is twice as common in patients of Afro-Caribbean ancestry and so any adverse decision on IRD would impact this population disproportionately.

belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here i	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Generalised gamma modelling of the adjusted overall survival: 2-stage re-censoring (novel therapies).	At a discussion with myeloma experts, we all agreed the generalised gamma provided the most reasonable outcome estimation with Ixa, Len and Dex compared with len and Dex alone.
Uncertainty around model selection for adjusted overall survival: 2-stage re-censoring (novel therapies).	The censoring for novel therapies was in line with therapies that are available elsewhere but not currently commissioned in England. These novel therapies would all have had a significant positive outcome, in terms of overall survival, on patients on these therapies. In other words, patients in the England on current pathways do not have access to these therapies so this censoring is appropriate.
The sustained effect of treatment.	Given the prolonged follow up of the study discussions around a waning effect is completely irrelevant.

Lack of progression free survival data in the final analysis of the pivotal trial (TOURMALINE MM-1).	The trial has prolonged follow up and was analysed appropriately according to the statistical plan. The progression free survival was reported appropriately and after prolonged follow up. I am not sure what a further analysis of PFS would give us.
Are there any important issues that have been missed in ERG report?	None that I can see.
Part 3 Key messages	1 IRD is an effective well tolerated all oral regime that prolongs PFS and OS significantly. 2 The usage on the CDF shows how this regime is widely used and has been particularly vital during the COVID 19 PANDEMIC. 3 The myeloma UK survey shows patients with myeloma appreciate the availability of this technology and maintain their QOL despite the fact this is a triplet regime 4 It is effective across all risk groups including patients with the highest risk disease and older, frailer patients. 5 To remove IRD from the MM treatment pathway would be greeted with huge disappointment, concern and anxiety by the myeloma community but most particularly patients with myeloma who would find such an outcome extraordinarily distressing.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement

1: IRD is an effective well tolerated all oral regime that prolongs PFS and OS significantly.

2 The usage on the CDF shows how this regime is widely used and has been particularly vital during the COVID 19 PANDEMIC.

3 The myeloma UK survey shows patients with myeloma appreciate the availability of this technology and maintain their QOL despite the fact this is a triplet regime

4 It is effective across all risk groups including patients with the highest risk disease and older, frailer patients.

5 To remove IRD from the MM treatment pathway would be greeted with huge disappointment, concern and anxiety by the myeloma community but most particularly patients with myeloma who would find such an outcome extraordinarily distressing.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (CDF review of TA505) [ID1635]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report, in section 1.1.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Tuesday 16 November 2021**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we

received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	[redacted] – Myeloma UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Generalised gamma modelling of the adjusted overall survival: 2-stage re-censoring (novel therapies).	No	Having consulted with our colleagues in the UK Myeloma Forum (UKMF) we endorse their response to this issue.
Uncertainty around model selection for adjusted overall survival: 2-stage re-censoring (novel therapies).	No	We understand that there are concerns in the model selection for adjusted overall survival focusing on subsequent therapies received by patients on both arms of the TOURMALINE-MM1 clinical trial. We would like to emphasise that myeloma is an incurable relapsing and remitting cancer. Patients at this stage in the disease pathway will be treated with multiple lines of treatments to control their myeloma. As stated above, having consulted with the clinical experts in the UKMF we would fully endorse their position on this issue.
The sustained effect of treatment.	No	We are concerned about the ERG approach to the sustained effect of treatment or 'treatment waning' being included in the decision problem for this appraisal.

		In the original appraisal (TA505) the final appraisal document (FAD) found that it was reasonable to consider the company's base-case assumption about treatment effect in its decision-making." In the absence of evidence to the contrary we believe that the same approach to treatment waning should be applied in the review as was taken in the original appraisal. As an organisation Myeloma UK takes part in all appraisals for myeloma treatments at NICE and we therefore have an overview of which key issues arise and how they are dealt with. We are concerned that there appears to be a lack of consistency in the definition, understanding and application of treatment waning across different appraisals. In addition, in our experience there has been often been a difference of opinion between the ERG and clinical experts on the relevance of treatment waning – particularly clinical experts have been very clear that treatment waning is not relevant. We believe there as an important and concerning lack of shared understanding about treatment waning among key stakeholders and participants in the process. We are concerned about the priority given to and time taken on this issue in a range of myeloma appraisals when there seems to be such a marked difference of opinion on its significance. This issue has a real impact on the speed of appraisals which is causing delays in access to treatments for patients.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Lack of progression free survival data in the final analysis of the pivotal trial (TOURMALINE MM-1).	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

Title: *Multiple myeloma (relapsed, refractory) - Ixazomib (with lenalidomide and dexamethasone) (CDF Review of TA505) Appraisal 1635.* ***ERG responses to technical engagement***

Produced by	*Warwick Evidence*
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Date completed	*Date completed (22/11/2021)*

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Declared competing interests of the authors
None.

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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 Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Please note that: *Sections highlighted in* [redacted] *are* [redacted]. *Sections highlighted in* [redacted]. *Figures that are CIC have been bordered with blue.*

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Content of report

In this report, we provide ERG responses to the company's technical engagement response form. We have validated the company's updated analyses.

We have updated the ERG base-case analysis based on the ERG's preferred assumption of using the Weibull parametric model of the adjusted overall survival: 2-stage re-censoring (novel therapies), using the company's estimate of the discounted price for lenalidomide throughout the model time horizon (as advised by NICE), and the updated PAS for ixazomib.

1.1 ERG responses to technical engagement response form

We respond to the issues arising following technical engagement in Table 1 and Table 2.

Table 1: ERG responses to technical engagement response form

Key issue	***Does this response contain new evidence, data or analyses?***	***Response***	**ERG response**
1.Generalised gamma modelling of the adjusted overall survival: 2-stage re-censoring (novel therapies).	*No*	*The generalised gamma curve was selected, by myeloma clinical experts at an advisory board, as reflecting expected outcomes for IXA+LEN+DEX and outcomes observed in clinical practice for LEN+DEX in the 2+ prior lines population. The clinical experts selected the generalised gamma curve after having considered a range of different options.*	The ERG acknowledges the company's statement that the clinical experts selected the generalised gamma model during the Advisory Board meeting. However, the ERG reiterate that this meeting was held by the company. The ERG cannot verify the independence of the board or their conflicts of interest. In trying to assess the validity of Advisory Board statements throughout this appraisal, the ERG conclude that it is seriously open to question. During clarification, the details provided regarding the Advisory Board were brief. During the board, twelve clinical experts were presented a range of options regarding OS. The extent of the range of options, their constitution and the manner in which they were presented to clinicians were not described. How the selections made by the clinicians were obtained, assembled and assessed (e.g., vote counting, averaging etc) was not described. The outcome from this procedure was the clinically recommended generalised gamma model, no uncertainty or range was attached for this estimate of the clinicians' deliberations. From a scientific viewpoint the operation of the Advisory Board would be difficult to replicate because of lack of information. From the ERG's perspective the operation of the Advisory Board is in essence "black box" into which unspecified options were fed and from which the clinically recommended generalised gamma model emerged.
2.Uncertainty around model selection for	*No*	*Table 1below (Table 18 in the ERG Technical Engagement report) compares the outcomes predicted using the unadjusted OS data with those*	The company did not present AIC BIC values for goodness of fit of generalised gamma relative to other parametric models. Using data available, the ERG suggest that on that on the basis of

adjusted overall survival: 2-stage re-censoring (novel therapies).		*predicted using the adjusted OS data (as per the Company's base case) – adjusted to remove the effect of subsequent therapies which are neither reimbursed nor routinely available for use in clinical practice in the UK, as per the NICE Position Statement.[1] The ERG conclude that these results "depart from clinical plausibility" in terms of LY gains (Key Issue 2 in the ERG report). The Company strongly disagrees with these statements.* *Firstly, it is unclear at multiple points throughout the report on what basis the ERG justifies its assertion that results are clinically implausible. Throughout the CS, appendices and post-submission engagement, the Company has been clear on its rationale and clinical support – from a UK advisory board in March 2021 – on the plausibility of the data presented. By contrast, the ERG – at multiple points in its report – provides an opinion on clinical implausibility without justification or reference to clinical expert opinion. This is a point that has been raised repeatedly by the Company and we are yet to receive clear justification from the ERG on the basis for its assertion. The Company wishes to reiterate its position – which has been validated with 12 consultant haematologists at a UK advisory board – that the treatment switching approach provides clinically plausible results.* *Taking the ERG's specific point around the life years accrued in the LEN+DEX and IXA+LEN+DEX arms. Adjustment using the two-stage estimator (TSE) methodology results in a reduction in the life years accrued in the LEN+DEX arm of 3.62 months. Whereas, a smaller reduction in the life years accrued in the IXA+LEN+DEX arm of 0.39 months is observed. These findings align with our interpretation of the confounding from subsequent therapies and align with the expectations from our outreach to clinical experts (as outlined above).*	information criteria scores, the generalised gamma model represents a poor fit relative to other models such as Weibull and exponential. As discussed in ERG repones to key issue 1, the company refers to an UK advisory board that was held in March 2021 and gathered 12 consultant haematologists. Without access to the information ("options") presented at the company Advisory Board, uncertainty remains concerning the selection of the generalised gamma model. (see ERG TE response 1 for details) Although the opinions provided by clinical advisors are invaluable with the scope of health technology assessment, it is important to bear in mind that expert opinions may present some limitations as acknowledged by their position in the hierarchy of evidence. As stated in clarification question A20, the company's submission is a revised submission superseding a previous submission in which the company identified a in their model, which was not highlighted by the company's UK advisory board (but presumably based on the arguments of non-plausibility pointed out throughout the former ERG report). With regards to model uncertainty, we note that the company disagrees with the ERG opinion, and does not provide new evidence to support its position compared to the CDF submission. Therefore, the ERG reiterates its original concern with regards to the lack of consistency of adjusted OS analyses, which tends to indicate that removing the effect of novel strategies has almost no impact on the IXA+LEN+DEX arm when examining the post-progression life years (4.89 life-years in unadjusted analyses versus 4.86 adjusted analyses, corresponding to only 11 days of difference). Conversely, it has a larger impact when considering median OS (4.42 years in unadjusted analyses versus 4.28 years in adjusted analyses, corresponding to a difference of 51 days).

Therefore, we disagree with the ERG's conclusion – and its assertion that the results are not consistent with the Company's position on the influence of subsequent therapies on OS – and believe that the results are clinically plausible. An in-depth rationale is provided below.

Table 2: Unadjusted OS data vs. adjusted OS data (Table 18 of ERG Report)

Model name	**Effect**	**Therapy**	**Median OS months**	**Median OS year**	**HR (95 % CI)**	**Total LYs**	**LYs**	
							Pre-Progr.	**Post-Progr.**
Unadjusted	*Presumed "positive" effect of novel therapies = INCLUDED*	*IXA+LEN+DEX*	*53*	*4.42*	*0.845 (0.642, 1.114)*	*4.89*	*2.25*	*2.65*
		LEN+DEX	*43*	*3.58*		*4.08*	*1.50*	*2.59*
		Incremental	*10*	*0.83*		*0.81*	*0.75*	*0.06*
TSE (re-censored + adjust for baseline characteristics†)*	*Presumed "positive" effect of novel therapies = EXCLUDED*	*IXA+LEN+DEX*	*51.4*	*4.28*	*0.713 (0.535, 0.952)*	*4.86*	*2.25*	*2.62*
		LEN+DEX	*41.5*	*3.46*		*3.78*	*1.50*	*2.29*
		Incremental	*9.9*	*0.83*		*1.08*	*0.75*	*0.33*

		CI, confidence interval; HR, hazard ratio; LY, life-year; OS, overall survival *In the TOURMALINE-MM1 (T-MM1) clinical trial, there was an imbalance in the type and number of subsequent therapies which are neither reimbursed nor routinely available across the IXA+LEN+DEX and LEN+DEX treatment arms. Patients in the LEN+DEX treatment arm received more novel therapies in subsequent lines and also received more subsequent lines in total when compared to the IXA+LEN+DEX arm. The effect of receiving novel therapies on survival is shown in Figure 1 (Figure 2 in the CS); patients who receive novel subsequent therapies are shown to have superior survival. This effect is more pronounced in the LEN+DEX arm compared with the IXA+LEN+DEX arm as shown in Figure 2 (Figure 3 of the CS). This difference is driven by the fact that more patients in the LEN+DEX arm than in the IXA+LEN+DEX arm received novel subsequent therapies which are known to have prognostic importance, for example: daratumumab (31/149=21% in LEN+DEX vs. 19/148=13% in IXA+LEN+DEX), elotuzumab (7/149=5% vs. 3/148=2%) and autologous stem-cell transplant (9/149=6% vs. 1/148=0.7%) – this information is presented clearly in Section A.6.1 and Appendix B of the CS. Additionally, patients in the LEN+DEX arm received a median of three lines of subsequent therapy (mean 3.3) vs. two in the IXA+LEN+DEX arm (mean 2.4). Figure 2 clearly demonstrates that the confounding is greater in the LEN+DEX arm. Therefore, any statistical adjustment to remove this confounding would be expected to have a greater impact in the LEN+DEX arm. Also in Figure 2, the difference in survival for patients receiving novel subsequent therapies vs. those who don't is smaller in the IXA+LEN+DEX arm and the*	

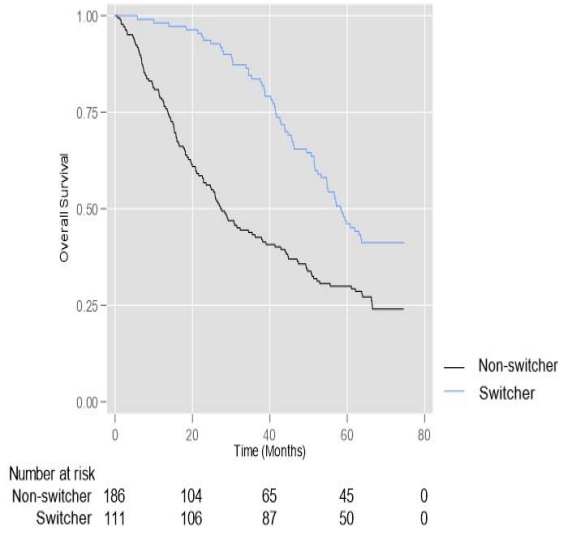
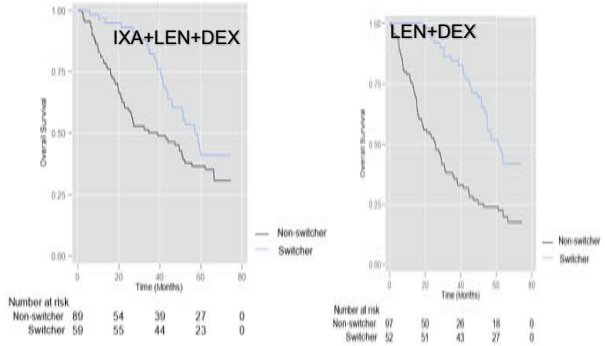
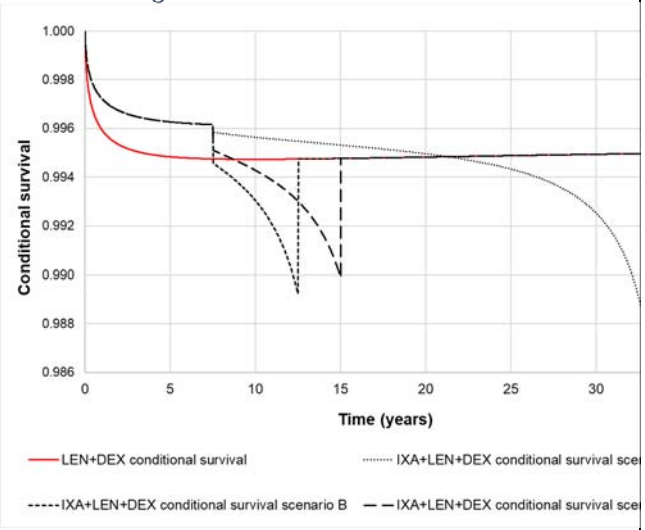
		curves move closer together at the end of follow-up. Based on this we would not expect as big a difference in the IXA+LEN+DEX arm. The methods used and results estimated from the statistical adjustment have been validated by clinical experts during an advisory board and in follow-up interviews. Clinicians considered that both the direction of change and the size of change were plausible given the subsequent therapies received in T-MM1. Therefore, we believe that the results are clinically valid and do reflect what would be expected in the absence of these novel subsequent therapies. Section A.6.1 and Section A.7.1 in the CS explain this in detail. *Figure 1: OS unadjusted Kaplan–Meier curves for pa (all patients)*  	

		Figure 2: OS unadjusted Kaplan–Meier curves for patients identified as switchers vs. non-switchers (separated by treatment arms)  *Abbreviations: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; OS, overall survival* *In addition, related to this issue, during Technical Engagement the ERG highlighted their concern that the impact of adjusting for novel subsequent therapies was greater in terms of the predicted hazard ratio compared with the median values. The effect of the adjustment reduces the hazard ratio from 0.845 (95% CI: 0.642 – 1.114; unadjusted) to 0.713 (95% CI: 0.535 – 0.952; adjusted) in the 2–3 prior therapies population. The corresponding median values (53 vs. 43; unadjusted and 51.4 vs. 41.5; adjusted, for IXA+LEN+DEX vs. LEN+DEX, respectively) provide a snapshot of the time at which 50% of the population are alive. The literature is clear that median values should be interpreted with caution and are not of statistical value; these reflect a single time point and do not account for the full duration of follow-up.[2] Reflecting the full duration of follow-up is particularly important in this setting where the potential for confounding is greater as the length of follow-up increases (i.e. in the latter part of the Kaplan–Meier plots). Consequently, we believe significantly more importance should be placed on the change in the HR (which is reflective of the*	

		entirety of the survival curves) rather than on the medians.	
3.The sustained effect of treatment.	*No*	*The ERG report explores treatment waning in exploratory scenarios. We fundamentally disagree with the ERG's approach to treatment waning, and we are concerned by some of the language used by the ERG to describe this within their report. We consider the methods used within the ERG's exploratory scenarios to be clinically implausible. Firstly, we want to emphasise that we now have a median follow-up of 85-months (over 7-years) from the T-MM1 clinical trial. Patients received treatment with IXA+LEN+DEX and LEN+DEX for a median of 18.2-months and 13.4-months, respectively. This leaves a window of 66.8 months (5.6-years) and 71.6 months (6.0-years) where patients are **not** receiving the **study treatments**. The mean time on treatment within the trial was 25.8 and 20.0, respectively. Using these values this leaves a window of 59.2-months (4.9-years) and 65-months (5.4-years) where patients are **not** receiving the **study treatments**. Therefore, we believe that the follow-up time post-discontinuation within the trial is sufficient to reflect any treatment waning.* *We are concerned by the wording in the ERG report around the "sustained effect of ixazomib after treatment has ended" and how this could be misinterpreted. We do not assume a sustained effect of ixazomib. We use the treatment effect estimated across the whole trial follow-up, including the effect of ixazomib **and** subsequent therapies relevant to UK clinical practice (in the base case). Therefore, in terms of OS, the hazard ratio or treatment effect in the IXA+LEN+DEX arm is no longer the isolated effect of treatment with IXA+LEN+DEX, but a composite measure reflecting a pathway of treatments. We have no evidence of a sustained effect of IXA+LEN+DEX and do not claim – and*	The company states "*We fundamentally disagree with the ERG's approach to treatment waning*" and takes the view that virtually all waning has been captured so that any model explored by the ERG becomes irrelevant. The company have then generated a new analysis (see company TE Figure 3) despite designating this issue as **No** under the column heading "Does this response contain new evidence, data or analysis". This additional figure does not represent the ERG approach but performs a different type of analysis starting from month zero. The ERG waning started at the end of the observation period (approximately 8 yrs.) and involved approximately 35% patients still alive in IXA+LEN+DEX arm at that time. Based on the company's submitted KM plots for ToT and OS (ERG report Figure 2) approximately 95% of patients had completed treatment by year 5 while at 8 years approximately 35% patients still alive in IXA+LEN+DEX arm. Here the company maintain the approach, and thus by corollary any method, used to explore waning beyond 8 years for the 35% survivors in the IXA+LEN+DEX arm will be "clinically implausible". This is because the company position is that all waning (except for approximately 5% of the IXA population) has already been captured within the 8 year observation period. The ERG maintain their opinion that waning of treatment effect for the 35% IXA survivors at 8 years is more likely than unlikely, and that that exploration of possible waning is a legitimate part of the ERG remit. How long these 35% survivors may have remained without treatment is unknown since no data for this was supplied in the submission. It is ERG opinion that this time was not likely to have been long, and probably insufficient to capture waning completely. The ERG conducted three exploratory scenarios (the method explained and supplied to the company previously on their request).

		have never claimed – this within the CS. This point was already flagged as part of the Company's factual accuracy check of the ERG report. *Another concern around the wording is in relation to the ERG's proposed approach to explore treatment waning: "The ERG's alternative approach would be to apply a waning of the post treatment continuing effect to the generalised gamma" (page 11 of the ERG report). None of the scenarios the ERG explore relate to the treatment effect within the model. The scenarios work by forcing the overall survival curves (not the treatment effect) to equal each other at specific time points. This is achieved by changing the overall survival probabilities and it results in a higher probability of dying in the IXA+LEN+DEX arm compared to the LEN+DEX arm, until such time as the curves are equal. We see no biological or pharmacological justification for this and it is an approach we consider to be completely clinically implausible.*	Scenario a] yielded a curve only very slightly different to that of the company base case generalised gamma model (ERG report Figure 9), and therefore, the ERG is surprised that such a result should be considered by the company to be "clinically implausible". The main conclusion from the ERG exploration of possible waning was that the company ICER is extremely sensitive to how OS is modelled beyond the observation period.
		It is unclear what clinical expert validation (if any) the ERG has sought on this important point. ***We consider it essential that NICE seeks clinical expert opinion on this issue, ideally in advance of the Appraisal Committee Meeting scheduled for December 15th.*** *We are also concerned about all reference to waning of the effect within the report as this implies a hazard ratio trending to 1.0 over time – this is not what the ERG has implemented. Further detail is provided below.* *The ERG considers three scenarios: Scenario A ("slow waning over 18-years"), Scenario B ("fast waning over 5-years") and Scenario C ("waning over 7.5-years"). Figure 3 presents the probability of dying each cycle within the model (i.e. the conditional survival). For example, if the conditional survival is 0.98 this means that 98% of the patients*	The ERG has sought clinical validation from two independent clinical advisors in the UK National Health Service. Both clinical advisors have read the ERG report and have provided their own statements as to the clinical appropriateness of the ERG report. Both ERG clinical advisors declare no conflicts of interest. We welcome any further clinical expert opinion on this issue, and we look forward to reading the independent submissions received from other consultees and commentators once received.

		that are still alive in cycle x will survive to cycle x+1. This plot demonstrates that all three of the scenarios which the ERG explores results in a higher probability of dying in the IXA+LEN+DEX arm compared to the LEN+DEX arm. This increased risk of dying is maintained until the curves become equal, at which point the probability of dying immediately improves to equal the LEN+DEX arm. As above, we do not think that any evidence exists to support these scenarios and we do not consider them to be clinically plausible. We repeat our earlier call for NICE to seek clinical expert opinion on these ERG scenarios and the whole concept of treatment waning in relation to this CDF Review of ixazomib. *Figure 3: Conditional survival derived from the ERG's waning scenarios*  	

		As explained in our CS (see Section A.7.2), the updated OS data from the T-MM1 trial reflects survival outcomes for >96% of patients who have discontinued treatment with IXA+LEN+DEX and for >99% of patients who have discontinued treatment with LEN+DEX. Therefore, we believe any treatment effect waning is already reflected within these updated OS data. For illustrative purposes, in our CS we included a scenario analysis which explored waning the treatment effect for both the IXA+LEN+DEX and LEN+DEX treatment arms from the end of the trial follow-up over a 5-year time period for the 4% and 1% of patients, respectively, still on these treatments in the trial. As shown in Table 20 of the CS and Table 29 of the Appendices to the CS, this had a negligible impact on the ICER (ICER reduced by [redacted] and £4 respectively compared to the base case). *This supports our position that treatment waning is not relevant to this CDF Review of ixazomib. This is consistent with the position reached by the Appraisal Committee at the conclusion of the original ixazomib appraisal (TA505) where the Committee's preferred base case for decision-making purposes did not include treatment waning (see Section 3.14 of TA505).*[3]	

Table 2: ERG responses to additional issues

Issue from the ERG report	***Relevant section(s) and/or page(s)***	***Does this response contain new evidence, data or analyses***	***Response***	**ERG response**

Additional issue 1: Lack of progression-free survival (PFS) data in the final analysis of the pivotal trial (TOURMALINE MM-1).	*Sections 1.1, and 1.3*	*No*	*On page 8 (and elsewhere), the ERG states that it "recognises that data on PFS were not collected beyond the second interim analysis (IA2) of T-MM1. Therefore, there are no updates to PFS available." The ERG further states on page 25 that "[it considers] that updated PFS would have been beneficial for the CDF review, as PFS is not affected by the post-progression treatment switching that leads to confounding. However, the ERG acknowledge that it was not in the statistical analysis plan."* *The Company has repeatedly made the following points during the CDF review process.* 1. *As stated on page 4 of the CS, during the original ixazomib appraisal (TA505) the Committee used data from the second*	The company has taken the opportunity to reiterate that the statistical end point for PFS was reached; an assertion never disputed by ERG. It is a fact that follow-up was shorter for PFS than for ToT or for OS. We concluded in our report that "no updates to PFS are available for consideration in the CDF." We consider this an additional issue; this is a point of opinion of the ERG following our appraisal of the evidence submitted.

			*interim analysis (IA2) of the T-MM1 study – with a median follow-up of 23-months – to assess the cost-effectiveness of IXA+LEN+DEX.[3,4] At IA2, PFS data were **mature**, and demonstrated a significant 9-month median PFS advantage for IXA+LEN+DEX vs. LEN+DEX (hazard ratio [HR] = 0.617, 95% confidence interval [CI] 0.445–0.855; p=0.033) in patients who have had 2 or 3 prior lines of therapy.[5]* 2. *As PFS data at IA2 were considered mature, collection of further PFS data was not included in the CDF Data Collection Agreement that was agreed with NHS*	

			England. PFS was not considered by the Committee to be a key uncertainty in the original ixazomib appraisal (TA505). 3. *Consistent with the points above, submission of new PFS data was not included in the Terms of Engagement provided by NICE for this appraisal.* 4. *As the ERG correctly states, as specified in the T-MM1 Statistical Analysis Plan (SAP), data on PFS were not collected beyond IA2 of T-MM1. However, to imply that updated PFS are not presented solely due to the T-MM1 SAP is both incorrect, and inconsistent with the CDF Data Collection Agreement*	

			and the NICE Terms of Engagement. *We are disappointed to note that a request made by the Company in relation to this issue during its factual accuracy check of the ERG report was not actioned by the ERG.* *Furthermore, on page 50 of the report, the ERG states "The company submitted the same PFS analysis as submitted in response to ACD following original STA appraisal (ID TA505); this is based on data up to interim analysis IA2 and is therefore less mature than data now submitted for ToT and for OS, each of which correspond to the final data cut."* *It is not correct to say that the data are "less mature". The primary endpoint of T-MM1, PFS, was actually reached at the first interim analysis (IA1) which occurred after a*	The ERG responded to and revised all **factual errors** in their response to factual accuracy check. The ERG did not revise any points of opinion or disagreement between themselves and the company. The company objects to the use of the term "less mature" to describe these issues. This is common parlance to describe what is considered here when referring to the immaturity of data. The ERG points to DSU TSD 14: "Survival analysis for economic evaluations alongside clinical trials - extrapolation

			median follow-up of 15 months. *A second non-inferential assessment of the PFS was conducted at IA2 (median follow-up of 23 months). Due to longer follow-up, IA2 was the data cut preferred by the NICE Committee, but the primary endpoint was reached (and therefore should be considered mature) at IA1.* *This issue recurs on page 40, "It should be borne in mind that the PFS KM are based on AI2 and are less mature than other KMs."* *It is the Company's position that additional PFS data are clearly beyond the agreed scope for this CDF Review of ixazomib.*	with patient-level data report by the decision support unit" which remarks: "For example, care must be taken in the common case where lifetime data are **immature** and non-censored observed values are only available on a small proportion of patients". The ERG also point to the paper: Prevalence of Immature Survival Data for Anti-Cancer Drugs Presented to the National Institute for Health and Care Excellence and Impact on Decision Making https://doi.org/10.1016/j.jval.2020.10.016 that documents "how often the National Institute for Health and Care Excellence (NICE) uses **immature** overall survival data to inform reimbursement decisions on cancer treatments, and the implications of this for resource allocation decisions".
Inclusion of inappropriate ITT analysis in the ERG report, beyond the scope of the current CDF Review	*Section 3.1.6 (pages 32 and 33)*	*No*	*Despite stating on page 31 of the report that "The ERG agrees with the company in not using the ITT analysis or per-protocol censoring and exclusion of switchers post-progression", on pages 32–33 the ERG conducts de novo analysis of published (non-patient-level data) for*	The publication of the final results from the trial places the submission in its context. The final TMM1 results show no survival advantage for IXA+LEN+DEX relative to LEN+DEX and raise the possibility that alternative treatment (e.g., with carfilzomib) may represent a better treatment option than ixazomib and that this may extend to sub-population(s).

			the T-MM1 ITT dataset. They state that they have "reviewed the final OS analyses of the T-MM1 trial beyond the scope of the CDF review, i.e. including the ITT T-MM1 population (RRMM with 1+prior therapy) and based on the original analyses planned in the T-MM1 SAP." *We believe that this analysis is not relevant to the current decision problem for a number of reasons:* *1. The analysis presented in the report is based on a broader patient population than that under consideration in this CDF Review. Patient populations differed in a number of key parameters that affect prognosis, including number of prior therapies received, and subsequent therapies received.* *2. The 1 prior therapy subpopulation from T-MM1 was excluded from the initial appraisal for ixazomib, after substantial discussion between*	The ERG considers the de novo analysis of published (non-patient-level data) for the T-MM1 ITT dataset in our report to be of use to the committee for decision-making. Therefore, it was included as *additional* ERG analysis in the ERG report for committee consideration.

			the Company and the NICE Committee *3. Extrapolating results from one patient population to another, based on a dataset that includes patients outside of the scope for this CDF Review is therefore wholly inappropriate* *It is unclear to the Company what value this analysis adds to the decision-making process beyond perhaps an attempt to discredit the treatment switching methodology and results – which are based on methods recommended by NICE in TSD 16 – utilised in the CS. This point was raised by the Company during its factual accuracy check of the ERG Report. The Company maintains that this analysis is not relevant to the current decision problem.*	
Lack of clarity in the ERG report on what constitutes ERG opinion vs clinical expert opinion	*Throughout the report, and specifically Section 3.2.2 (pages 42 and 47)*	*No*	*Throughout this review process, the Company has been clear and transparent about its assumptions, and the clinical rationale that supports them. An advisory board with 12 Consultant Haematologists was conducted in March 2021, and the consensus from*	See ERG response to point 1 regarding the potential advisory board composition and transparency in their conflicts of interest. The company states: "*Throughout this review process, the Company has been clear and transparent about its assumptions, and the clinical rationale that supports them. An advisory board with 12 Consultant Haematologists was conducted in March 2021*."

			these myeloma clinical experts was used to inform the economic model. Given the extensive clinical validation conducted by the Company, it is disappointing to read phrases such as "The ERG thinks there is so little difference in predicted survival between generalised gamma (dashed lines) and Weibull (dotted lines) that clinical experts would be unable to distinguish one from the other and therefore on this basis the ERG thinks the Weibull based ICER is as equally valid as the generalised gamma-based ICER" *We would question whether it is appropriate for the ERG to suggest what clinical experts would, or would not, be able to distinguish. In the March advisory board conducted to help inform this review, clinical experts noted the similarity of the curves, but ultimately selected the generalised gamma over the Weibull.* *Multiple requests were made by the Company to the ERG to clarify in their report what is ERG opinion, what has been validated with myeloma clinical experts, and the justification for the positions*	The ERG disagrees with this statement since transparency of assumptions (and clinical plausibility) is not evident while details of the Advisory Board undertakings are remain unavailable. See response 3 regarding ERG clinical validation The ERG suggests that "ERG opinion" was clearly delineated during in ERG's response to the FAC submitted by the company. To reiterate:

			taken by the ERG. Despite the Company's requests, the technical engagement report does not provide these clarifications, and there are numerous references to "implausible outcomes" without rationale or justification to support such assertions. As currently written, the ERG report implies that these statements are facts when they are likely opinions or judgements. The Company would like to put on record that it requested clarification in the report on: *1. what is ERG opinion,* *2. what is based on clinical expert advice, and* *3. for both, what is the justification for the position taken by the ERG* *The aim of this was to provide the Committee with information on what is/is not clinical expert opinion, and to enable the Company to explore further if clinical experts thought that any of the results were clinically implausible. To date, the Company has received no response from the ERG to these requests and we remain unclear what clinical*	1. *what is ERG opinion:* text which states "ERG opinion" 2. *what is based on clinical expert advice:* clinical expert statements are phased with "The ERG clinical advisor notes". The ERG clinical experts independently validated the final ERG report and provided comments prior to submission. They have also provided comment and consultation during the response to TE. 3. *for both, what is the justification for the position taken by the ERG:* The ERG justifications for its critique and conclusions are presented in the ERG report.

			validation (if any) has been undertaken by the ERG. Therefore, we would suggest that all references to "clinical implausibility" within the ERG report should be interpreted with caution.	
Rationale for excluding RPSFT method to adjust for treatment switching.	*Section 3.1.2 (page 27)*	*No*	*The ERG states that "The company also considered the Rank Preserving Structural Failure Time (RPSFT) Models method to adjust for bias due to switching to subsequent treatments, but because the T-MM1 trial was multicentre, the common treatment effect assumption across multiple trials was not deemed to be valid (CS Document, Section A.7.1, pages 26-29)."* *As already highlighted in the Company's factual accuracy check, it is incorrect to say that the RPSFT method was not selected because T-MM1 was multicentre. In the CS (Section A.7.1, page 29), we clearly state that "The RPSFTM methods were also considered. However, in MM, the common treatment effect assumption has been shown to be invalid across multiple trials. This was confirmed by UK clinical experts who noted the relative efficacy of different treatment regimens*	The ERG are happy to submit 1 erratum page to ERG report page 27 with the following minor change: Remove *"The company also considered the Rank Preserving Structural Failure Time (RPSFT) Models method to adjust for bias due to switching to subsequent treatments, but because the T-MM1 trial was multicentre, the common treatment effect assumption across multiple trials was not deemed to be valid (CS Document, Section A.7.1, pages 26-29)."* Replace "The Rank Preserving Structural Failure Time (RPSFT) methods were also considered to adjust for bias due to switching to subsequent treatments. However, in MM-1, as it was multicentre trial, the common treatment effect assumption has been shown to be invalid across multiple trials. This was confirmed by UK clinical experts who noted the relative efficacy of different treatment regimens varies depending on the line of therapy. Therefore, these methods were discounted from further analysis."

			varies depending on the line of therapy. Therefore, these methods were discounted from further analysis." *The ERG statement is inaccurate, it misrepresents the Company's position and is not consistent with the information submitted by the Company to NICE. This was highlighted by the Company during the factual accuracy check of the ERG report, but has not been amended by the ERG.*	
ERG misrepresentation of NICE methods	*Section 3.1.1 (pages 25–26)*	*No*	*In its report the ERG correctly states that "the company adjusted the updated OS HR estimates to account for the impact of subsequent therapies which are not routinely funded in the UK (i.e., not available, or only funded via the CDF)."* *However, it goes on to state that "The company (and company's clinical advisors) propose an expected "UK clinical practice" pathway for subsequent line(s) of treatment (CS Document, page 8). As far as the ERG can ascertain, no guidelines exist describing this pathway; even if the proposed expected UK pathway is accurate, it is unlikely to remain unchanged in the*	The ERG agrees that the company have adhered to the scope as stated in the ToE Table 12 of the ERG report. The ERG do not consider that it has implied in any way that the company have departed from the scope. The ERG suggests that in conducting an assessment exercise it is legitimate to view an intervention in wide context regarding both the scope and the results obtained by the company's procedures. It seems clear that the submission posits a treatment pathway that has been judged applicable for UK patients. The ERG in consultation with our independent clinical advisors conclude that a NHS England treatment pathway for MM is unlikely to remain unchanged in the near future. The ERG has still not seen relevant UK guidelines.

			near future as more research is published regarding the clinical effectiveness of new treatments beyond three or four lines. However, the company survival analysis assumes that their expected pathway will continue to operate for a further 26 years (from approximately 8 to 34 years) beyond the trial final cut." *In the Company's view, the ERG fundamentally misrepresents our approach, and also deviates from the scope and approved methods for NICE appraisals. In no section of the submission documents does the Company state that the therapies included in the switching analysis comprise the only therapies that will be used in routine practice in the NHS for the model time horizon. As the ERG is no doubt aware, therapies currently funded via the CDF are used by UK clinicians, and treatment pathways are subject to change as new, efficacious therapies are approved.* *However, the Company has adhered consistently to the*	

			remit and scope for this CDF Review, namely:[6] 1. *That "the scope for re-consideration will remain the same as the final scope used for the published guidance" i.e. the treatment pathway and comparators as they were during the original appraisal, and* 2. *Consistent with NICE's Position Statement, medicines available only via the CDF and not via routine commissioning should not be included as a comparator or subsequent therapy.*[1] *The adjustments to the OS data conducted by the Company address both of these considerations, are consistent with methods used for previous appraisals in RRMM,*[7] *and the Company maintains that its approach to treatment switching are wholly consistent with approved NICE methods.*	
Residual ERG critiques that the Company	*Section 3.1.6.3 (page*	*No*	*The ERG states on page 36 that "The KM for TSE-OS,*	The company states: "*This issue was addressed in the Company responses to the Additional ERG Clarification*

addressed fully during clarification questions (1/2)	*34–35), and Section 3.2.1 (page 36)*		*copied from the submitted economic model, implies that the TSE-OS KMs extend to approximately 7.8 years, corresponding to the depiction in CS Figure 8, page 35 (see also ERG Section 9.1) but not corresponding to Figure 7 page 33. The ERG cannot explain these differences.* *The unadjusted OS KM plots (CS Figure 1) extend to about 90 months approximately 7.5 years (unfortunately time axis tick marks are lacking in this and other CS figures). The ERG is unsure why OS extends beyond ToT but believe this may be an error in view of IPD data supplied to the ERG by the company during the second round of clarifications (received October 7 2021: document ID1635 ixazomib Takeda clarification questions A3_A4 05102021CM noACIC). This indicates that for the two-stage adjusted OS, the first death event or censoring time occurred at 10 weeks and the last death event or censoring time occurred at 324 weeks (6.21 years). The relevant part of the CS clarification document is shown Table 14. The same time of 324 weeks*	*Questions (document ID1635 Company response to additional ERG clarifications [CIC])*." The ERG did receive this document. However, in the ERG opinion, this issue was not resolved during clarification. Therefore, it remains an outstanding issue which was included in the ERG report. The ERG did not find *document ID1635* helpful in answering their clarification question. There was no direct statement in the company response which rendering of 2-stage adjusted KM plot in CS Figures 7 and 9 was the correct one. The ERG adopted the commonly used methods described in ERG report and judged that the KM plot in CS Figure 7 rather than that in CS Figure 9 was correct. The ERG routinely has asked for KM data in the form requested of the company. These requests have usually been granted by companies and have censorings and failure summing to the total number of patients. In additional clarification, the ERG asked why this was not the case in this instance. The ERG supplied the figure below and requested clarification comparing the KM plot from data in the economic model and that derived from KM data supplied in clarification. A request made because long tails in KM plots can strongly influence parametric models. The company said they were unable to replicate the curves and in order to provide further clarification the company would need more information with regards to how the black curve was derived.

			for last death or censoring was also shown for the LEN+DEX arm." *On page 34, the ERG also states that it "had difficulties interpreting and validating the properties of the TSE-OS models presented in the CS because there were apparent contradictions within the CS (KM depictions in Figures 7 and Figure 8), and between the information supplied in clarification document (round two clarification) ID1635 ixazomib Takeda clarification questions A3_A4 05102021CM noACIC and information provided within the economic model."* *This issue was addressed in the Company responses to the Additional ERG Clarification Questions (document ID1635 Company response to additional ERG clarifications [CIC]).* *As stated on page 5 of this document, "the maximum time we have Kaplan–Meier data for IXA+LEN+DEX is 401 weeks for the unadjusted OS analysis and 324 weeks for the adjusted OS analysis – see the screenshots below from the response to A3 from the Clarification Questions.*	 The ERG followed its standard format/process in making requests regarding KM data, the ERG concedes that the request for KM data may not have been worded / presented as clearly as needed for this particular company who state they have not previously experienced such request. In a considerable number of assessments, the ERG has requested and been granted KM data by pharmaceutical companies. This experience as stated by the responder has not been the case for Takeda.

			When the adjusted OS data are selected there is no Dynamic Chart function set up in the model. Therefore, the tail of the Kaplan–Meier curve is defaulting to the last survival estimate until 401 weeks; from week 324 to week 401 the same survival estimate is used resulting in a longer flat tail. This has no impact on any of the model calculations and did not influence the parametric curve selected in the base case." *The ERG report does not incorporate the Company's responses to the latest round of clarification questions, despite the Company submitting its responses prior to receiving the draft version of this report.* *The Company has addressed the ERG's criticism and it is disappointing to find the same critique in the published report, particularly given the implied – but incorrect – suggestion that the Company submitted inconsistent data and used the data incorrectly in the statistical analyses.*	
Residual ERG critiques that the Company addressed fully during	Section 3.1.7 (page 35)	No	In the referenced section, the ERG states that *"ToT and PFS correlated well for the LEN+DEX arm. However, for*	No additional ERG comment provided in repones to company opinion.

clarification questions (2/2)			*the IXA+LEN+DEX arm, there was a mismatch as discontinuation preceded progression. Although these comparisons are based on rather unsatisfactory data (in that PFS analysis was only available to IA2 cut off) the mismatch in one arm, but not the other, suggests there may be bias in the costing of treatments that may favour the IXA+LEN+DEX arm."* In the original NICE submission [TA505], the relationship between ToT and PFS was discussed at length. In the Committee Papers it is stated: *"During the second committee meeting, the Committee accepted that ToT can be and generally is less than PFS and that the gap is larger for the IXA+LEN+DEX arm within the T-MM1 observed period (in part due to the depth of response achieved by a triplet compared to a doublet regimen as was described within the consultation submissions). However, the Committee questioned the magnitude of the difference between PFS and ToT, particularly within the modelled period. The ERG commented within their*	

			addendum that assuming a Weibull distribution for ToT as well as PFS negated this issue."[8] As part of the Clarification Response for this original appraisal, Takeda provided a detailed rationale and evidence supporting the link between response and PFS which supported the extended PFS beyond treatment discontinuation in the IXA+LEN+DEX arm. For more information, please refer to the original Committee Papers.[8] We do not think that this discussion needs to be re-visited, particularly as: 1. the rationale for PFS extending beyond treatment discontinuation in the IXA+LEN+DEX arm remains the same as in the original appraisal, 2. the PFS data have not been updated in this CDF Review and a Weibull curve has been applied to extrapolate outcomes (in line with the original NICE	

			submission and ToE), 3. the ToT data have been updated and are almost complete and as such there is substantially reduced uncertainty associated with these data, in addition a Weibull curve has been applied to extrapolate outcomes (in line with the original NICE submission and ToE), and this was not specified as an uncertainty for which more data was required as part of the CDF terms from the original submission.	
Request by the ERG for confidential patient-level data	Section 9.3.1 (relating to ERG request for IPD) and Sections 1.3, 1.4, 3.22 and 6.5 (relating to IPD reconstruction by the ERG)	No	During clarification questions (September 27) the ERG requested patient-level information (QA.1). The Company responded to this request as best it was able within the limitations of being unable to provide confidential patient-level study data to outside organisations. In its report (pages 76–77), the ERG implies that the Company misunderstood the request, and that requests of	No additional ERG comment provided in repones to company opinion.

			this nature are routine for NICE technology appraisals. To the Company's knowledge this is not correct, and the Company does provide individual patient-level data to outside parties. However, in response to the ERG's request, we provided the Kaplan–Meier data as a separate Excel document – note these were also available within the economic model. The Company also notes that the ERG has reconstructed an approximation of the IPD for a number of its analyses. The Company would advise treating with caution any conclusions drawn from reconstructed IPD.	

1.2 Validation of the company's cost-effectiveness analysis results using the updated PAS for ixazomib

In this section we document our validation and replication of the ICERs (Appendices to Technical Engagement) submitted by the company, which are based on the updated PAS for ixazomib.

The ERG has replicated the company's additional analyses results reported in Appendix A and Appendix B in the Appendices to Technical Engagement, with the results being in good agreement.

1.3 ERG's preferred base-case and sensitivity analyses

In this section we report the ERG's deterministic results for the comparison between IXA+LEN+DEX and LEN+DEX in *"Adults with relapsed or refractory multiple myeloma, who have had 2 or 3 lines of prior therapy, which is a subgroup of patients of final TMM1 study data"*. Additionally, we report the one-way and probabilistic sensitivity analyses results.

1.3.1 ERG's base-case deterministic results

Based on our critique of the company's economic model, the ERG suggested amendments are as follows:

- Using the Weibull parametric to model adjusted overall survival: 2-stage re-censoring (novel therapies)

Under the ERG's preferred assumptions, and the company's assumed level of discount for lenalidomide throughout the model, the base-case results in Table 3 generate an ICER of approximately £40,400.

Table 3: Cost-effectiveness results (deterministic), using the ERG's assumptions and PAS for ixazomib

Technologies	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
LEN+DEX	[redacted]	2.43	[redacted]	-	-
IXA+LEN+DEX	[redacted]	3.08	[redacted]	0.65	£40,440
ICER, Incremental cost-effectiveness ratio; QALY, Quality adjusted life years					

1.3.2 ERG's one-way sensitivity analysis results

In Figure 2, we report the one-way sensitivity analyses in the form of a tornado diagram based on the ICERs for the comparison between IXA+LEN+DEX and LEN+DEX. The parameters with the greatest impact on model outcomes were coefficients relating to the estimation of utility.

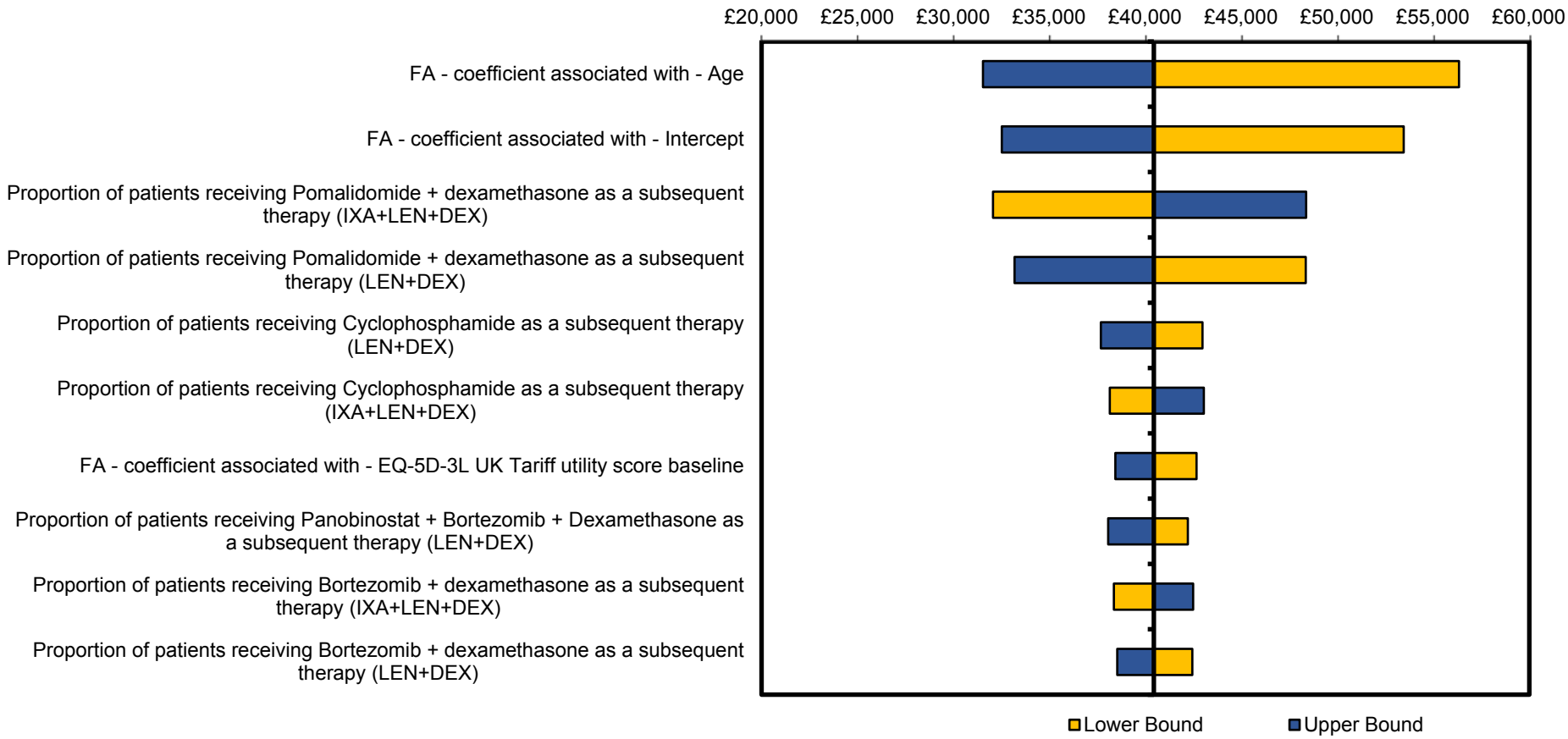


Figure 1: Tornado plot of deterministic sensitivity analysis: impact on ICER results (ERG) *(based on updated PAS for ixazomib)*

Abbreviations: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; FA, final analysis.

1.3.3 ERG's probabilistic sensitivity analysis results

We present the probabilistic sensitivity analysis results in Table 4. The results produced an ICER of approximately £40,700, which is similar to the deterministic ICER.

Table 4*:* Probabilistic sensitivity analysis results for ERG's base-case (based on PAS for ixazomib)

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
LEN+DEX	[redacted]	2.42	[redacted]	-	-
IXA+LEN+DEX	[redacted]	3.08	[redacted]	0.652	£40,651
ICER, Incremental cost-effectiveness ratio; QALY, Quality adjusted life years					

In Figure *2* and Figure 3, we report the results on a scatterplot and CEAC, respectively. The results in Figure 3 show that at a willingness-to-pay threshold of £30,000 per QALY, treatment with IXA+LEN+DEX has a 0.12 probability of being cost-effective.

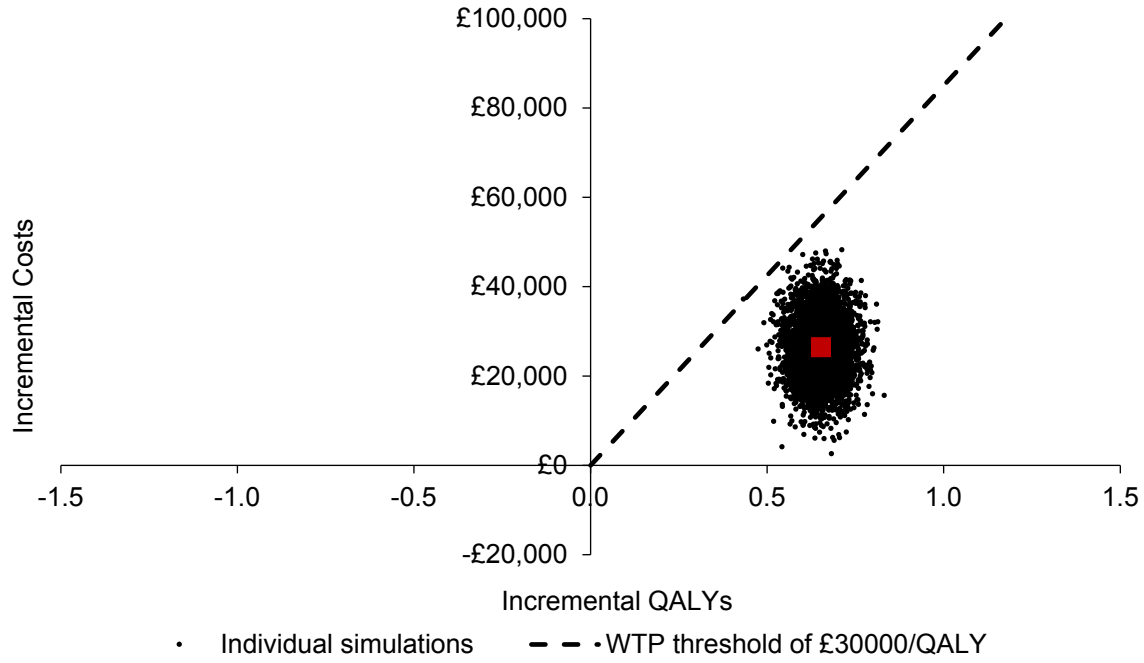


Figure 2*:* Incremental cost-effectiveness scatterplot for the comparison between LEN+DEX versus IXA+LEN+DEX (ERG) (based on *updated* PAS for ixazomib)

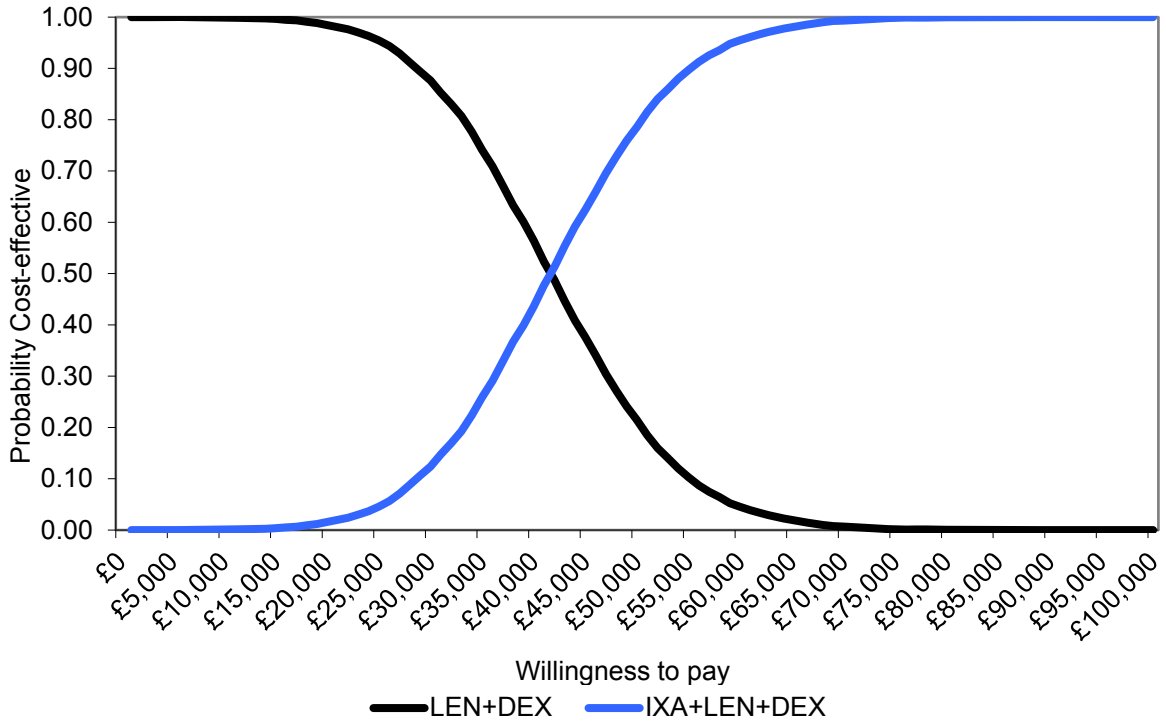


Figure 3: Cost-effectiveness acceptability curves for LEN+DEX and IXA+LEN+DEX (ERG) (based on updated PAS for ixazomib)

ERG Summary

Using the ERG's preferred assumptions simultaneously and the discount agreement for ixazomib, these results generated an ICER of approximately £40,400 per QALY. One-way sensitivity analysis results continued to show that the parameters with the greatest impact on model outcomes were coefficients relating to the estimation of utility. The ERG's PSA results showed that at a willingness-to-pay threshold of £30,000 per QALY, treatment with IXA+LEN+DEX has a 0.12 probability of being cost-effective.

Title: *Multiple myeloma (relapsed, refractory) - Ixazomib (with lenalidomide and dexamethasone) (CDF Review of TA505) Appraisal 1635.* ***Additional analyses post PMB***

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Declared competing interests of the authors
None.

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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 Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Please note that: *Sections highlighted in [redacted] are '[redacted]. Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue.*

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This appendix includes the following:

- Analysis to show OS estimates with other extrapolations
- An explanation of the waning of treatment effect issue, and to explain what the ERG analysis entail
- Update of the treatment waning scenario analyses

1.1 Analysis to show overall survival estimates with other extrapolations

In this section we report the percentages of people alive at different timepoints by parametric model for people in for IXA+LEN+DEX and LEN+DEX.

Additionally, we report the disaggregated life-year results by treatment for each parametric model.

1.1.1 Overall survival estimates by parametric model

In Table 1 we show the percentages of people alive at different timepoints based on the choice parametric model used to model the adjusted overall survival: 2-stage re-cens (novel therapies).

Table 1: Percentages of people alive at different timepoints, by parametric model

Overall survival	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma
IXA+LEN+DEX						
1-year	85.17	89.29	89.34	90.57	88.32	89.59
5-year	44.67	43.57	44.2	43.88	43.99	43.60
10-year	19.96	14.15	22.86	21.02	9.18	16.01
15-year	8.91	3.97	13.72	12.41	0.46	5.79
20-year	3.98	1.00	8.99	8.31	0.00	2.10
30-year	0.79	0.05	4.54	4.60	0.00	0.28
LEN+DEX						
1-year	80.07	85.15	82.60	84.95	83.87	84.93
5-year	32.77	30.77	32.55	31.48	31.25	30.74
10-year	10.74	6.24	14.69	13.52	3.40	7.80
15-year	3.52	1.03	8.08	7.69	0.05	1.97
20-year	1.15	0.15	4.97	5.05	0.00	0.5
30-year	0.12	0.00	2.29	2.76	0.00	0.03

1.1.2 Disaggregated life-year results, by treatment for each parametric model for overall survival

In Table 2 we show the disaggregated life-year results based on the choice parametric model used to model the adjusted overall survival: 2-stage re-cens (novel therapies).

Table 2: Disaggregated life-year results, by parametric model

Technologies	Pre-progression LYs	Post-progression LYs	Total LYs
Exponential			
LEN+DEX	1.50	2.44	3.93

IXA+LEN+DEX	2.25	2.87	5.11
Weibull			
LEN+DEX	1.50	2.21	3.71
IXA+LEN+DEX	2.25	2.45	4.69
Log-normal			
LEN+DEX	1.50	2.97	4.46
IXA+LEN+DEX	2.25	3.57	5.81
Log-logistic			
LEN+DEX	1.50	2.95	4.44
IXA+LEN+DEX	2.25	3.48	5.72
Gompertz			
LEN+DEX	1.50	2.08	3.57
IXA+LEN+DEX	2.24	2.17	4.41
Generalised gamma (base-case)			
LEN+DEX	1.50	2.29	3.78
IXA+LEN+DEX	2.25	2.62	4.86

1.1.3 Deterministic scenario analysis results for each parametric model for overall survival (using the company's preferred assumptions)

In Table 3 we present the scenario analysis results based on choosing different parametric models for the adjusted overall survival: 2-stage re-cens (novel therapies).

Table 3: Deterministic scenario analysis results, by parametric model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (cost per QALY)
Exponential					
LEN+DEX	[redacted]	2.56	[redacted]	-	-
IXA+LEN+DEX	[redacted]	3.33	[redacted]	0.77	£34,459
Weibull					
LEN+DEX	[redacted]	2.43	[redacted]	-	-
IXA+LEN+DEX	[redacted]	3.08	[redacted]	0.65	£40,558
Log-normal					
LEN+DEX	[redacted]	2.88	[redacted]	-	-
IXA+LEN+DEX	[redacted]	3.74	[redacted]	0.86	£31,100
Log-logistic					
LEN+DEX	[redacted]	2.86	[redacted]	-	-
IXA+LEN+DEX	[redacted]	3.69	[redacted]	0.82	£32,984
Gompertz					
LEN+DEX	[redacted]	2.34	[redacted]	-	-
IXA+LEN+DEX	[redacted]	2.90	[redacted]	0.56	£47,477
Generalised gamma (company's base-case)					
LEN+DEX	[redacted]	2.47	[redacted]	-	-

IXA+LEN+DEX	[redacted]	3.18	[redacted]	0.71	£37,519

1.2 Waning of the treatment effect

In this section, we provide a brief note about the waning of the treatment effect issue, with further details presented in the ERG's report (*see* Table 1 and Section 3.3) and ERG responses to the company's technical engagement form (*see* Table 1). We then present the ERG's approach to waning of the treatment effect. Afterwards, we consider the method used by PenTAG to implement a waning of the treatment effect because sufficient details were provided on its conduct. We provide a summary to PenTAG's method, then undertook scenario analyses based on this approach.

1.2.1 Waning of the intervention treatment effect concern

In the opinion of the ERG, we consider waning/discontinuation of treatment and waning of the intervention treatment effect two separate entities. Though we accept that waning of treatment to be captured within the observed time of the trial, we consider that the period of observation from the end of treatment to the end of observation is too short to fully capture a potential waning of ixazomib's treatment effect.

It appears to the ERG, that waning of ixazomib's treatment effect is likely to start at some point before the 18 years have expired. It may be possible for waning to start after patients have ceased to be observed. Even if waning started immediately after cessation of ixazomib administration, only a small fraction of the potential treatment waning effect would be captured during the subsequent observation period.

The company has provided justification to support why waning of the treatment effect should not be included in the analysis. Briefly, the company stated that they believe that the follow-up time post-discontinuation within the trial to be sufficient to reflect any waning of the treatment effect, and that *they used 'the treatment effect estimated across the whole trial follow-up, including the effect of ixazomib **and** subsequent therapies relevant to UK clinical practice (in the base case). Therefore, in terms of OS, the hazard ratio or treatment effect in the IXA+LEN+DEX arm is no longer the isolated effect of treatment with IXA+LEN+DEX, but a composite measure reflecting a pathway of treatments.'*

The ERG considers that a lack of waning of the treatment effect for a further approximately 18 years is unlikely and some waning of ixazomib's treatment effect should be included in the models for the people alive and at risk at the end of observation.

1.2.2 ERG's approach to waning of the treatment effect

Using the Warwick's approach to implementing a waning of the intervention treatment effect, extrapolated parametric models gradually approach closer and closer to zero with extending time (without reaching zero). For practical purposes a model "time horizon" is taken to be when fewer than e.g., 1 in 1000 individuals still survive so that at the "lifetime horizon" both intervention and comparator arms reach to vanishingly small proportion of survivors. The ixazomib submission did not state what the time horizon was.

If waning of intervention treatment effect is applied, in essence the survival curve for the intervention will approach somewhat closer to the comparator survival curve than would be the case with no waning. There are many ways by which this may be achieved. The ERG used a method which, upon request from Takeda was shared with the company and was subsequently criticised by them, however the manufacturer has not suggested any alternative method and has adopted the position that any waning beyond the observation period as used by the ERG would be inappropriate.

A problem with implementing any waning procedure is that many options are available but which of these is most appropriate is very difficult to ascertain. Therefore, the ERG did not include waning in its base-case but presented several scenarios analyses. In this particular case the ERG applied waning only to the survival curve beyond the observation period (and only to survivors at the end of observation) this means there is no data for the 2+ prior population from the trial or submission over this time period to guide the waning procedure. Hence, as one scenario, the ERG employed very minimal waning leading to a small change in the intervention survival curve and noted that this minor adjustment impacted on the ICER and consequently indicated considerable sensitivity of the economic model to how survival is modelled and extrapolation beyond observation period. The ERG considered other scenarios where waning of the intervention treatment effect was completed at five years and 7.5 years, respectively.

1.2.3 PenTAG ERG approach to waning of the treatment effect

The PenTAG ERG implemented a waning of treatment effect to the intervention (pembrolizumab combination) commencing at the point of discontinuation. Treatment waning was applied gradually, with the gradual effect occurring linearly using a weighted hazard produced at each model cycle, which generated an adjusted overall survival estimate for people randomised to pembrolizumab combination. Using this gradual approached avoided

stepped changes in hazards. The ERG undertook scenarios, which applied treatment waning of the effect gradually until five years and 10 years.

Using the PenTAG's approach may have advantages over our method:

- May avoid the death rate in the waning IXA+LEN+DEX arm being greater during waning than in the LEN+DEX arm
- Waning is applied to hazards as opposed to the survival function
- OS curves meeting in the long run rather than during the waning period
- Any survival benefit between IXA+LEN+DEX and LEN+DEX at the start of the waning period is accounted for throughout the waning period

We have now updated our scenario analyses since PMB based on penTAG ERG's approach, with the results reported in Section 1.2.4. In Figure 1 to Figure 3, we show three ERG scenarios by applying a waning of ixazomib treatment effect of the generalised gamma model of the adjusted two-stage re-censoring (novel therapies). These figures show the adjusted overall survival: 2-stage re-cens (novel therapies) for IXA+LEN+DEX and LEN+DEX, and the starting point where waning of ixazomib treatment effect commences and ends.

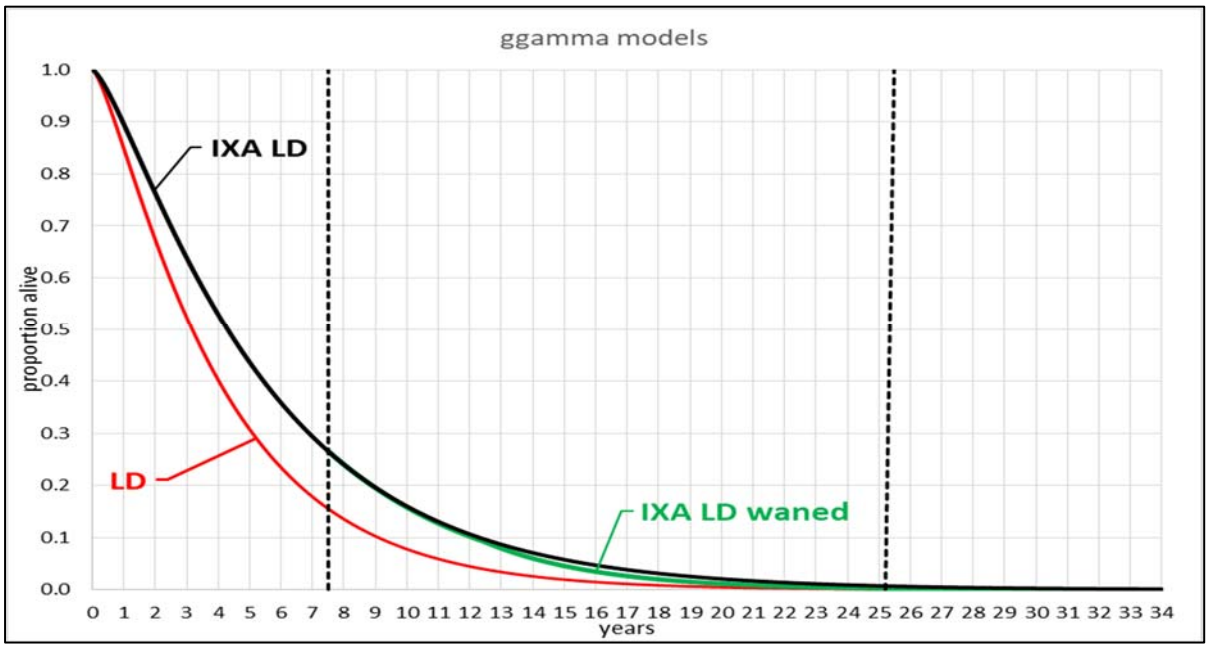

Figure 1: Scenario with waning of ixazomib treatment effect taking 18 years to be completed

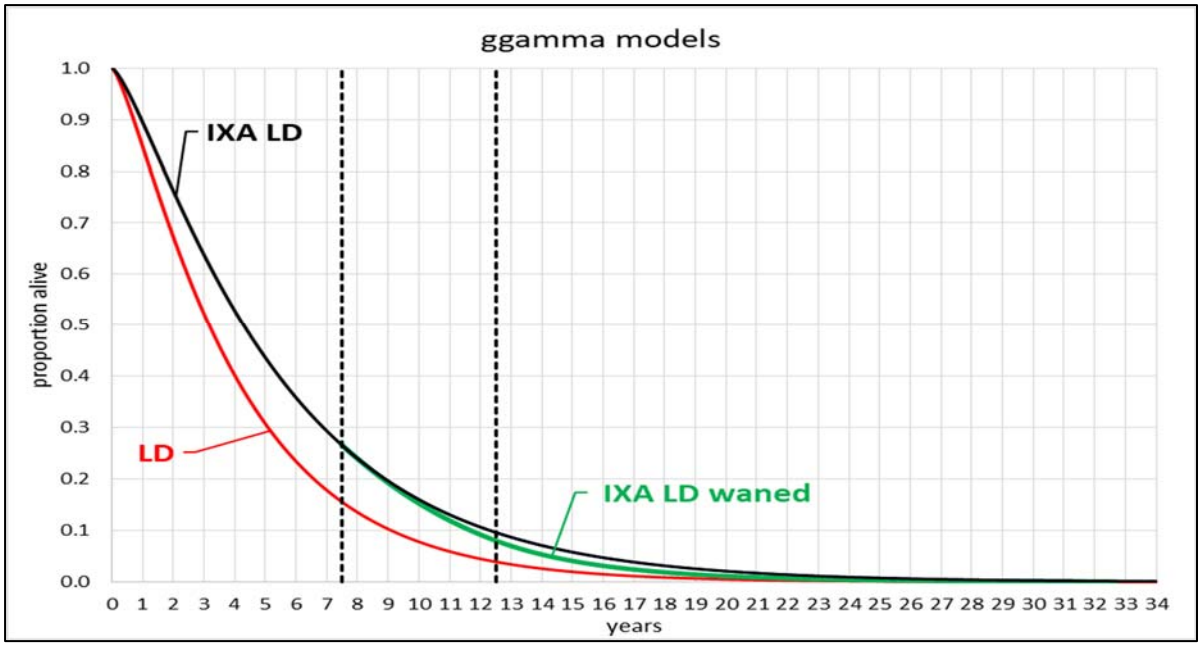

Figure 2: Scenario with waning of ixazomib treatment effect taking five years to completion

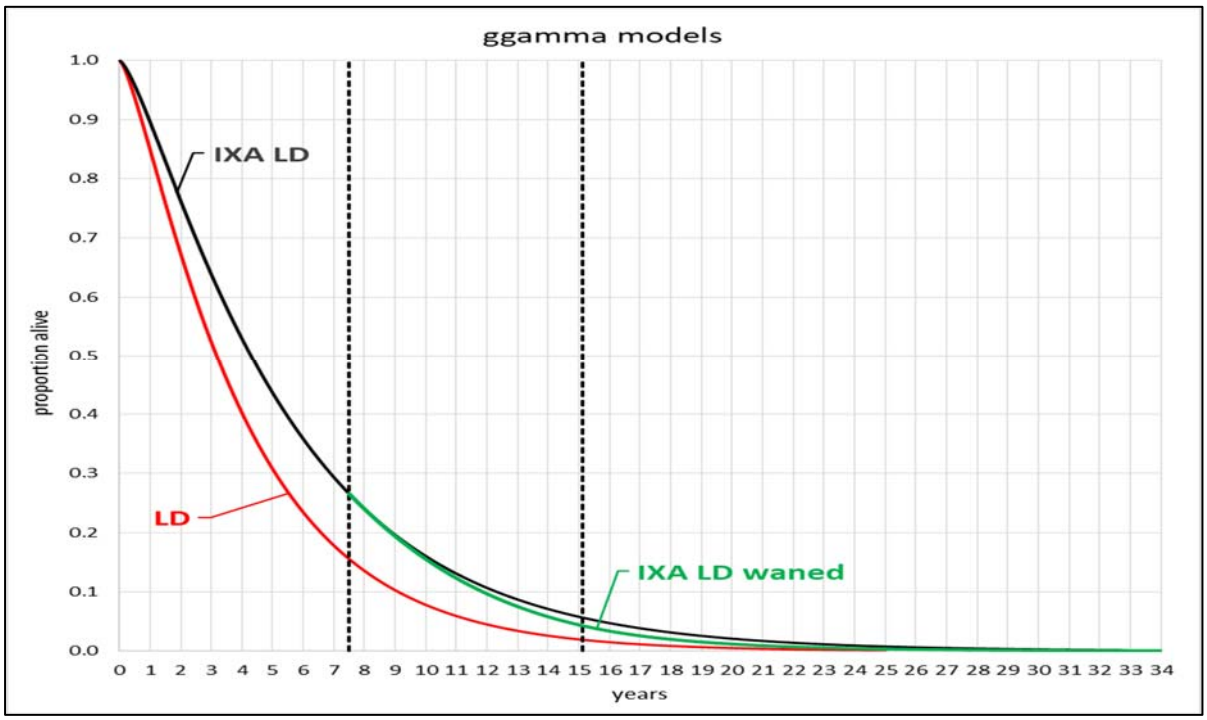

Figure 3: Scenario with waning of ixazomib treatment effect taking 7.5 years to completion

1.2.4 ERG exploratory analyses results based on waning scenarios (with other assumptions as preferred by the company)

Table 4 shows the results of the treatment waning scenario analyses. Applying post treatment waning of effect taking five years to complete to the generalised gamma parametric model for the adjusted overall survival: 2-stage re-censored (novel therapies) had the greatest impact the ICER based on the company's preferred assumptions.

Table 4: Treatment waning scenario analysis results

Scenario	Scenario detail	Brief rationale	ICER (£/QALY)	Impact on base-case ICER
Company's preferred assumptions (base-case)			**£37,519**	**-**
Post treatment waning of effect (Weibull model for adjusted overall survival: 2-stage re-cens. (novel therapies)	Assume waning of company's Weibull IXA+LEN+DEX model over a lifetime from year 7.5 **(18 years to complete)**	The ERG queries the sustained effect of ixazomib after treatment has ended. While the ERG acknowledges that waning of treatment (during the treatment itself) has almost completely been captured within the observed time of the trial, we consider that the prolonged sustained effect of the treatment (after treatment has finished) that is currently included in the company models should be considered separately. The ERG provides three scenarios to explore the impact of changes to the sustained effect of treatment for ixazomib (after treatment has finished) on the ICER.	£41,349	+£3,830
	Assume waning of company's Weibull IXA+LEN+DEX model over a lifetime from year 7.5 **(5 years to complete)**		£43,180	+£5,661
	Assume waning of company's Weibull IXA+LEN+DEX model over a lifetime from year 7.5 **(7.5 years to complete)**		£42,396	+£4,877
Post treatment waning of effect (generalised gamma model for adjusted overall	Assume waning of company's generalised gamma IXA+LEN+DEX model over a lifetime from year 7.5 **(18**	As above.	£39,076	+£1,557

survival: 2-stage re-cens. (novel therapies)	**years to complete)**			
	Assume waning of company's generalised gamma IXA+LEN+DEX model over a lifetime from year 7.5 **(5 years to complete)**		£40,476	+£2,957
	Assume waning of company's generalised gamma IXA+LEN+DEX model over a lifetime from year 7.5 **(7.5 years to complete)**		£39,706	+£2,187

ERG Summary

We undertook several scenarios to assess the impact these changes would have to the company's base-case ICER. Using the company's PAS and applying post-treatment waning of effect taking five years to complete to the generalised gamma parametric model for the adjusted overall survival: 2-stage re-censored (novel therapies) had the greatest impact the ICER.