NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ixazomib citrate for treating relapsed or refractory multiple myeloma

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

Pre-meeting briefing

Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

Glossary (1)

- 2nd line: received at least 1 prior therapy
- 3rd line: received at least 2 prior therapies
- 4th line: received at least 3 prior therapies
- AEs: adverse events
- ASCT: autologous stem cell transplant
- BoR: best overall response
- BORT: bortezomib
- BORT+DEX: bortezomib in combination with dexamethasone
- CDF: cancer drugs fund
- CI: confidence interval
- CR: complete response
- CrI: credible interval
- DEX: dexamethasone
- ECOG: Eastern Cooperative Oncology Group
- EORTC QLQ: European Organisation for Research and Treatment of Cancer quality of life questionnaire
- HR: hazard ratio
- HRQoL: health-related quality of life
- ICER: incremental cost-effectiveness ratio
- iv: intravenous
- ITT: intention-to-treat
- IXA+LEN+DEX: ixazomib in combination with lenalidomide and dexamethasone

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Glossary (2)

- LEN: lenalidomide
- LEN+DEX: lenalidomide in combination with dexamethasone
- MA: marketing authorisation
- MY-20: EORTC multiple myeloma module
- NE: not estimable
- NMA: network meta-analysis
- OR: odds ratio
- ORR: overall response rate
- OS: overall survival
- PD: progressed disease
- PFS: progression-free survival
- PR: partial response
- QALY: quality-adjusted life year
- RCT: randomised controlled trial
- RRMM: relapsed/refractory multiple myeloma
- sc: subcutaneous
- SD: stable disease
- SmPC: summary of product characteristics
- THAL: thalidomide
- TMM1: TOURMALINE-MM1 (trial of ixazomib)
- ToT: time on treatment
- TTP: time to progressions
- TRAE: treatment-related adverse event
- tx: treatment
- VGPR: very good partial response

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Key clinical issues

- Does the company's placement of ixazomib (restricted to 2nd and 3rd line) reflect its anticipated use in clinical practice?
- Have all relevant comparators been included?
  - Is panobinostat used 3rd line?
  - What are the current established treatment options in England for people who have received 1st-line BORT (either as induction before ASCT, or in people ineligible for ASCT)?
- Does IXA+LEN+DEX improve clinical outcomes — including PFS, OS and response rates — compared with LEN+DEX?
  - Are these benefits maintained long-term?
  - Are there any subgroups in whom IXA+LEN+DEX is more effective? For example, based on number of prior therapies.
- In the network meta-analysis, is it appropriate to:
  - use the Montefusco study? (as in the company NMA)
  - use TTP as a proxy for PFS? (as in the ERG exploratory NMA)
- Does IXA+LEN+DEX improve clinical outcomes compared with BORT+DEX?

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Key cost-effectiveness issues (1)

- Does the committee consider that using data from the 1st, rather than 2nd, interim analyses of TMM1is sufficiently robust?
- When modelling 3rd line positioning of IXA+LEN+DEX, is it more appropriate to use data from the pre-specified subgroup of people who had 2–3 prior therapies in TMM1 as a proxy, or data specific to people with 2 prior therapies (which represents a post-hoc analysis)?
- The summary of product characteristics for LEN+DEX and IXA+LEN+DEX state that treatment should be continued until disease progression or unacceptable toxicity. Time on treatment (ToT) might therefore be shorter than PFS.
  - How many people stop treatment before disease progression? Did the model overestimate this? In practice, would the ToT to PFS ratio for IXA+LEN+DEX be similar or different than for LEN+DEX?
  - More appropriate to use the ToT curve or the PFS curve to model treatment costs?
- Which is the most plausible method to extrapolate OS in the 1 prior therapy group? (company base case uses delayed exponential and the ERG are in favour of the Weibull). And for PFS - Weibull or generalised gamma?

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Key cost-effectiveness issues (2)

- Did the company overestimate the cost of BORT in its base case model?
  - Are the restrictions in the SmPC applied in practice? That is, a maximum of 8 cycles, with only 2 cycles given after a complete response?
  - Is the stopping rule in TA129 applied in practice (treatment stops in people who do not have a complete or partial response after 4 cycles)?
  - Do patients complete every treatment cycle that they start?
- Quality of life
  - Was it appropriate for the company to assume a higher utility for progressed disease than stable disease?
  - How do subcutaneous injections affect HRQoL? Does the model accurately reflect this?
  - Is there an association between baseline HRQoL and response? Does HRQoL decline with each relapse and age?
- Should post-progression treatments be modelled as a one-off or ongoing cost?
- CDF: does IXA+LEN+DEX have plausible potential to be cost-effective at the current price?

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Disease background

- Multiple myeloma is a form of cancer that arises from plasma cells (a type of white blood cell) in the bone marrow
- Myeloma cells produce a large amounts of an abnormal antibody known as paraprotein which lacks the capacity to fight infection and suppress the production of normal cells (white, red and platelets)
- Multiple myeloma refers to the presence of these cells in more than one affected bone
- Common symptoms
  - Bone pain, bone fractures, anaemia, infections, hypercalcaemia
- Incidence and survival
  - 4,700 people diagnosed in England in 2013
  - Approx. 58% of cases diagnosed in people aged 70 and over
  - More common in men than women and a higher prevalence in people of African and Caribbean family origin
  - 5-year survival rate in England and Wales approx. 47%

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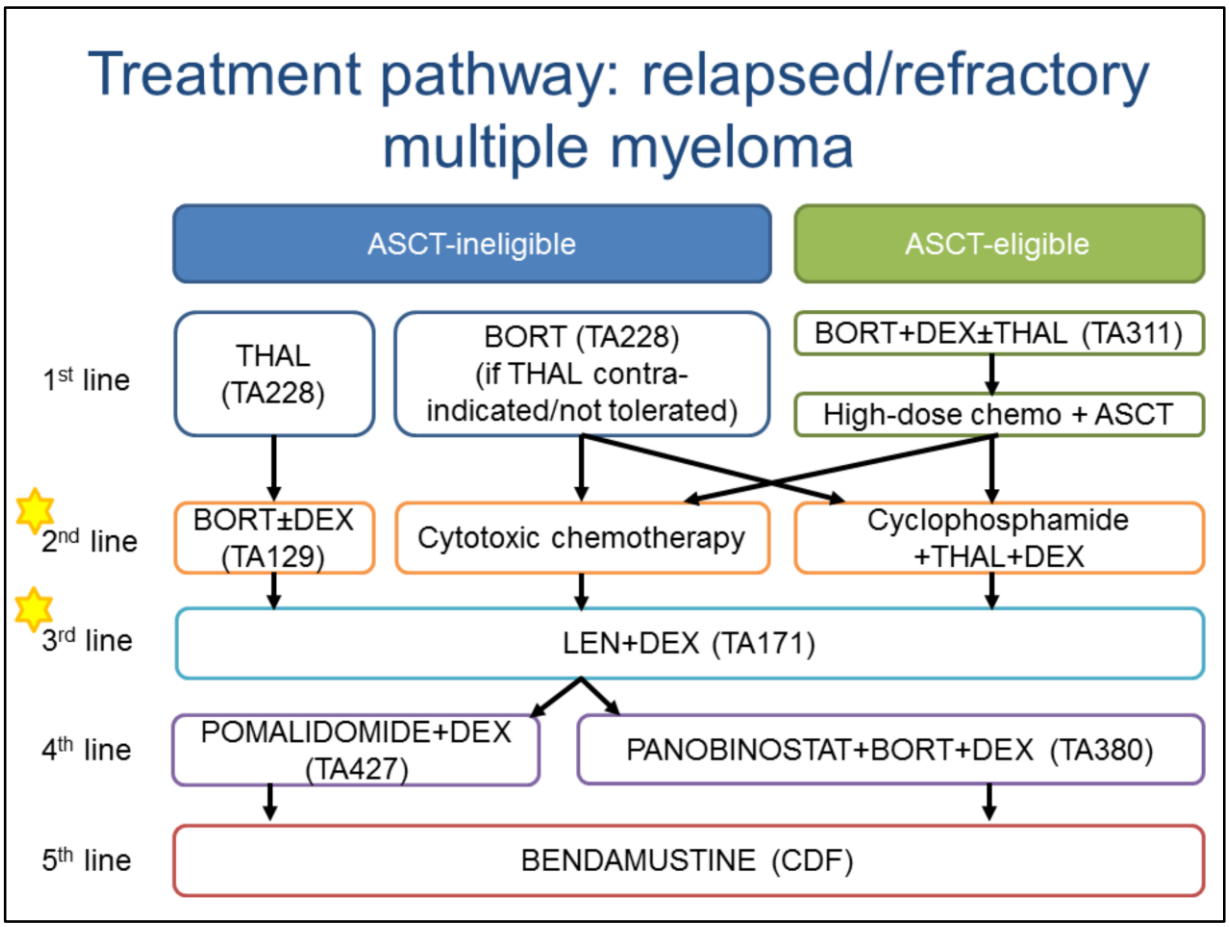

Proposed positioning of ixazomib in combination with lenalidomide and dexamethasone (IXA+LEN+DEX)

- The company propose that IXA+LEN+DEX will be used as a second line or third line treatment. They cite clinician feedback that the predominant use of ixazomib is expected to be in a third line agent prior to panobinostat and other later line agents.

First line treatment options

- TA228 recommends thalidomide (or bortezomib) in combination with an alkylating agent (melphalan) and a corticosteroid (prednisone) for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate.
- TA311 recommends bortezomib in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

Second line treatment options:

- NICE recommends bortezomib monotherapy as an option for treating multiple myeloma at first relapse (TA129). In clinical practice in England, bortezomib is often given in combination with dexamethasone.
- For people who have had first-line treatment with bortezomib (that is, people who have bortezomib as part of induction therapy before ASCT or people who are ineligible for ASCT and cannot have thalidomide), bortezomib re-treatment is not reimbursed under TA129.

Bortezomib re-treatment was previously available on the Cancer Drugs Fund, but was de-listed in March 2015. Lenalidomide in combination with dexamethasone was another second line option previously available on the Cancer Drugs Fund (regardless of first-line treatment), but this was de-listed in November 2015. With these treatments no longer available, people in England may be offered cytotoxic chemotherapy (such as melphalan) or cyclophosphamide in combination with thalidomide and dexamethasone (CTd).

- Note that second line use of lenalidomide in combination with dexamethasone is currently being appraised by NICE (in a part review of TA171); publication data to be confirmed.

Fourth line treatment options:

- NICE recommends panobinostat in combination with bortezomib and dexamethasone as an option for treating multiple myeloma, that is, for 'adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent' (TA380). In clinical practice in England, panobinostat regimens are predominantly used at fourth line.

Ixazomib (Ninlaro)

Conditional marketing authorisation (Nov 2016)	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
Mechanism of action	Proteasome inhibitor
Administration & dosage	Oral tablet, 4 mg once a week on days 1, 8, and 15 of a 28-day cycle (with lenalidomide 25 mg daily on days 1-21 of the cycle and dexamethasone 40 mg on days 1, 8, 15, and 22 of the cycle)
Duration of treatment	Until disease progression or unacceptable toxicity Treatment for longer than 24 cycles should be based on an individual benefit risk assessment, as the data on the tolerability and toxicity beyond 24 cycles are limited
Cost	£6,336/cycle (3 tablets, list price) £10,778.48/cycle with LEN + DEX A confidential patient access scheme has been approved

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The marketing authorisation for ixazomib is conditional on the company providing the following:

- Final OS results from the China continuation study, a multicentre, placebo-controlled RCT in relapsed/refractory multiple myeloma (by December 2016)
- Primary endpoint PFS results from RCTs in ASCT-eligible and ASCT-ineligible patients with newly diagnosed multiple myeloma (by December2017 and December 2018)
- Descriptive data from a global, prospective, non-interventional, observational study in multiple myeloma (by December 2019)

The company is also obligated to provide updated OS analyses from TMM1 (the third interim analysis and final report) by December 2019

Details can be found on page 148 of the European Public Assessment Report (EPAR): http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003844/WC500217623.pdf

Note that the CHMP initially recommended **against** granting a marketing authorisation for ixazomib, stating that "The data are currently immature, especially for overall survival which is not yet evaluable. Efficacy data in the overall ITT population from the first and second interim analyses do not provide the statistically compelling evidence expected for an application based on a single pivotal trial. Point estimates for efficacy measures are not sufficiently outstanding in the context of other available treatment options."

After re-examination of the marketing authorisation application, the CHMP's overall conclusions were as follows (pages 133-147 of the EPAR):

- "the CHMP considered that the primary endpoint, PFS was met and the result was robust in

the first planned interim analysis … However, updated efficacy data from a second interim analysis representing the most up-to date data, showed a reduced difference in effect between arms. The CHMP acknowledged the applicant's argumentations that the second interim analysis is only a sensitivity analysis, and should be interpreted as such and concluded that it is difficult not to acknowledge the positive result of a large clinical trial (n=722) in this clinical setting"

- "the results in the heavily pre-treated population (new proposed indication) contrast with what is observed in patients treated with one previous line only and there does not seem to be a biological rationale or statistical evidence to exclude a significant effect also in patients with 1 prior line of treatment … the CHMP acknowledged the several mechanisms that could explain the increased sensitivity to ixazomib in the subgroup of patients with at least two prior therapies, compared to one prior therapy however it is not possible confirm them by observations in clinical practice."
- "recently approved drugs for the treatment of multiple myeloma have shown improvements in median in PFS in the range of 4 to 6 months; therefore the 5.9 months improvement observed in the ITT population is considered clinically relevant."
- "there is some uncertainty about the magnitude of the treatment effect."
- "In the pivotal trial, the median OS is not evaluable yet and the data is considered immature in this respect. The efficacy evaluation is primarily based on assessment of progression free survival and requires verification of the effect on overall survival."
- "The delay in disease progression observed with ixazomib is clinically relevant. Concerning the possible uncertainty about the magnitude of the effect, this uncertainty seems acceptable given the favourable toxicity profile, and considering that ixazomib is the first agent to allow oral triple combination therapy in this patient population, which represents a therapeutic innovation in terms of convenience for patients. Therefore, the benefit risk for ixazomib in combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy is considered positive, albeit the efficacy evidence is not as comprehensive as normally required."

The CHMP heard from its scientific advisory group that (pages 131-133 of the EPAR):

- "The number of events is considered in line with what is generally expected in the field for trials of this size in this population. Hence the ITT analysis is therefore considered mature and the observed effect (about 6 month difference in median PFS) as clinically relevant. Although subsequent analyses showed slightly less statistical significance, this slight fluctuation is not considered to invalidate the conclusions of the primary analysis, based on the totality of the data."
- "The OS analysis is not considered sufficiently mature and it is also possible that in view of new agents with impact on OS a clear difference in terms of OS might be difficult to observe in the long term. In multiple myeloma in this

treatment setting, however, PFS is considered a clinically relevant endpoint and the magnitude of the effect quite significant. In addition, the favourable trend in OS in the ITT populations is promising and one can rule out a detrimental effect on OS with reasonable certainty."

- "If any opportunistic subgroup would need to be selected on the basis of available data, it would possibly be for 3 prior treatments which is the subgroup that stands out most in the Forest plot, while 2 prior lines is not very different to 1 prior line. In conclusion, there does not seem to be a strong rationale or statistical evidence to exclude a significant effect also in patients with 1 prior line of treatment."

	Final scope	Company submission and rationale for deviations
Pop.	People with relapsed or refractory multiple myeloma (RRMM) who have had at least 1 therapy	
Int.	Ixazomib in combination with lenalidomide and dexamethasone (IXA+LEN+DEX)	
Comp.	For people who have had ≥1 therapy: • BORT (±DEX) • BORT retreatment (±DEX) • LEN+DEX (subject to NICE appraisal [part review of TA171]) For people who have had ≥2 therapies: • LEN+DEX • Panobinostat+BORT+DEX	The company excluded: • BORT monotherapy because it is rarely used in clinical practice • BORT retreatment because it is no longer available on the CDF • LEN+DEX because it is no longer available on the CDF and received negative preliminary guidance from NICE • Panobinostat because it is predominantly used at 4th line
Outcomes	• PFS and OS • response rates • time to next treatment • AEs • quality of life	As per scope, except 'time to next treatment' was not collected in the clinical trial of IXA+LEN+DEX 10

Notes about the comparators in the scope

- The interpretation of 'people who have had at least 1 therapy' is that it relates to people who have had only 1 prior therapy (that is, the comparators reflect second line therapy). This was discussed and agreed by NICE at the decision problem meeting.
- The interpretation of 'people who have had at least 2 therapies' is that it relates to people who have had only 2 prior therapies (that is, the comparators reflect third line therapy). This reflects the anticipated use of ixazomib in the treatment pathway. NICE heard from clinical experts during the scoping process that it is unlikely that people will have ixazomib (which is given in combination with lenalidomide and dexamethasone) as a fourth line therapy because this would mean re-treating the disease with lenalidomide – the current standard of care third line. Lenalidomide re-treatment is not common practice because it is not clinically effective.
- Exclusion of comparators:
    - Bortezomib re-treatment for multiple myeloma was de-listed from the CDF in March 2015. Commissioning experts and clinical advisors to NICE (and the ERG) agree that bortezomib re-treatment is not currently established practice.
    - Lenalidomide as a second line treatment for multiple myeloma was de-listed from the CDF in November 2015. Commissioning experts and clinical advisors to NICE agree that second-line lenalidomide is not currently established practice.
    - Panobinostat: The exclusion of panobinostat as a comparator in people who have had 2 prior therapies was judged appropriate by the committees who appraised carfilzomib (ID934) and pomalidomide (TA427) in multiple myeloma, based on advice

from clinical experts in at the October 2016 committee meetings that, in clinical practice in England, panobinostat regimens are predominantly used at fourth line. The company for this appraisal of ixazomib submitted market research data from IMS (October/November 2016) which suggested that lenalidomide is the most commonly used treatment at 3rd line (69% market share) and that panobinostat has a low market share at both 3rd and 4th line (7% and 19% respectively).

Further detail can be found in the company submission: pages 15-20

Comparator in people who have 1st line BORT

- As per the current decision problem, because bortezomib re-treatment is no longer available on the CDF, and final guidance on using LEN+DEX at second line is not yet available, none of the comparators listed in the scope are relevant for the subgroup of people who have received 1 line of treatment with bortezomib
- Commissioning experts and clinical experts have advised NICE that the appropriate comparator for IXA+LEN+DEX in people who have had first-line BORT, based on current practice in England, is:
  - Cyclophosphamide+thalidomide+dexamethasone (CTD)
  - cytotoxic chemo eg melphalan
- The company, in its response to clarification, noted that these treatment regimens are used in practice and are relevant comparators, but it did not provide any analyses of these comparators because they were not listed in the scope
- The committee may therefore be unable to make a recommendation for IXA+LEN+DEX in this subgroup, and the company will be provided the opportunity to submit evidence on this comparison (if available) after the scope is updated and consulted on.

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To note:

- 57% of people in TMM1 had received an ASCT prior to study entry (TA311 recommends induction treatment with bortezomib and dexamethasone, with or without thalidomide, before ASCT).
- 69% of people in TMM1 had received bortezomib prior to study entry.
- Preliminary guidance for using LEN+DEX second line (in the part review of TA171) is negative.

Decision problem summary: comparators

IXA+LEN+DEX positioning	Comparator
For people who have had 1st line THAL	BORT+DEX
For people who have had 2 therapies	LEN+DEX

Pending	
For people who have had 1st line BORT	Cyclophosphamide+THAL+DEX (CTd)
	Cytotoxic chemotherapy
	LEN+DEX (subject to ongoing NICE part review of TA171)

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Clinical effectiveness

1 RCT of IXA+LEN+DEX in RRMM: TOURMALINE-MM1 (TMM1) trial

- TMM1 is an ongoing phase III double-blind randomised controlled trial
- 147 sites in 26 countries including 9 in the UK (n=21)
- Population: Adults with relapsed and/or refractory multiple myeloma (RRMM) who had received 1-3 prior lines of therapy, had measurable disease and ECOG performance status 0–2
- Randomisation stratified by
  - number of prior therapies: 1 (n=425) compared with 2 or 3 (n=297)
  - previous proteasome inhibitor exposure: naïve compared with exposed
  - International Staging System disease stage: I or II compared with III
- Intervention: IXA+LEN+DEX (n=360); comparator: LEN+DEX (n=362)
- The protocol specified that treatment continued until disease progression or unacceptable toxicity, whichever occurred first. However, the results showed that some patients were treated beyond progression.
- Primary endpoint: progression-free survival
- HRQoL was assessed every 4 weeks until progression and every 12 weeks post-progression using EQ-5D, EORTC QLQ-C30 and MY-20
- 2 interim analyses (IA1 and IA2) at ~15 month and ~23 month follow up

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TMM1 is ongoing. There have been 2 interim analyses:

- The first interim analysis (IA1) was after a median ~15 month follow up (30 October 2014).
- The second interim analysis (IA2) was after a median ~23 month follow up (12 July 2015).

A third interim analysis of overall survival is planned for Q2 2017 and the final analysis of overall survival is planned for Q3 2019.

TMM1 baseline characteristics

Characteristic	IXA+LEN+DEX (n=360)	LEN+DEX (n=362)	Overall (n=722)
Age, median (range), yrs	66 (38–91)	66 (30–89)	66 (30–91)
Line of therapy			
1	212 (59)	213 (59)	425 (59)
2 or 3	149 (41)	148 (41)	297 (41)
Time since diagnosis, median (range), months	44.2 (3–281)	42.2 (4–306)	42.8 (3–306)
Prior stem cell transplant	212 (59)	199 (55)	411 (57)
Prior proteasome inhibitor (PI), n (%)	249 (69)	253 (70)	502 (70)
Prior bortezomib	248 (69)	250 (69)	498 (69)
Prior carfilzomib	1 (<1)	4 (1)	5 (<1)
Refractory to prior PI, n (%)	4 (1)	8 (2)	12 (2)
Prior immunomodulatory (IMiD), n (%)	193 (54)	204 (56)	397 (55)
Prior lenalidomide	44 (12)	44 (12)	88 (12)
Prior thalidomide	157 (44)	170 (47)	327 (45)
Refractory to prior IMiD, n (%)	41 (21)	50 (25)	91 (23)

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TMM1 results: first interim analysis

	IXA+LEN+DEX	LEN+DEX	HR or OR (95% CI)
PFS: n; median, months			
ITT population	**129; 20.6**	**157; 14.7**	**HR: 0.74 (0.59, 0.94) p=0.012**
1 prior therapy	80; 20.6	88; 16.6	HR: 0.88 (0.65, 1.20)
2–3 prior therapies	**49; NE**	**69; 12.9**	**HR: 0.58 (0.40, 0.84) p<0.05**
OS: n; median, months			
ITT population	51; NE	56; NE	HR: 0.90 (0.62, 1.32)
1 prior therapy	31; NE	26; NE	HR: 1.24 (0.74, 2.10)
2–3 prior therapies	20; NE	30; NE	HR: 0.62 (0.35, 1.09)
ORR: n (%)			
ITT population	**282 (78.3)**	**259 (71.5)**	**OR: 1.44 (1.03, 2.03) p=0.04**
1 prior therapy	163 (76.9)	159 (74.6)	OR: 1.13 (0.72, 1.77)
2–3 prior therapies	**119 (80.4)**	**100 (67.1)**	**OR: 2.03 (1.19, 3.45) p<0.05**

Bold red denotes statistically significant differences. HR, hazard ratio; NE, not estimable; OR, odds ratio

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Source: table 41 company submission

The primary endpoint of improving PFS was met at the first interim analysis and this was the final statistical analysis of this endpoint.

- At the 15 month follow-up there was a 26% reduction in risk of progression or death with IXA+LEN+DEX compared with LEN+DEX in the ITT population This difference between treatment arms was statistically significant: hazard ratio 0.74 (95% confidence interval 0.59 to 0.94), p=0.012. The company stated that the ~6 month improvement in median PFS (20.6 compared with 14.7 months) in favour of the IXA+LEN+DEX arm is clinically meaningful.
- A non-inferential PFS analysis was conducted at a median follow up of 23 months with 372 PFS events. The hazard ratio of PFS for IXA+LEN+DEX compared with LEN+DEX was 0.82 (95% confidence interval 0.67 to 1.0) in the ITT population. Estimated median PFS was 20 months in the IXA+LEN+DEX group and 15.9 months in the LEN+DEX group.
- Results from the second interim analysis showed a reduced difference in effect between arms in the ITT population for PFS, response rates and time to progression compared to the first interim analysis. That is, the benefit of IXA+LEN+DEX compared with LEN+DEX appeared to reduce in the second interim analysis.

At both the first and second interim analyses, OS data were not yet mature; the median OS was not reached in either trial arm.

- At the first interim analysis, 107 (22%) of the pre-specified 486 deaths required for the final OS analysis had occurred (51 in the IXA+LEN+DEX arm and 56 in the LEN+DEX arm).
- At the second interim analysis, 171 (35%) of the pre-specified deaths had occurred (81 in the

IXA+LEN+DEX arm and 90 in the LEN+DEX arm).

- The company suggested that the data indicate a non-significant survival benefit in favour of IXA+LEN+DEX
    - First interim analysis: hazard ratio of OS for IXA+LEN+DEX compared with LEN+DEX was 0.900 (95% confidence interval 0.62 to 1.32) in the ITT population. The 18-month survival rates were 83% in the IXA+LEN+DEX arm and 80% in the LEN+DEX arm.
    - Second interim analysis: : hazard ratio of OS for IXA+LEN+DEX compared with LEN+DEX was 0.87 (95% confidence interval 0.64 to 1.18) in the ITT population.

The company used the results from the first interim analysis to inform the efficacy outcomes its base case cost-effectiveness analysis (OS, PFS, ORR). It used the results of the second interim analysis in a scenario analysis. Adverse events in the model were based on data from the second interim analysis.

TMM1 results: second interim analysis

	IXA+LEN+DEX	LEN+DEX	HR or OR (95% CI)
PFS: n; median, months			
ITT population	177; 20	195; 15.9	HR: 0.82 (0.67, 1.0)
1 prior therapy	109; 18.7	112; 17.6	HR: 0.99 (0.76, 1.29)
2–3 prior therapies	**68; 22.0**	**83; 13.0**	**HR: 0.62 (0.45, 0.86)**
OS: n (%); median, months			
ITT population	81 (23); NE	90 (25); NE	HR: 0.87 (0.64, 1.18) p=0.359
1 prior therapy	48; NE	45; NE	HR: 1.11 (0.74, 1.66)
2–3 prior therapies	33; NE	45; NE	HR: 0.65 (0.41, 1.02)
ORR: n (%)			
ITT population	283 (78.6)	265 (73.2)	OR: 1.35 (0.96, 1.91)
1 prior therapy	164 (77.4)	166 (77.9)	OR: 0.97 (0.61, 1.53)
2–3 prior therapies	**119 (80.4)**	**99 (66.4)**	**OR: 2.09 (1.23, 3.56)**

Bold red denotes statistically significant differences. HR, hazard ratio; NE, not estimable; OR, odds ratio 17

Source: table 41 company submission and response to clarification question A4 (95% CI for overall response rate odds ratio)

To note:

- Post hoc analyses by the company showed a regional difference in PFS in patients from North Asia who were enrolled later into the study and who had a disproportionate effect on the second analysis compared with the first analysis. In the study population excluding patients from North Asia ("non-North Asia"), the median PFS in the ixazomib and placebo regimens was 20.5 and 15.6 months, respectively (HR=0.785)

Overall safety profile of TMM1

Adverse events, n (%)	**IXA+LEN+DEX (n=361)[a]**	**LEN+DEX (n=359)[a]**
Median follow up	*23.3 months*	*22.9 months*
Any AE	355 (98)	357 (99)
Any grade ≥3 AE	267 (74)	247 (69)
Any serious AE	168 (47)	177 (49)
AE resulting in dose reduction of any drug	203 (56)	181 (50)
AE resulting in discontinuation of any drug in the regimen	91 (25)	73 (20)
AE resulting in discontinuation of full drug regimen	60 (17)	50 (14)
On-study death	15 (4)	23 (6)

[a] Two of the 360 patients randomised to IXA did not receive treatment, and at the time of the first interim analysis 2 of the 362 patients randomised to the placebo group accidentally received IXA and were therefore conservatively included in the IXA group for analyses of exposure and safety. A third patient was similarly included in the IXA group for analyses of exposure and safety at the second interim analysis.

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Source: table 54 company submission.

Common adverse events in TMM1 (second interim analysis)

	IXA+LEN+DEX (n=361)			LEN+DEX (n=359)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Common haematologic AEs of any cause, n (%)						
Neutropenia	118 (33)	64 (18)	17 (5)	111 (31)	63 (18)	22 (6)
Thrombocytopenia	**112 (31)**	**43 (12)**	**26 (7)**	57 (16)	19 (5)	13 (4)
Anaemia	103 (29)	34 (9)	0	98 (27)	48 (13)	0
Common non-haematologic AEs of any cause, n (%)						
Diarrhoea	**164 (45)**	23 (6)	0	139 (39)	9 (3)	0
Rash SMQ[c]	**131 (36)**	**18 (5)**	0	82 (23)	6 (2)	0
Rash HLT[c]	**72 (20)**	9 (2)	0	45 (13)	6 (2)	0
Constipation	**126 (35)**	1 (<1)	0	94 (26)	1 (<1)	0
Fatigue	106 (29)	13 (4)	0	102 (28)	10 (3)	0
Nausea	**104 (29)**	6 (2)	0	79 (22)	0	0
Red denotes differences of ≥5% between the 2 treatments						

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Source: table 55 company submission.

Common adverse events were defined as reported in ≥20% patients in either arm.

Data for 'Rash SMQ' based on a standardised MedDRA query (SMQ) pooling 27 preferred terms; data for 'Rash HLT' taken from the high-level term (HLT) of Rashes, eruptions and exanthems NEC, per the data on rash reported in the United States prescribing information

Adverse events in TMM1: second interim analysis

	IXA+LEN+DEX (n=361)			LEN+DEX (n=359)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Common non-haematologic AEs of any cause, n (%)						
Peripheral oedema	**101 (28)**	**8 (2)**	0	73 (20)	4 (1)	0
Peripheral neuropathy[d]	**97 (27)**	**9 (2)**	0	78 (22)	6 (2)	0
Back pain	**87 (24)**	**3 (<1)**	0	62 (17)	9 (3)	0
Vomiting	**84 (23)**	4 (1)	0	42 (12)	2 (<1)	0
Upper respiratory tract infection	83 (23)	2 (<1)	0	70 (19)	3 (<1)	0
Nasopharyngitis	81 (22)	0	0	73 (20)	0	0
Insomnia	73 (20)	7 (2)	0	**98 (27)**	11 (3)	0
Muscle spasms	66 (18)	0	0	**95 (26)**	2 (<1)	0

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Red denotes differences of ≥5% between the 2 treatments

Treatment discontinuation in TMM1 (second interim analysis)

Reason for treatment discontinuation, n (%)	IXA+LEN+DEX (n=360)[a]	LEN+DEX (n=362)
Any	222 (62)	229 (63)
Progressive disease	124 (34)	146 (40)
Adverse event	60 (17)	50 (14)
Common AEs resulting in discontinuation		
Diarrhoea	6 (2)	1 (<1)
Peripheral neuropathy NEC	7 (2)	2 (<1)
Fatigue	4 (1)	2 (<1)
Thrombocytopenia	4 (1)	4 (1)
Cardiac failure	1 (<1)	3 (<1)
Neutropenia	3 (<1)	3 (<1)
Decreased platelet count	1 (<1)	3 (<1)
Withdrawal by patient	7 (2)	11 (3)
Protocol violation	0	1 (<1)
Lost to follow-up	1 (<1)	0

[a]Two patients did not receive the allocated intervention

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Source: table 52 company submission.

Network meta-analysis to compare IXA+LEN+DEX with BORT+DEX

- The company reported that there was insufficient evidence to create networks for the key outcomes using data specifically for 1 prior therapy.
  - The results below use evidence networks for the whole population (that is, everyone who has had ≥1 prior therapy).
  - The company assumed that this is sufficiently representative of the results for a one prior therapy sub-group.
- The base case networks included observational studies and RCTs. Scenario analyses including only RCTs did not have a large impact on the results.

Outcome	Hazard ratio (HR) or odds ratio (OR) for IXA+LEN+DEX vs. BORT+DEX[a]
Progression-free survival (PFS)[b]	HR 0.72 (95% CrI 0.41, 1.19)
Overall survival (OS)	HR 0.31 (95% CrI 0.13, 0.65)
Overall response rate (ORR)	OR 0.88 (95% CrI 0.35, 1.85)
Best overall response (BoR) of very good partial response (VGPR) or better[b]	OR 3.82 (95% CrI 1.32, 8.93)
Discontinuation due to AEs	OR 2.58 (95% CrI 0.81, 6.32)

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The company noted that the NMA results were largely consistent across several scenario analyses and summarised the results of the NMA as follows:

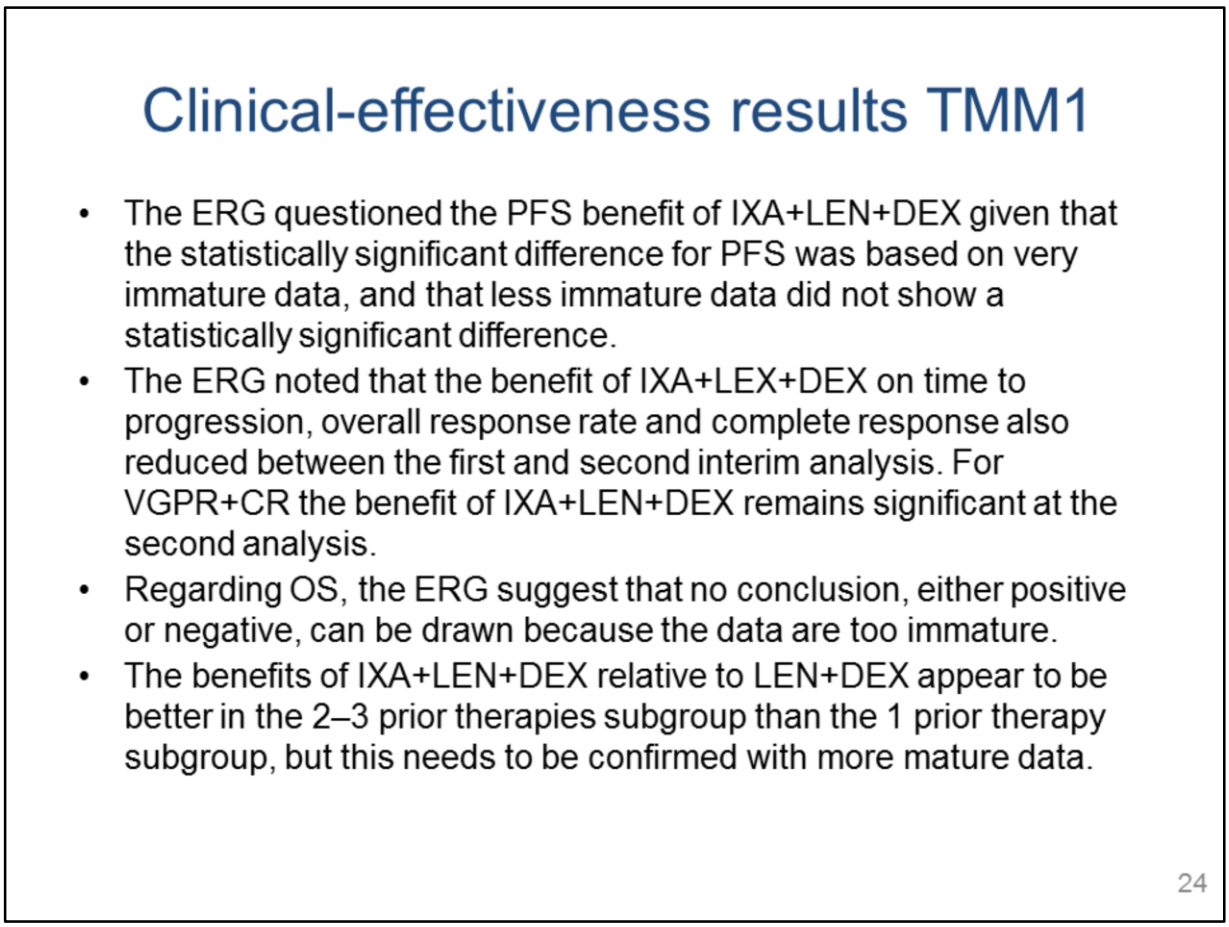
- There is a statistically significant difference between IXA+LEN+DEX and BORT+DEX for OS and BoR.
- The difference between IXA+LEN+DEX and BORT+DEX was not statistically significant for PFS or ORR, but indicated a trend in favour of IXA+LEN+DEX.
- The analysis of treatment discontinuations due to AEs indicated higher discontinuations with IXA+LEN+DEX than with BORT+DEX, but this difference was not statistically significant.
- The credible intervals (CrI) were wider for the ORR, BoR and discontinuations due to AEs networks, indicating a potential higher level of uncertainty in these results.

Table footnotes:

[a] The NMA results for the comparison between IXA+LEN+DEX and LEN+DEX are not presented because they are nearly identical to the results from TMM1; the results of the NMA for this comparison were informed by only the TMM1 trial, and there is no indirect evidence in any of the networks for each population and outcome. See section 4.10 of the company submission for more detail.

[b] The hazard ratio for PFS and odds ratio for BoR was obtained from a network considering all doses of bortezomib observed in the literature (most studies consider a dose of 1.0mg/m^2); due to a lack of data no network could be formed considering the dose specified in the bortezomib marketing authorisation in the UK (1.3mg/m^2).

ERG critique of the company's clinical-effectiveness evidence



The ERG made the following comments on the quality of the company's clinical evidence and data collection:

- Overall, the quality of the systematic review was deemed to be reasonable.
- The company's assessment of the risk of bias of the pivotal RCT (TMM1) was generally appropriate.
- The quality of TMM1 was good with a low risk of bias.
- The population in the trial appear to be relevant to those treated in the NHS and the ERG does not have any reason to consider the results of the trial to be significantly biased. However, clinical effectiveness data are characterised by a high degree of immaturity since the benefit of ixazomib on OS cannot yet be determined.

Benefits of IXA+LEN+DEX in people who had 2–3 prior therapies may be driven by benefit in people with 3 prior therapies

		OS (1st interim analysis)		OS (2nd interim analysis)	
Prior tx	**n**	**HR**	**95% CI**	**HR**	**95% CI**
2–3	297	0.62	(0.35, 1.09)	0.65	(0.41, 1.02)
1	441	1.210	(0.727, 2.017)	1.092	(0.732, 1.629)
2	208	0.770	(0.382, 1.553)	0.725	(0.419, 1.256)
3	73	0.318	(0.100, 1.017)	0.455	(0.181, 1.146)

		PFS (1st interim analysis)		ORR (1st interim analysis)	
Prior tx	**n**	**HR**	**95% CI**	**HR**	**95% CI**
2–3	297	0.58	(0.40, 0.84)		
1	441	0.832	(0.616, 1.123)	1.214	(0.785, 1.880)
2	208	0.749	(0.484, 1.161)	1.658	(0.873, 3.149)
3	73	0.366	(0.169, 0.791)	2.890	(0.983, 8.495)

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The ERG suggest that the benefit in the 2–3 prior therapies subgroup appears to be driven by favourable results in the subgroup of patients who have had 3 prior therapies (that is, fourth line treatment). They noted that, although the confidence intervals of the 3 prior subgroup and the 2 prior subgroup cross each other, there is a consistent trend for the point estimates for the 3 prior subgroup to be better than the point estimates for the 2 prior subgroup. The company has not positioned IXA+LEN+DEX as a fourth line treatment; fourth line comparators were not included in the scope following advice that IXA+LEN+DEX would not be used fourth line.

For more detail, see section 5.3.4.3 of the ERG report and the company's response to clarification question A2.

NMA (1)

The ERG was concerned about the high level of heterogeneity across the studies in the company's NMA. The studies had differences in:

- the proportion of people at 1st/2nd/3rd relapse at baseline
- history of myeloma treatments (first line treatment is an effect modifier)
- dosages of DEX.

The ERG disagreed with using the Montefusco study in the PFS network.

- The Montefusco study included cyclophosphamide as part of the intervention and comparator regimens (LEN+DEX+cyclophosphamide versus BORT+DEX+cyclophosphamide). No data are available to support the company's assumption that the relative effect of LEN+DEX versus BORT+DEX is unaffected by adding cyclophosphamide. In addition, the ERG considered the study to be non-randomised and poor quality.
- The ERG believes that the company used Montefusco because there were not enough published studies reporting PFS. The ERG considers that TTP can be a good proxy for PFS because the definitions are very similar.

The ERG did not agree with the company's statement that there was insufficient evidence to create networks using data specifically for 1 prior therapy.

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To note:

- The company also acknowledged in its submission that the Montefusco study was of poor quality.
- The definitions of TPP and PFS are as follows:
    - TTP results only count progression as an event (death are censored)
    - PFS results count both progressions and deaths as events, whichever occurs first.
- The ERG provided further evidence to support their suggestion that TTP can be considered as a good proxy for PFS: the hazard ratio for TPP was similar to the hazard ratio for PFS in the TMM1 trial of ixazomib (for both the first and second interim analyses) and in the MM-009 and MM-010 trials of lenalidomide.

NMA (2)

The ERG considered that the large survival benefit for IXA+LEN+DEX relative to BORT+DEX was implausible and likely to be an overestimate.

- The OS results contrasted the PFS results (IXA+LEN+DEX reduced the risk of death by **69%** relative to BORT+DEX, but reduced the risk of progression or death by only **28%**); the ERG questioned this because there is evidence of a good correlation between PFS and OS in multiple myeloma.
- The ERG identified an error in the company's NMA inputs in the OS network which explains the overestimation of OS for IXA+LEN+DEX relative to BORT+DEX. The company used 0.57 as the HR for death of DEX compared with BORT based on the APEX trial. However the HR of 0.57 reported in the APEX trial corresponded to the HR for death of BORT compared with DEX.

The ERG conducted its own exploratory NMA which corrected the error in the OS network, excluded the Montefusco study from the PFS network (and included alternative sources of PFS outcomes, using TTP as a proxy where relevant) and excluded studies of poor methodological quality.

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For more information refer to:

- Pages 98-102 of the ERG report (section 4.10.2) which details further evidence supporting the ERG's consideration that the survival benefit associated with IXA+LEN+DEX should be similar to that of BORT+DEX.
- Pages 108-125 of the ERG report (section 4.11.1) which details the methods and results of the ERG's exploratory NMA.

Results of the ERG exploratory NMA: people with ≥1 prior therapy

	ERG NMA	Company NMA
Hazard ratio for IXA+LEN+DEX vs. BORT+DEX		
Progression-free survival	0.75 (95% CI 0.41, 1.38)	0.72 (95% CrI 0.41, 1.19)
Overall survival	0.91 (95% CI 0.43, 1.92)	0.31 (95% CrI 0.13, 0.65)
Hazard ratio for BORT+DEX vs. LEN+DEX		
Progression-free survival	0.98 (95% CI 0.56, 1.71)	1.06 (95% CrI 0.61, 1.85)
Overall survival	0.99 (95% CI 0.54, 1.83)	3.11 (95% CrI 1.52, 6.35)

The results of the ERG's exploratory NMA indicate that there is no evidence that BORT+DEX is more or less effective than IXA+LEN+DEX or LEN-DEX for PFS or OS.

The ERG consider that the company NMA and model underestimate OS and overestimates associated PFS with BORT+DEX.

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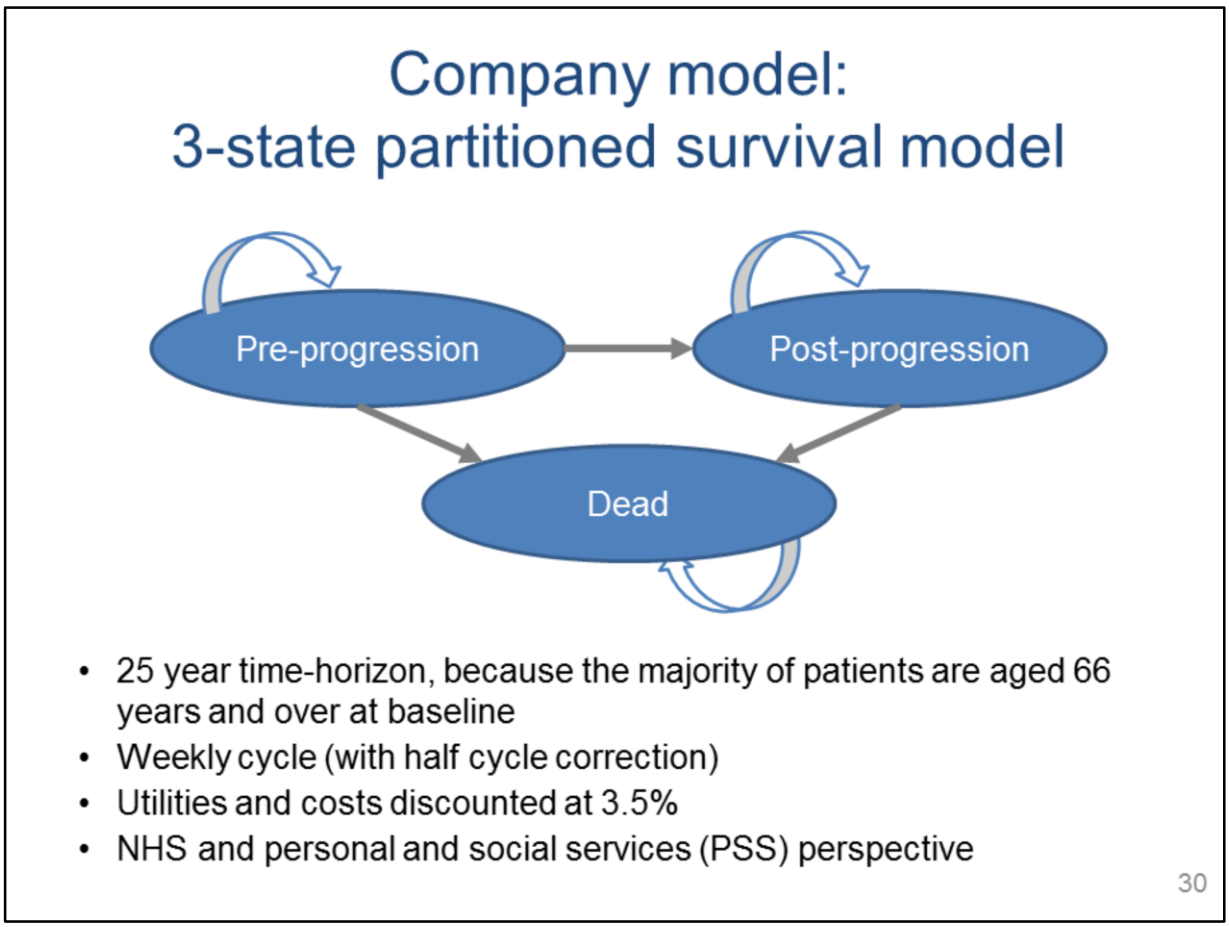
Section 4.11.2 (pages 126-137) of the ERG report describes further exploratory analysis supporting the findings of the ERG's NMA.

Cost effectiveness



The company developed a partitioned-survival model based on 3 health states: pre-progression, post-progression and death. Death can occur from either progression-free or progressed disease and death is an absorbing health state. A partitioned-survival model considers estimates for each clinical endpoint separately (that is, overall survival, progression-free survival and time on treatment are modelled independently) and therefore maintains consistency with the published clinical data. As a result, although the marketing authorisation for ixazomib states that treatment should stop when the disease progresses, the model allowed treatment to continue after disease progression (that is, time on treatment could exceed progression-free survival), reflecting the observed trial data.

Assumptions for health states

- *Pre-progression*: During this stage it is assumed that a patient's disease is in a stable or responding state, and not actively progressing. Patients in this state are assumed to incur costs associated with treatment, including drug acquisition costs, costs of drug administration, and costs associated with medical management of the condition and the management of adverse events. Given that treatment-related adverse events can result in stopping treatment, some patients in the progression-free health state will not be receiving any treatment. Patients in this health state were further subdivided by their Best Overall Response (BoR), which is treatment-specific, into:
    - VGPR+ (which included stringent complete response, complete response and very good partial response [VGPR])
    - partial response (PR)

    - stable disease (SD)

- *Post-progression*: In this stage, a patient's disease is assumed to have returned or progressed, following which it is reasonable to assume that in clinical practice patients would still be eligible for active therapy, and therefore patients are assumed to move onto next-line treatment and eventually best supportive care before death. The company assumed that the treatment effect of any subsequent line of therapy was captured in TMM1 OS estimates and therefore efficacy associated with post-progression therapy was not explicitly modelled; subsequent lines of therapy following progression have been considered in this economic evaluation only in terms of their costs. Disease progression was defined as the time from the date of randomisation to the date of first documentation of disease progression based on central laboratory results and International Myeloma Working Group (IMWG) criteria as evaluated by an Independent Review Committee (IRC), or death due to any cause, whichever occurred first.
- *Death*: This is an absorbing health state; once patients experience death they remain in this health state for the rest of the model time horizon.

These health states relate to clinical benefit and do not account for costs; costs are primarily determined by the Time on Treatment (ToT) curves.

Modelling subsequent treatments in the post-progression health state

- The company modelled subsequent treatments assuming a "basket" of subsequent therapies, where the proportion of patients receiving each therapy as reported in the TMM1 clinical trial is multiplied by the average cost associated with each treatment. This was then multiplied by the proportion of patients receiving active subsequent therapy (24.4%) and applied as a one-off cost to patients moving to the post-progression health state.
- Subsequent treatment regimens in the TMM1 trial regimens included: bendamustine, cyclophosphamide, doxorubicin, bortezomib, carfilzomib, lenalidomide, melphalan, pomalidomide and thalidomide.
- The company did not include bortezomib, carfilzomib or pomalidomide when modelling the cost of subsequent treatment because it considered that they did not reflect clinical practice in the UK at the time of the submission.
  - The company assumed that these patients (n=137) would receive panobinostat+BORT+DEX and reflected this is the modelled costs
  - Since the company submission, pomalidomide has been recommended by NICE as an option for treating multiple myeloma in adults at third or subsequent relapse; that is, after 3 previous treatments including both lenalidomide and bortezomib (TA427, January 2017).

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- To estimate the distribution of patients across subsequent therapies from the TMM1 trial, the company pooled data from the IXA+LEN+DEX and LEN+DEX arms because no significant differences were found between the trial arms.
- The company's assumption that people who received bortezomib-, carfilzomib- or pomalidomide-based regimens as subsequent treatment in the TMM1 trial would receive panobinostat in UK clinical practice was based on feedback from clinical experts.
- Of the 176 (24.4%) patients in the TMM1 trial who received subsequent treatment after disease progression:
  - 25 (14%) of these received pomalidomide
  - 99 (56%) received bortezomib
  - 13 (7%) received carfilzomib
- The total patients receiving each subsequent therapy sums to more than the initial 176, this is because some patients go on to receive multiple lines of subsequent therapy.

Modelling clinical outcomes

- The company base case used results from the first interim analysis of TMM1
- For people who had received 1 prior therapy (second line positioning):
  - Relative efficacy between IXA+LEN+DEX and BORT+DEX was based on data from the NMA. The NMA produced hazard ratios for OS, PFS and ORR for BORT+DEX relative to LEN+DEX which were then applied to the LEN+DEX subgroup data from the TMM1 trial.
  - The company used data from people who had received ≥1 prior therapy in TMM1 (that is, the ITT population) as a proxy, because a network could not be formed for the 1 prior therapy population.
- For people who had received 2 prior therapies (third line positioning):
  - Relative efficacy between IXA+LEN+DEX and LEN+DEX was modelled using TMM1 trial data directly
  - The company used outcomes from the 2–3 prior therapies population because it was a pre-specified stratification factor in the TMM1 trial; any analysis of the 2 prior therapies group would be post hoc.

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The company provided the following justification for using results from the first interim analysis of TMM1 (15 month follow-up) rather than the second interim analysis (23 month follow-up):

- The first interim analysis is the primary analysis data cut for the PFS endpoint
- Although a later interim data cut is available with more mature OS and ToT data (23 months follow up compared with 15 months), these data are still immature (median OS not reached in either arm)

The company provided the following justification for using 2–3 prior therapy data as a proxy for third line positioning:

- It considered that post hoc analysis of the 2 prior therapies only subgroup would not benefit from prior stratification, meaning likely imbalances in important clinical, patient and disease-related factors across the IXA+LEN+DEX and LEN+DEX arms which would confound the interpretation of the results.
- The company noted that, of the 281 TMM1 trial patients who had received 2–3 therapies, 208 (74%) had received 2 prior therapies and 73 (26%) had received 3 prior therapies. The company considered that any efficacy benefits seen in the combined 2 or 3 prior therapies subgroup (used as a proxy for third line positioning) would have been driven primarily by the 2 prior therapies patients.
- The company did not explore the impact on the ICERs of using a post hoc analysis of the 2 prior therapies group, but provided the clinical outcomes for this group (see slide 25), which the ERG incorporated in the model as a scenario analysis.

Survival analysis: extrapolation

	Distribution used in base case	Treatment effect (TE) or hazard ratio (HR) Source: TMM1 (LEN+DEX) or NMA (BORT+DEX)	
1 prior therapy population			
		IXA+LEN+DEX vs. LEN+DEX (95% CI)	**BORT+DEX vs. LEN+DEX (95% CI)**
PFS	generalised gamma[a]	TE 0.94 (0.72, 1.22)	HR 1.06 (0.61, 1.85)[b]
OS	delayed exponential (from month 5)[c]	HR 1.12[d] (0.63, 2.00) (from month 5)	HR 3.11 (1.52, 6.35)[e] (from month 5)
ToT	Weibull[f]	TE 1.01 (0.80, 1.29)	HR 1.00 by assumption due to lack of data[g]
2 prior therapies population			
		IXA+LEN+DEX vs. LEN+DEX (95% CI)	
PFS	generalised gamma	TE 0.62 (0.44, 0.87)	
OS	Weibull	TE 0.67 (0.43, 1.05)[h]	
ToT	exponential	HR 1.36 (0.97, 1.90)	

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To extrapolate PFS, OS and ToT for the duration of the model, the company explored the applicability of 6 parametric distributions (exponential, log-normal, log-logistic, Gompertz, generalised gamma and Weibull). The fit of each parametric model was assessed using **covariate-adjusted** data. That is, the company applied covariate adjustment to account for potential imbalances between the 2 treatment arms, because they found that there were several patient risk factors that appeared to be associated with differences in clinical endpoints (including ECOG performance score 2, ISS stage III, primary refractory status, age >65 years, and renal dysfunction – see table 64 of the company submission). A scenario analysis, provided in response to clarification question 11d, explored the impact of using unadjusted estimates.

The distributions selected for the company base case are summarised in the table above. Further detail is provided in section 5.3.3 of the company submission and in response to clarification question B3. Appendix 11 to the company submission presents the company's exploration of the fit of each parametric model to the covariate-adjusted data. Section 5.2.6 of the ERG report provides additional detail on the company's methods, that was not provided in the company submission.

The company concluded that the assumption of proportional hazards was supported for PFS, OS and ToT in the 2+ prior therapies population and for PFS in the 1 prior therapy population. For these outcomes, the company fitted a single parametric model to the LEN+DEX data and estimated relative efficacy for IXA+LEN+DEX compared with LEN+DEX. Proportional hazards did not hold for OS or ToT in the 1 prior therapy population. The company explored the impact on the model results of selecting different parametric curves in section 5.3.5 and 5.8 of its submission.

Note that the hazard ratio for OS is based on the company NMA, in which the ERG identified an

error. The ERG also had concerns about the validity of the PFS network.

Table footnotes

The potential for the PFS curve to cross the OS curve was curtailed by applying the minimum of PFS and OS if PFS was greater than OS at a given time point. The same approach was used to avoid the ToT curve crossing the OS curve. This was apparent in only early model cycles and was adjusted to attain clinical validity.

[a] The company recognised that the Weibull model had slightly better AIC/BIC scores than the generalised gamma model for PFS in the 1 prior therapy population, but it selected the generalised gamma to maintain consistency between the curve fits across the 2 populations. The company also considered that the visual fit of the modelled generalised gamma IXA+LEN+DEX curves with the observed IXA+LEN+DEX PFS data indicates that this method provides a good fit to the data. Using the Weibull had a negligible impact on the ICER.

[b] The hazard ratio for PFS was obtained from a network considering all doses of bortezomib observed in the literature; due to a lack of data no network could be formed considering the dose specified in the bortezomib marketing authorisation in the UK.

[c] Because the proportional hazards assumption was violated for OS in the 1 prior therapy population, the company fit a delayed exponential model to the data which satisfied the proportional hazards assumption. Kaplan-Meier hazards observed from the TMM1 clinical trial were applied for the first 5 months. Note that, although the accelerated failure time (AFT) assumption was satisfied, the company considered that the AFT models (the generalised gamma, Weibull, log-logistic and lognormal functions) resulted in clinically implausible estimates, for example the generalised gamma curve estimates 13.62% and 17.97% of patients are alive after a 25-year time horizon (52% of patients are over the age of 65 at baseline). The company's base-case method predicted that on the IXA+LEN+DEX arm 25.83% of patients would be alive after 10 years, 13.02% at 15 years and 6.57% at 20-years. The company considered that these estimates are clinically valid because although most patients with relapsed/refractory multiple myeloma have a poor prognosis, it is a heterogeneous disease and therefore a small proportion of patients can experience relatively long survival. The company also noted that people receiving second line therapy have a better prognosis than those patients at third line or later.

[d] The company submission reported a hazard ratio of 0.89 but confirmed at clarification that this was in favour of LEN+DEX. The inverted hazard ratio for IXA+LEN+DEX compared with LEN+DEX is 1.12.

[e] The hazard ratio for OS (and hazard ratios for overall response rate) was obtained from a network considering only those studies which used the dose specified in the marketing authorisation for bortezomib in the UK. A scenario analysis considers the hazard ratio from a network considering all studies and all doses observed in the literature [HR: 3.05, 95% CI: 1.78 – 5.22].

[f] The proportional hazards assumption was violated for time on treatment in the 1 prior therapy population.

[g] The network meta-analysis did not provide ToT for BORT+DEX, so the company assumed that the ToT for BORT+DEX was equivalent to the LEN+DEX arm (which

was based on TMM1 trial data). However, the summary of product characteristics for BORT+DEX state that the maximum number of treatment cycles is eight. Therefore, the company model assumed that after eight 21-day treatment cycles patients in the BORT+DEX arm no longer receive treatment with BORT+DEX.

[h] The 95% confidence intervals for the treatment effects and hazard ratios span over 1 for overall survival in the 2 prior therapies population, indicating a non-significant difference between IXA+LEN+DEX and LEN-DEX**.** The company suggest that the extrapolation includes a lot of uncertainty because median survival has not yet been reached in the trial data informing the model.

The model overestimates time on treatment (ToT)

The company considered that the model overestimated ToT compared with clinical practice in the UK

- The model estimated ToT by extrapolating duration of treatment data from the TMM1 trial. Clinical experts and real-world evidence suggest that the duration of treatment with LEN+DEX in the trial was longer than in clinical practice, implying that the duration of treatment with IXA+LEN+DEX is also above that which would be expected in clinical practice.
- In clinical practice, treatment with LEN+DEX is stopped at or before disease progression.

The company did several scenario analyses to explore the uncertainty associated with time on treatment:

- ToT capped by PFS (treatment cannot continue after progression): no impact on ICER
- ToT with IXA+LEN+DEX reduced by 25%: ICER reduced by 25% in the 1 prior therapy population and 37% in the 2+ prior therapies population)
- ToT was based on observed data in TMM1 study: ICER reduced by 37% in the 1 prior therapy population and 50% in the 2+ prior therapies population.

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To note:

- In in intention-to-treat population in TMM1, 42.18% and 34.75% of patients remain on treatment with IXA+LEN+DEX and LEN+DEX after 24 treatment cycles. Real-world evidence from the UK, cited by the company, showed that after 24 treatment cycles only 17.59% of patients remained on LEN+DEX treatment.
- The ERG report highlighted that the company's approach to modelling treatment costs using the ToT curves actually underestimates treatment costs because ToT curves were consistently below PFS curves (see slide 48).

Costs

- The company included the following costs in the model
  - drug acquisition costs for ixazomib, comparator treatments, concomitant medication and subsequent treatments after ixazomib
  - administration costs for comparators and subsequent treatments, for intravenous treatments only; no administration costs were assumed for oral and subcutaneous treatments
  - NHS resource use associated with routine medical management, hospitalisations and the treatment of adverse events
  - monitoring costs
  - one-off end-of-life cost.
- The company included patient access schemes for LEN+DEX (in the comparator arm for 3rd line treatment, and the intervention arm for 2nd line and 3rd line treatment) and BORT+DEX (the 2nd line comparator)
  - LEN+DEX: drug cost for people who remain on treatment for >26 cycles met by the company
  - BORT+DEX: rebate scheme for people who do not obtain at least a partial response after a max. of 4 cycles
- Dosing of BORT based on average body surface area in TMM1 (1.87m^2)

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Administration costs

- Administration cost was calculated per treatment cycle and then multiplied by the average number of treatment cycles sourced from available literature.
- The company did not include administration costs for bortezomib because, although the marketing authorisation for bortezomib includes intravenous and subcutaneous administration, clinical experts advised NICE during the appraisals of carfilzomib and panobinostat in multiple myeloma it is delivered subcutaneously in clinical practice in England.
- The company included drug costs dosing intensities to capture the impact on costs of potential dose reductions and missed doses. The dose intensity of IXA+LEN+DEX was reported to be 93.10% in the TMM1 clinical trial and for LEN+DEX was reported to be 94.90%. Dose intensity was not reported in the BORT+DEX trial, therefore this was assumed to be 100%.

Concomitant medication

- The company included concomitant medications based on the drugs used in TMM1.
- Due to lack of data, the weekly cost of concomitant medications was assumed equal for all comparators.
- Due to lack of data on concomitant medications associated with post-progression therapies, the cost of concomitant medications was applied to patients in the post-progression health state.

Resource-use costs

- Resource costs were applied to all patients on treatment. Patients who moved onto active subsequent therapy continued to receive routine care, and thus incurred the routine care costs. Patients who do not move onto active subsequent therapies were assumed to receive an anti-cancer treatment plan.
- The company assumed the same resource costs for all chemotherapy treatments with the exception of panobinostat, which is a more toxic treatment, and therefore patients receive a transthoracic echocardiogram each treatment cycle.

Hospitalisations

- Captured non-routine health care use in the pre- and post-progression health states.
- Obtained from the patient-level data from the TMM1 using the ITT population (because the company did not find any difference between the trial subgroups in the number of hospitalisations) but considered separately by treatment arm and progression status.

Adverse events

- The proportion of patients whose adverse events were treated, and the proportion treated in a primary care versus secondary care setting, was obtained from the company submission to NICE for TA171. Where no data were available, assumptions were reviewed by a UK clinical expert

End of life

- The cost of end-of-life care was sourced from the PSSRU (2015): £10,670 per decedent.
- The company assumed that 20% of patients receive end of life care (consistent with previous submissions in RRMM - TA338 and TA171), resulting in a one-off cost of £2,134 per person.

Lenalidomide patient access scheme (PAS)

- The lenalidomide PAS is operational when lenalidomide, in combination with dexamethasone, is used to treat multiple myeloma in people who have received 2 or more prior therapies (that is, third line or later). This is linked of the positive recommendations in TA171.
- The lenalidomide PAS can be considered when costing the combination of lenalidomide and dexamethasone with ixazomib, but only for the third line use of ixazomib.
- The company included the lenalidomide PAS in the ixazomib arm at both second line and third line; its inclusion at second line (people with 1 prior therapy) was not appropriate. The ERG removed the lenalidomide PAS from its exploratory analyses in people with 1 prior therapy.

See table 91 of the company submission for the cost breakdown for each health state.

Utility values are derived from patient level EQ-5D data from TMM1 trial

- Health-related quality of life was captured in the model using a regression equation fit to the patient level data from the TMM1 clinical trial.
- The explanatory variables included in the regression equation:
  - Best overall response, divided into 4 categories:
    - VGPR+ (which included stringent complete response, complete response and very good partial response)
    - partial response (PR)
    - stable disease (SD)
    - progressed disease (PD)
  - Hospitalisation
  - Grade 3 or 4 treatment-related adverse events (TRAEs)
  - New primary malignancies
  - Whether a patient was ≤3 months prior to death.
- The company also applied a utility decrement of 0.025 to patients receiving intravenous or subcutaneous treatment (bortezomib). The company consider that this decrement is likely to be an underestimate of the impact in this population because of the frailty of patients with multiple myeloma.

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To note:

- Response status was based on patients best overall response (BOR) during the study induction period and not necessarily the response observed at time of EQ-5D assessment
- The company obtained the utility decrement for intravenous and subcutaneous treatments (0.025) from 2 previous NICE appraisals in small-cell lung cancer; no information specific to multiple is available, but this decrement was also used in the appraisal of pomalidomide in relapsed/refractory multiple myeloma (TA427).

Utility values by health state (95% CI)				
	Pre-progression health state			Post-progression health state
	VGPR+	Partial response	Stable disease	Progressed disease
VGPR+	0.712 (0.690, 0.732)	-	-	-
Partial response	-	0.674 (0.609, 0.729)	-	-
Stable disease	-	-	0.653 (0.579, 0.714)	-
Progressed disease	-	-	-	0.654 (0.587, 0.711)
Adverse event	0.696 (0.648, 0.737)	0.658 (0.567, 0.733)	0.636 (0.537, 0.718)	-
New primary malignancy	0.412 (0.299, 0.507)	0.375 (0.218, 0.504)	0.353 (0.188, 0.488)	0.355 (0.196, 0.486)
Hospitalisation	0.641 (0.425, 0.776)	0.604 (0.344, 0.773)	0.582 (0.315, 0.757)	0.584 (0.322, 0.755)
≤3 months until end of life	0.580 (0.469, 0.667)	0.542 (0.388, 0.664)	0.521 (0.359, 0.648)	0.522 (0.366, 0.646)
VGPR, very good partial response				

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Source: table 79 company submission

To note:

- VGPR+ includes stringent complete response (sCR), complete response and very good partial response
- The company explains that the utility value for progressed disease is better than for stable disease because of the benefits of subsequent lines of treatment.

Company base case model results

(including the ixazomib patient access scheme)

Cost-effectiveness results for people who have had 1 prior therapy

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER/QALY
BORT+DEX	£40,612	1.74			
IXA+LEN+DEX	£201,274	3.93	£160,662	2.19	£73,333

When the ERG corrected the error in NMA and removed the LEN+DEX PAS from the intervention arm: **BORT+DEX dominated IXA+LEN+DEX**, with incremental costs for IXA+LEN+DEX of £169,000 and incremental QALYs of −0.382.

Cost-effectiveness results for people who have had 2 prior therapies

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER/QALY
LEN+DEX	£91,428	2.204			
IXA+LEN+DEX	£222,532	3.174	£131,104	0.9694	£135,237

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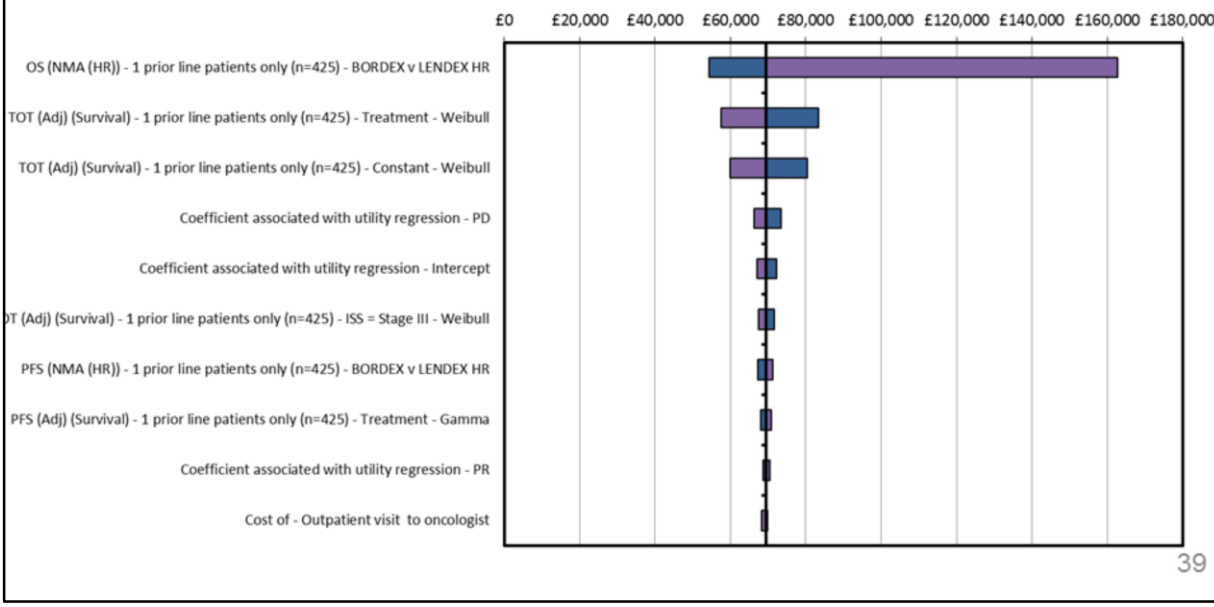
Sources: company patient access scheme submission page 15 (2 prior therapies) and response to clarification question B3 (1 prior therapy). The ERG-corrected ICER for the 1 prior therapy group is reported in the ERG revised addendum, table 8.

Notes about the cost-effectiveness results in the population who have had 1 prior therapy:

- The results for 1 prior therapy population were corrected in response to clarification question B3 from (£69,565 to £73,333) and the corrected ICER is presented above.
- The company's base case cost-effectiveness analysis uses the results of the company's NMA, which contained an error in the OS network for people with 1 prior therapy (see the ERG critique on slides 26-27). The company's base case analysis in people with 1 prior therapy also erroneously incorporated the patient access scheme for LEN+DEX in the intervention arm. The ERG provided an addendum which used the company NMA but corrected the error in the OS network, and removed the LEN+DEX PAS. The results are presented above.
- The company made other corrections to the model in response to clarification questions B3 and B13, but these did not affect the base case results in the submission. Any ICERs presented by the company in their response to clarification incorporated corrections based on questions B3, B13 and B19.

Deterministic sensitivity analyses showed that survival is the main driver of the company base case model (1)

Tornado diagram of the ten most influential parameters from the company one-way sensitivity analyses in people who have had 1 prior therapy



Source: figure 2 company PAS submission

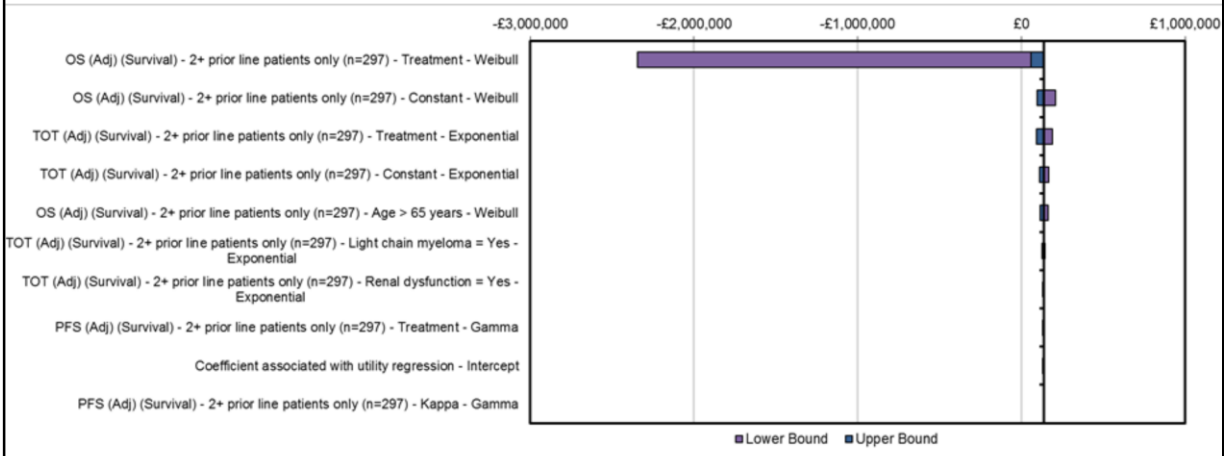
The parameters with the greatest impact on model outcomes were:

- the hazard ratio applied to the LEN+DEX data to obtain the overall survival for BORT+DEX
- the coefficients for the adjusted time on treatment (ToT) parametric curve.

The hazard ratio for overall survival directly impacts the incremental life years associated with IXA+LEN+DEX and BORT+DEX, and therefore is a driver of the ICER. Modelled ToT has a significant impact on costs within the model (a larger ToT results in larger costs) and so this is also a driver of the results.

Deterministic sensitivity analyses showed that survival is the main driver of the company base case model (2)

Tornado diagram of the ten most influential parameters from the company one-way sensitivity analyses in people who have had 2 prior therapies



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Source: figure 2 company PAS submission

Key scenario analyses

Base case assumption	Scenario analysis
First interim analysis from TMM1 (used for PFS, OS and ToT)	Second interim analysis from TMM1 used for PFS, OS and ToT)
ToT independent of PFS i.e. patients may be treated beyond progression	Cap ToT by PFS i.e. ToT cannot exceed PFS
ToT for IXA+LEN+DEX vs LEN+DEX estimated via extrapolation of duration of treatment data in the TMM1	ToT based on duration of treatment observed in the TMM1 trial
	ToT with IXA+LEN+DEX reduced by 25%
Covariate-adjusted clinical endpoints (to account for potential imbalances between the treatment arms in TMM1)	Non-covariate adjusted clinical endpoints
Utility modelled using the regression equation fit to the data from TMM1	Health state specific utilities obtained from the TA171 and TA338 NICE submissions
Efficacy data for IXA+LEN+DEX were obtained directly from TMM1	Efficacy data for IXA+LEN+DEX sourced from NMA base case
PAS price of ixazomib (confidential)	Price of ixazomib set to £0

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To note:

- The company also explored the impact of fitting alternative parametric distributions to extrapolate OS, PFS and ToT. The results were sensitive to the distribution chosen for OS and ToT (with the ICER increasing in most scenarios), but less sensitive to the method of extrapolating PFS.
- In the final scenario analysis the company set the price of ixazomib to £0 to explore the paradox that the cost-effectiveness of the regimen is adversely affected by the incremental costs of lenalidomide in the additional PFS time patients experience with ixazomib, such that it is difficult to demonstrate cost-effectiveness of ixazomib even at zero price.

Results of company scenarios
(including the ixazomib PAS)

	ICER for 1 prior therapy (£/QALY)	ICER 2 prior therapies (£/QALY)
Base case	£73,333	£135,237
2nd interim analysis from TMM1[a]	£84,370	£119,803
Cap ToT by PFS	No change	£136,511
ToT based on observed TMM1 data	£43,578	£67,769
ToT with IXA+LEN+DEX reduced by 25%	£51,930	£85,104
Non-covariate adjusted clinical endpoints	£68,879	£146,332
Health state specific utilities from: TA171 TA338	 £71,168 £75,091	 £124,118 £131,038
Efficacy data for IXA+LEN+DEX sourced from NMA base case	£56,034	£147,423
Price of ixazomib set to £0	£29,800	£14,109
[a] This scenario reduced the incremental QALYs from 2.336 to 1.842 in the 1 prior therapy population, and increased the incremental QALYS from 0.964 to 0.992 in the 2 prior therapies population		

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Source: company patient access scheme submission page 17-23 (results of scenario analyses), response to clarification question B3 (base case), and response to clarification question A5 (2nd interim analysis from TMM1; not reported in PAS submission)

Note: the company corrected its base case ICER in the 1 prior therapy population in response to clarification question B3 (from £69,565 to £73,333) and the corrected base case ICER is presented above. The company did not correct the results of the scenario analyses. These results are based on the company NMA, which contained an error in the OS network for the 1 prior therapy population (identified by the ERG, see slides 26-27); the results above are not corrected for the error in the NMA.

Additional scenario analyses: The company performed additional scenario analyses in the 2 prior therapies population (that were not relevant to the 1 prior therapy population) relating to the cost of LEN+DEX. In the base case, LEN+DEX was costed in the IXA+LEN+DEX regimen as per standard methods using ToT and UK cost references.

- Exploratory scenario A: only additional LEN+DEX in the IXA+LEN+DEX regimen, over and above what is received in the LEN+DEX regimen, was costed. This scenario captures the additional cost of LEN+DEX required due to the increase in ToT associated with IXA+LEN+DEX. This substantially reduced the ICER for IXA+LEN+DEX to £63,675/QALY gained compared with LEN+DEX.
- Exploratory scenario B: additional LEN+DEX over and above what is received in the LEN+DEX regimen was not costed. This scenario only captures the cost of the LEN+DEX that would be received in current practice anyway. This slightly reduced the ICER for IXA+LEN+DEX to £125,672/QALY gained compared with LEN+DEX.

ERG critique of the company's cost-effectiveness evidence

Survival gains

Life-year and QALY gains by health state: 1 prior therapy

	Undiscounted life years			QALYs		
	PFS	PPS	OS	PFS	PPS	Total
BORT+DEX	1.916	0.716	2.632	1.219	0.410	1.596
IXA+LEN+DEX	2.168	5.007	7.175	1.415	2.547	3.932
Δ	0.253	**4.291**	4.543	0.196	**2.138**	2.336

Life-year and QALY gains by health state: 2 prior therapies

	Undiscounted life years			QALYs		
	PFS	PPS	OS	PFS	PPS	Total
LEN+DEX	2.283	1.315	3.598	1.440	0.798	2.204
IXA+LEN+DEX	3.535	1.776	5.311	2.174	1.033	3.174
Δ	**1.252**	0.461	1.713	**0.733**	0.235	0.969

OS, overall survival; PFS, progression-free survival; PPS, post-progression survival

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The company base case model estimates that IXA+LEN+DEX results in an increase in progression-free survival of 0.25 years, and an increase in post-progression survival of 4.29 years, compared with BORT+DEX. The balance of the survival gains is reflected in the balance of QALY gains (that is, most of the QALY gain is achieved in the post-progression health state). The ERG noted that the increase in post-progression survival with IXA+LEN+DEX relative to BORT+DEX is much larger than the progression-free survival benefit, resulting in an overall survival gain of 4.54 years. The company did not comment on this. The ERG believes that there is no plausibility for the considerable increase in post-progression survival given that most people will stop treatment at the time of progression and there is nothing in the mechanism of action of proteasome inhibitors like ixazomib that could explain this observation of continued benefit after progression (that is, altering the course of disease subsequent to progression).

The ERG considered that the results of the comparison with LEN+DEX were more plausible, where the benefits of IXA+LEN+DEX were driven by survival gains in the progression-free health state.

The ERG believe that the company model substantially underestimates the survival benefit with BORT+DEX, which is explained by the error in the company NMA (see slide 27).

For more detail, see pages 185–7 of the ERG report.

Costs and benefits of BORT

The company overestimated the cost of BORT+DEX by assuming:

- a maximum of nine 3 week cycles (rather than 8 cycles as per the SmPC, and the 5 week cycles used in practice)
- patients complete every treatment cycle that they start (rather than applying the PFS or ToT curve, because some patients stop mid-cycle)
- treatment is discontinued at progression and the patient access scheme (PAS) for BORT was applied only if disease progressed within 4 cycles (whereas TA129 includes a stopping rule and PAS based on partial response at 4 cycles); this resulted in no costs being refunded as per the PAS, because no patients progressed before the 4th cycle
- people with complete response continue to the maximum number of cycles (in practice people receive only 2 cycles after complete response, as per the SmPC)
- a HR of 1.00 for ToT compared with LEN+DEX due to a lack of data (rather than using the HR for PFS compared with LEN+DEX [1.06])

The company underestimated the benefits of BORT+DEX:

- The company's NMA underestimated the OS associated with BORT
- The company used a trial of BORT monotherapy to estimate the distribution of best overall response (BoR) for BORT+DEX (that is, the proportion of people in the VGPR+ health state, PR health state and SD health state) and erroneously used BoR rates for DEX instead of BORT

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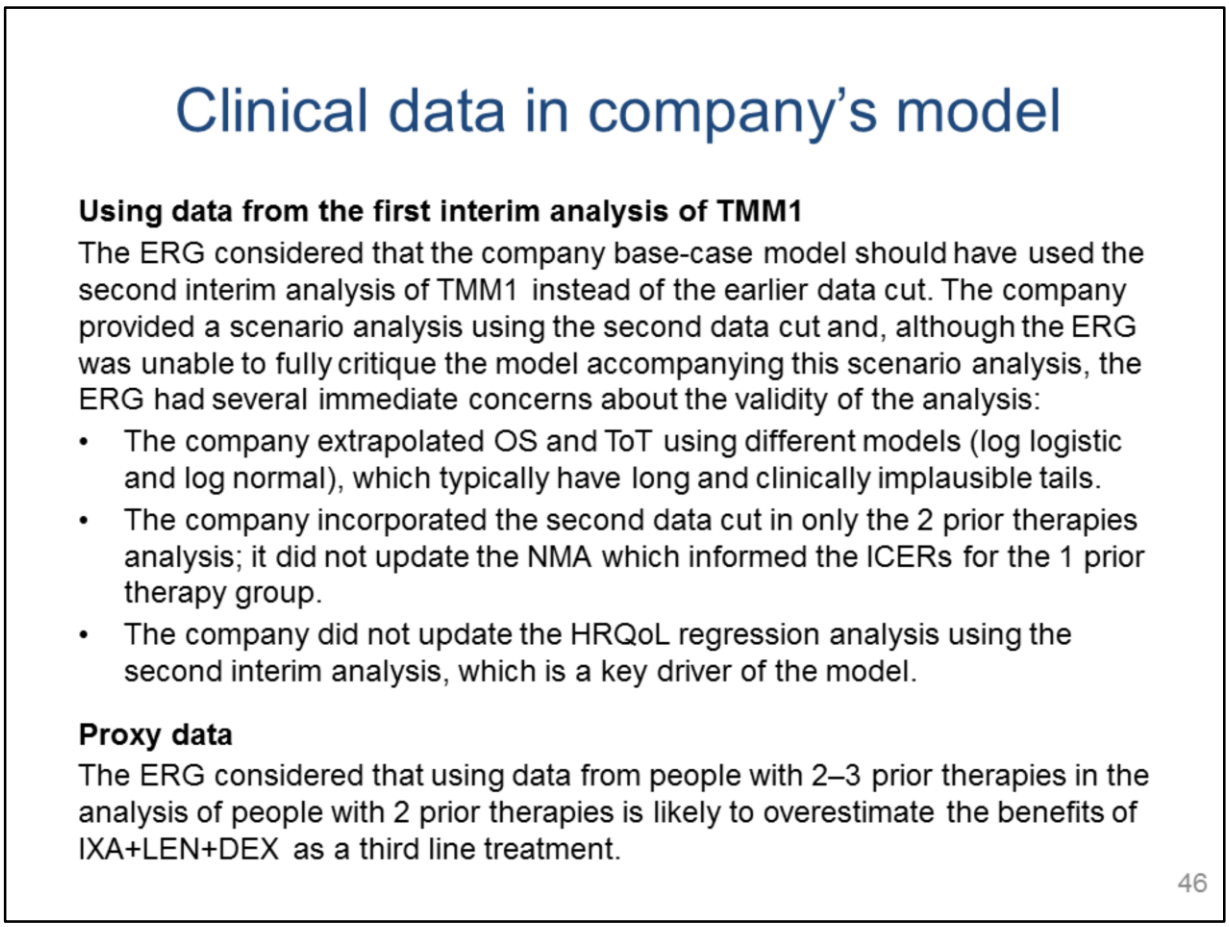
The ERG also identified a cost associated with BORT+DEX which the company had omitted from its cost-effectiveness analysis: the resource cost of outpatient visits to have subcutaneous injections administered.



Using data from the first interim analysis of TMM1

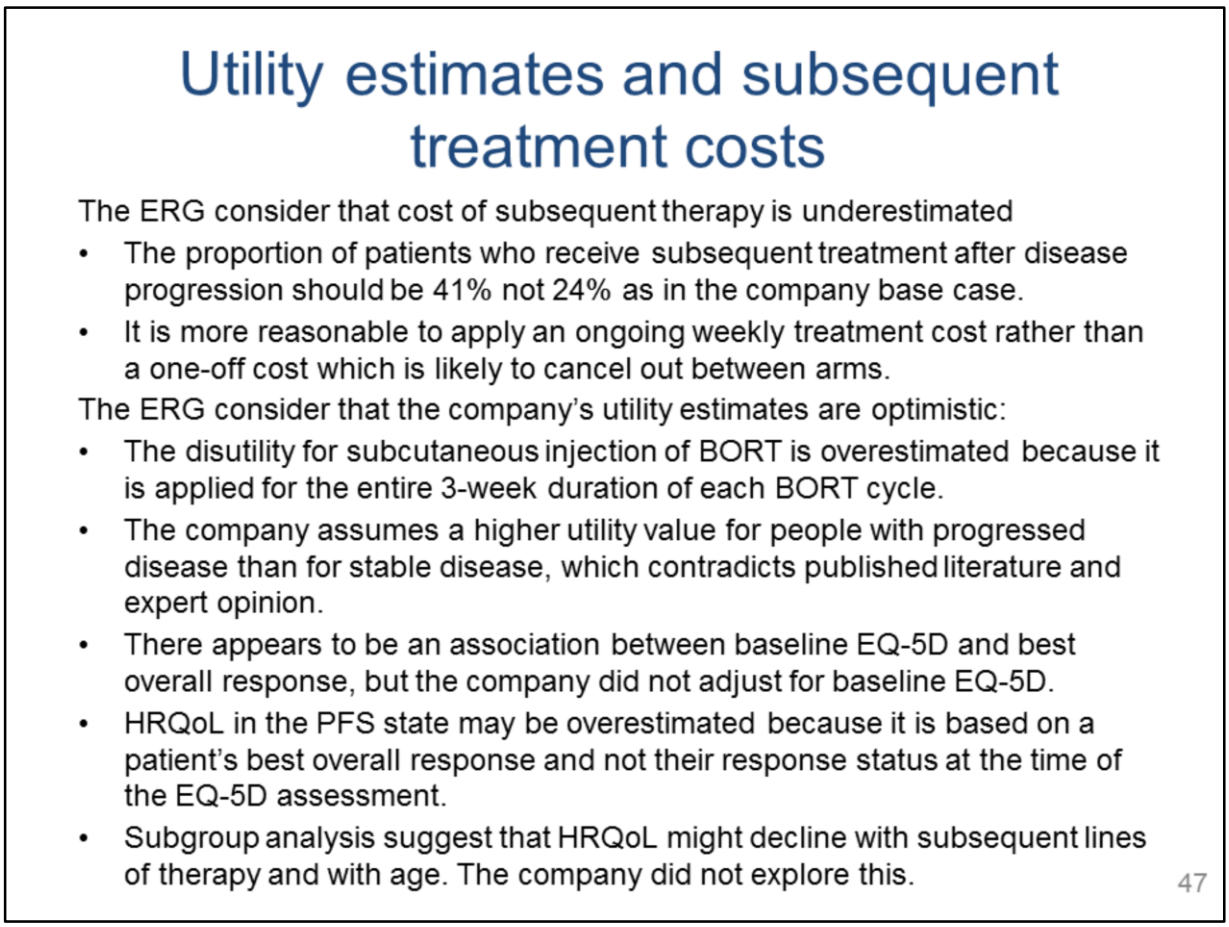
The ERG consider that a model based on the second interim analysis from TMM1 (together with a revised NMA based on the second interim analysis) would require an entirely new company submission and critique. For more detail of the ERG's concerns about the company's scenario analysis using the second interim data cut from TMM1, see pages 205-6 of the ERG report.

The ERG also noted that, in light of the immature survival data, there is a strong argument for exploring a reduction of the treatment effects after the end of the trial period, in line with the NICE methods guide. This has not been done and is not something that is simple to implement within the company model structure.

Proxy data: 2 prior therapies subgroup

- The ERG's conclusion that using data from people with 2–3 prior therapies as a proxy for third line positioning is likely to overestimate the benefits of IXA+LEN+DEX is based on analysis of the subgroup results from TMM1 - the benefit of IXA+LEN+DEX in the 2–3 prior therapies subgroup appears to be driven by favourable results in the subgroup of patients who have had 3 prior therapies (see slide 25).
- To provide further support for this conclusion, the ERG compared the Kaplan–Meier curves for the 2 prior therapies subgroup with the curves for the 2–3 prior therapies subgroup, which suggested that the OS and PFS gains in the 2 prior subgroup are less than for the 2–3 prior therapies subgroup (see pages 197–202 of the ERG report).
- The ERG explored the effect on the ICER of using data specific to people with only 2 prior therapies in a scenario analysis. This was based on post hoc analysis of the 2 prior therapies

subgroup of the TMM1 trial (the pre-specified subgroups in the trial were less granular: people with 1 prior therapy and people with 2–3 prior therapies).



The ERG consider that cost of subsequent therapy is underestimated

- The company estimated that 24% of patients receive subsequent treatment after disease progression, based on dividing the number of people who progressed and received further therapy (n=176) by the baseline number of patients in the trial (n=722). The ERG note that the denominator should have been number of patients who had progressed.
- The ERG also noted that the company might have underestimated the cost of concomitant medication because it did not include administration costs for subcutaneous (enoxaparin or nadroparin) or intravenous (zoledronic acid or pamidronic acid) treatments. The ERG noted that the cost of concomitant medication is small relative to the myeloma treatments, and has only a small impact on the ICERs.

The ERG were concerned about the company's utility estimates for several reasons:

- Applying the disutility for sc injection for the entire 3-week duration of each BORT cycle means that patients lose 4% of their quality of life due to sc injections over their entire treatment period. It appears to the ERG that the company attributes the disutility of sc injections to the hospital visits rather than the sc injection itself. But if this is the case, disutilities should be applied to hospital visits for other treatments as well.
- The company assumes a higher utility value for people with progressed disease than for stable disease. In TA171 and TA338, utilities associated with progressed disease (0.610–0.640) were lower than the utilities associated with progression-free survival or stable disease (0.650–0.810).
- HRQoL in the PFS state may be overestimated because it is based on a patient's best overall

response and not their response status at the time of the EQ-5D assessment. The analysis uses duration of response from trial, which measures time from the first documented partial response or better until progression; this will overestimate the duration of best overall response because it will take time to attain best overall response and patients wont remain in best overall response for duration of PFS. The ERG consider that the effect of this is unclear, but suggest that utility values in the PFS state might be overestimated because data are extrapolated well beyond the trial period.

Survival extrapolations and use of ToT

The ERG disagreed with the distributions used in the company's base case:

- For OS in the 1 prior therapy group: the ERG consider that Weibull is more appropriate than the delayed exponential function[a]
- For PFS in the 1 prior therapy group: the ERG note that Weibull has the lowest AIC and BIC, and the company did not justify using a generalised gamma distribution.[b]
- For ToT in the 2 prior therapies group: the ERG would expect the same distribution to be appropriate for ToT and PFS, but noted that the company selected exponential for ToT and generalised gamma for PFS.

The ERG consider that the PFS curve may have been more appropriate for modelling treatment costs than the ToT curve

- The treatment costs in PFS may have been underestimated because ToT curves were consistently below PFS curves[c].
- The ERG considered that the level of treatment discontinuation before disease progression[d] was high, even when considering that some people stop treatment due to adverse events and may have stable disease that does not require immediate intervention.

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[a] The Weibull curve had the lowest Bayesian information criterion (BIC) value and resulted in a more clinically plausible prediction of the number of people alive at the end of the time horizon. With the Weibull distribution, close to zero patients were alive, whereas the delayed exponential predicted 3% of patients in the IXA+LEN+DEX arm and 5% in the LEN+DEX arm would still be alive at the end of the time horizon.

[b] The choice of distribution for PFS had a negligible impact the company's ICERs because the costs in the model were determined by the ToT curves. The ERG suggest that PFS curves may be more appropriate for modelling treatment costs than the ToT curves (as described on this slide), and therefore the model will become more sensitive to method for extrapolating PFS.

[c] The reason that ToT curves were consistently below PFS curves was because patients in TMM1 who were lost to follow-up or withdrew consent were handled differently in the company's analyses of PFS and ToT. Patients lost to follow-up/withdrawing from the study were censored for the PFS analysis but counted as events for the ToT analysis. Any patients lost to follow up without having disease progression retain the benefits of treatment but without incurring the costs. This reduces the ToT curves below PFS curves and underestimate the treatment costs for PFS.

[d] In the subgroup with 1 prior therapy: in the IXA+LEN+DEX arm, the area under the ToT curve is 82% of the area under the PFS curve. In the subgroup with 2 prior therapies: in the IXA+LEN+DEX arm the area under the ToT curve is only 65% of the area under the PFS curve, while in the LEN+DEX arm it is 75%. The ERG considered that this rate of stopping treatment before progression was high, and considered it unreasonable that the ToT to PFS ratio would be much lower in the IXA+LEN+DEX arm than in the LEN+DEX arm (see section 5.3.4.8 ERG report for more details).

Summary of ERG critique (1)

ERG comment	Addressed in exploratory analyses?
Inappropriate extrapolation of OS, ToT and PFS	Yes: SA01-SA03
PFS better than ToT for modelling costs	Yes: SA08
Overestimated BORT+DEX cost because:	
Maximum of 9 cycles (rather than 8 cycles)	Yes: ERG base case
Patients complete every treatment cycle that they start	No
Treatment is discontinued at progression (TA129 stopping rule not included) and no PAS refunds given	No
People with complete response receive max # of cycles	No
Same ToT as LEN+DEX	Yes: ERG base case
Underestimated the benefits of BORT+DEX because:	
NMA underestimated OS (because of an error in hazard ratios plus other methodological issues)	Yes: scenario (1 prior therapy)
Error in estimation of best overall response	Yes: ERG base case

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SA## refers to sensitivity analyses conducted by the ERG, which were applied to the ERG's alternative base case and the ERG's 2 scenario analyses.

Summary of ERG critique (2)

ERG comment	Addressed in exploratory analyses?
Lenalidomide PAS not applicable for 1 prior therapy group	Yes: ERG base case
Clinical data from people with 2–3 prior therapies used as proxy in 2 prior therapies subgroup	Yes: scenario (2 prior therapies)
Cost of subsequent therapy is underestimated	Yes: SA09
Concerns with utilities	
disutility for sc injection overestimated	Yes: base case
progressed disease utility > stable disease utility	Yes: SA06
company did not adjust for baseline EQ-5D	No
HRQoL in the PFS state may be overestimated	Partially: SA06
HRQoL might decline with subsequent lines of therapy	No
Should have used the second interim analysis of TMM1	No

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SA## refers to sensitivity analyses conducted by the ERG, which were applied to the ERG's alternative base case and the ERG's 2 scenario analyses.

ERG exploratory analyses

All results include the ixazomib patient access scheme

ERG alternative base case: summary of changes

1. Limit BORT+DEX to a maximum of 8 cycles (the company had modelled a maximum of 9).
2. Apply the BORT+DEX PFS HR to the LEN+DEX ToT curve (the company had assumed ToT for BORT+DEX was the same as ToT for LEN+DEX).
3. Update the distribution of best overall response for BORT+DEX (that is, the proportion of people in the VGPR+ health state, PR health state and SD health state) using the ENDEAVOR trial of BORT+DEX.
   - The company used a trial of BORT monotherapy, and erroneously used BoR rates for DEX instead of BORT.
4. Add a nurse led outpatient cost to each BORT+DEX administration subsequent to the first administration of each cycle.
5. Remove the company 0.025 disutility for sc BORT+DEX administrations.
6. Apply administration costs for the intravenous concomitant medications.
7. 100% dosing intensity to align the assumptions between treatments.
8. Apply the 5 months' delay in the exponential OS extrapolation equally in both arms in the 1 prior therapy subgroup (an error identified and corrected by the company in response to clarification question B3).
9. Remove lenalidomide PAS from intervention arm in 1 prior therapy group.

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Note that the results in the ERG report and appendix do not include the effect of removing the lenalidomide patient access scheme (PAS) from the intervention arm in the 1 prior therapy group. Please refer to the ERG addendum for the results after the lenalidomide PAS was removed.

Results of ERG alternative base case
(including the ixazomib PAS)

Cost-effectiveness results for people who have had 1 prior therapy *('ERG analysis 1')*

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER/QALY
BORT+DEX	£44,707	1.779			
IXA+LEN+DEX	£238,733	3.932	£194,026	2.153	£90,117
Note that these results are based on the results from the company NMA, and therefore include the error in the OS network. The ERG corrected this error as part of its exploratory NMA. The ICER based on the ERG NMA is presented on the next slide.					

Cost-effectiveness results for people who have had 2 prior therapies *('ERG analysis 2')*

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER/QALY
LEN+DEX	£97,655	2.204			
IXA+LEN+DEX	£231,377	3.174	£133,722	0.969	£138,000

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Sources:

- ERG addendum due to lenalidomide PAS: table 1 (1 prior therapy group)
- ERG appendix: table 7 (2 prior therapies subgroup)

ERG scenario analyses
(including the ixazomib PAS)

For people who have had 1 prior therapy *('ERG analysis 4')*

The ERG applied the results of its exploratory NMA to its alternative base case.

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER/QALY
BORT+DEX	£69,872	4.356			
IXA+LEN+DEX	£238,733	3.932	£168,861	−0.424	Dominated

For people who have had 2 prior therapies *('ERG analysis 5')*

The ERG applied PFS, OS and ToT data from the post-hoc analysis of people who had received 2 prior therapies only in TMM1 (the company's base case used data from the 2–3 prior therapies subgroup as a proxy for third line positioning). These results are based on the most optimistic extrapolation of PFS, OS and ToT, and include all changes in the ERG's alternative base case.

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER/QALY
LEN+DEX	£115,334	3.592			
IXA+LEN+DEX	£232,973	4.222	£117,639	0.631	£186,000

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Sources:

- ERG addendum due to lenalidomide PAS: table 3 (1 prior therapy group)
- ERG appendix: table 10 (2 prior therapies subgroup)

The ERG did an additional scenario to compare IXA+LEN+DEX with LEN+DEX in the 1 prior therapy population. In this analysis, including the PAS for ixazomib, LEN+DEX dominated IXA+LEN+DEX (that is, LEN+DEX provided more QALYs at a lower cost than IXA+LEN+DEX). LEN+DEX was listed as a comparator in the NICE scope for people with 1 prior therapy, subject to the ongoing NICE appraisal of lenalidomide (part review of TA171). LEN+DEX is not currently available as a second line treatment option for relapsed/refractory multiple myeloma in England.

ERG sensitivity analyses

The ERG applied the following changes to its alternative base and scenario analyses

- SA01: Varying the OS curves functional forms
- SA02: Varying the PFS curves functional forms
- SA03: Varying the ToT curves functional forms
- SA06: Applying the utility values from TA171 and TA338
- SA07: Assuming a five week cycle for BORT+DEX
- SA08: Costing treatments using PFS curve rather than ToT curve
- SA09: Increasing the proportion of patients receiving subsequent treatment after progression from 24% to 41%, applying an incident cost of £1,081 (as in the company base case) and an ongoing weekly cost of £1,561 (instead of a one off cost). *Note that this does not include the cost of pomalidomide, which is now NICE-recommended and could affect the ICER.*

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Results of ERG sensitivity analyses: people with 1 prior therapy *(including the ixazomib PAS)*

	ICER for IXA+LEN+DEX vs. BORT+DEX (£/QALY)	
	ERG base case	**ERG scenario: ERG NMA**
ERG base case/scenario	£90,117	IXA+LEN+DEX is dominated by BORT+DEX
SA01: OS curves[a]	£69,846–£195,000	
SA02: PFS curves[a]	£89,451–£90,509	
SA03: ToT curves[a]	£81,164–£148,000	
SA06a: TA171 utilities	£91,103	IXA+LEN+DEX is dominated by BORT+DEX
SA06b: TA338 utilities	£96,246	
SA07: 5 wk BORT cycle	£90,706	
SA08: PFS instead of ToT	£107,000	
SA09: post progression costs	£135,000	

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Source: ERG addendum due to lenalidomide PAS: tables 4–7

[a] In SA01-SA03 the ERG explored the following parametric functions: Exponential, Weibull, Log Normal, Log Logistic, Gompertz, Gamma

Results of ERG sensitivity analyses: people with 2 prior therapies *(including the ixazomib PAS)*

	ICER for IXA+LEN+DEX vs. LEN+DEX (£/QALY)	
	ERG base case	**ERG scenario: data from post hoc analysis of subgroup (2 prior therapies only)**
ERG base case/scenario	£138,000	£186,000
SA01: OS curves[a]	£93,024–£243,000	£186,000–£290,000
SA02: PFS curves[a]	£138,000–£142,000	£187,000–£195,000
SA03: ToT curves[a]	£138,000–£203,000	£186,000–£336,000
SA06a: TA171 utilities	£127,000	£173,000
SA06b: TA338 utilities	£134,000	£180,000
SA08: PFS instead of ToT	£176,000	£265,000
SA09: post progression costs	£151,000	£202,000

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Source: ERG appendix: tables 11–14

[a]In SA01-SA03 the ERG explored the following parametric functions: Exponential, Weibull, Log Normal, Log Logistic, Gompertz, Gamma

Company comments on innovation

The company suggests that IXA+LEN+DEX is innovative because:

- IXA+LEN+DEX is an all oral treatment regimen
  - First oral proteasome inhibitor
  - Lower toxicity than other treatments
  - Convenient administration; reduced travel is important because bone degradation, fractures and fatigue are common symptoms of the disease
    Note: the 3rd line comparator (LEN+DEX) is also an all oral combination
- The triple combination gives the benefits of a proteasome inhibitor, immunomodulatory agent and steroid
- There are benefits not captured by the QALY calculations:
  - Unmet need in 2nd and 3rd line
  - Convenient all-oral treatment taken at home
    - *Note: the company base-case model includes a disutility for subcutaneous treatments; the ERG removed this disutility from its exploratory analyses*
  - Reduced carer burden
  - Benefits for people still in employment

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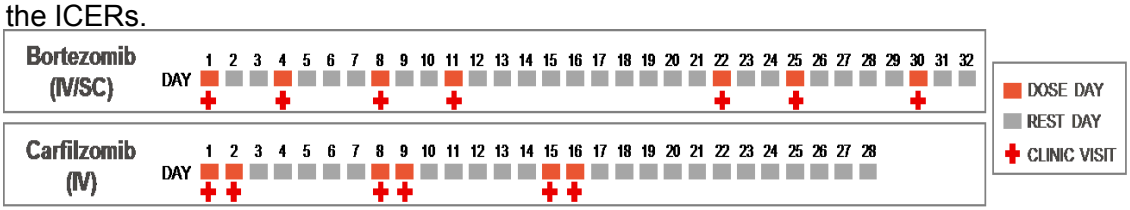
The ERG noted that removing the disutility for subcutaneous injections had a minimal impact on the ICERs.



Equalities

- During the scoping process, it was noted that:
  - multiple myeloma mostly affects older people who often have concomitant conditions and so there may be an impact on the equality of access for these patients
  - multiple myeloma is more common in people of African and Caribbean family origin.
- The committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population. No evidence was presented at the scoping workshop that suggested that ixazomib citrate was less effective or had more safety issues in people of African and Caribbean family origin compared with other groups.
- No equalities issues were identified in evidence submissions from consultees.

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Authors

- **Sophie Cooper**
  Technical Lead
- **Raisa Sidhu**
  Technical Adviser
- with input from the Lead Team (David Bowen, Malcolm Oswald and Paula Ghaneh)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of ixazomib citrate within its marketing authorisation for relapsed or refractory multiple myeloma.

Background

Multiple myeloma is a form of cancer that arises from plasma cells (a type of white blood cell) in the bone marrow. Myeloma cells produce large quantities of an abnormal antibody, known as paraprotein. Unlike normal antibodies, paraprotein has no useful function and lacks the capacity to fight infection. Myeloma cells supress the development of normal blood cells that are responsible for fighting infection (white blood cells), carrying oxygen around the body (red blood cells) and blood clotting (platelets). The term multiple myeloma refers to the presence of more than one site of affected bone at the time of diagnosis. People with multiple myeloma can experience bone pain, bone fractures, tiredness (due to anaemia), infections, hypercalcaemia (too much calcium in the blood) and kidney problems.

In 2013, about 4,700 people were diagnosed with multiple myeloma in England.[1] It is most frequently diagnosed in older people, with 59% of people diagnosed aged 70 years and over.[2] Multiple myeloma is more common in men than in women and the incidence is also reported to be higher in people of African and Caribbean family origin. The 5-year survival rate for adults with multiple myeloma in England and Wales is estimated to be 47%.[3]

The main aims of therapy are to prolong survival and maintain a good quality of life by controlling the disease and relieving symptoms. Initial therapy can include induction treatment with bortezomib (given with dexamethasone, or with dexamethasone and thalidomide) before having chemotherapy and stem cell transplantation (NICE technology appraisal 311). If high-dose chemotherapy with stem cell transplantation is inappropriate, NICE technology appraisal guidance 228 recommends thalidomide (or bortezomib if the person is unable to tolerate or has contraindications to thalidomide) in combination with an alkylating agent and a corticosteroid.

Subsequent therapy is influenced by previous treatment and response to it, duration of remission, comorbidities and patient preference. NICE technology appraisal guidance 129 recommends bortezomib monotherapy as an option for treating progressive multiple myeloma in people who are at first relapse having received 1 prior therapy and who have undergone, or are unsuitable for bone marrow transplantation. NICE technology appraisal guidance 171

recommends lenalidomide in combination with dexamethasone as a treatment option for people with multiple myeloma who have received at least 2 prior therapies. NICE technology appraisal guidance 380 recommends panobinostat in combination with bortezomib and dexamethasone as an option for treating relapsed and/or refractory multiple myeloma in adults who have had at least 2 prior regimens including bortezomib and an immunomodulatory agent. Other subsequent treatment options may include repeating high-dose chemotherapy or chemotherapy with alkylating agents and anthracyclines, thalidomide and corticosteroids.

The technology

Ixazomib citrate (Ninlaro, Takeda UK) is an oral small molecule proteasome inhibitor, which acts by inducing apoptosis via the disruption of proliferative tumour cells.

Ixazomib citrate does not currently have a marketing authorisation in the UK for treating multiple myeloma. A randomised controlled trial compared ixazomib citrate with placebo, both in combination with lenalidomide and dexamethasone, in adults with relapsed or refractory multiple myeloma.

Intervention	Ixazomib in combination with lenalidomide and dexamethasone
Population	People with relapsed or refractory multiple myeloma who have had at least 1 therapy
Comparators	For people who have had at least 1 therapy: • bortezomib (with or without dexamethasone)* • bortezomib retreatment (with or without dexamethasone) • lenalidomide with dexamethasone (subject to ongoing NICE appraisal [part review of technology appraisal 171]) For people who have had at least 2 therapies: • lenalidomide with dexamethasone • panobinostat with bortezomib and dexamethasone

* NICE recommends bortezomib monotherapy as an option for treating multiple myeloma at first relapse. In clinical practice, bortezomib is often given in combination with dexamethasone.

Outcomes	The outcome measures to be considered include: • progression-free survival • overall survival • response rates • time to next treatment • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. If the evidence allows, subgroup analyses based on number of lines of previous therapy will be considered.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Bortezomib monotherapy for relapsed multiple myeloma (2007) NICE technology appraisal 129. Guidance on static list. Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (2009) NICE technology appraisal 171. Guidance on static list. Panobinostat for treating multiple myeloma in people who have received at least one prior therapy (2016) NICE technology appraisal 380. Review date January 2019.

	Appraisals in development: Carfilzomib in combination with dexamethasone for treating multiple myeloma in people who have received at least 1 prior therapy. NICE technology appraisal ID934. Date of publication TBC. Elotuzumab for previously treated multiple myeloma. NICE technology appraisal ID855. Date of publication TBC. Lenalidomide for treating multiple myeloma after 1 prior treatment with bortezomib (part review of Technology Appraisal guidance 171). NICE technology appraisal ID667. Date of publication TBC. Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib (review of TA338). NICE technology appraisal ID985. Date of publication April 2017. Suspended appraisal, Carfilzomib in combination with lenalidomide and dexamethasone for previously treated multiple myeloma. NICE technology appraisal ID677. Suspended appraisal, Lenalidomide for treating newly diagnosed multiple myeloma. NICE technology appraisal ID747. **Related Guidelines:** NICE Guideline 35, Myeloma: diagnosis and management of myeloma. February 2016. **NICE pathway:** Multiple myeloma: http://pathways.nice.org.uk/pathways/myeloma
Related National Policy	National service framework: 'Improving outcomes: a strategy for cancer', December 2014 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/388160/fourth_annual_report.pdf NHS England Manual for prescribed specialised services 2013/2014. Blood and marrow transplantation services (all ages) https://www.england.nhs.uk/commissioning/spec-services/npc-crg/blood-and-infection-group-f/f01/ Department of Health, NHS Outcomes Framework 2015-2016, Nov 2014. Domains 1, 2, 4 and 5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf

References

1. Cancer research UK, Myeloma incidence statistics [accessed March 2016]

2. Cancer research UK, Myeloma survival statistics [accessed March 2016]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma [ID807]

Final matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Takeda UK (ixazomib citrate) Patient/carer group • Black Health Agency • Bloodwise • Cancer Black Care • Cancer Equality • Cancer52 • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Leukaemia Cancer Society • Leukaemia CARE • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • Myeloma UK • Rarer Cancers Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care Professional groups • Association of Cancer Physicians • British Committee for Standards in Haematology • British Geriatrics Society • British Psychosocial Oncology Society • British Society for Haematology • Cancer Research UK • Royal College of General Practitioners • Royal College of Nursing	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Possible comparator companies • Celgene (lenalidomide) • Focus Pharmaceuticals (dexamethasone) • Janssen (bortezomib) • Novartis (panobinostat) Relevant research groups • Cochrane Haematological Malignancies Group • Institute of Cancer Research • Leuka • Leukaemia Busters • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network

Consultees	**Commentators (no right to submit or appeal)**
• Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • UK Clinical Pharmacy Association • UK Health Forum • UK Myeloma Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS Aylesbury Vale CCG • NHS Coastal West Sussex CCG • NHS England • Welsh Government	• National Institute for Health Research <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do share it. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies;
Healthcare Improvement Scotland;; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma ID 807

Submission by Takeda UK Ltd

15th December 2016

File name	Version	Contains confidential information	Date
		Yes/no	

Contents

List of Tables

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Abbreviations

ACD	Appraisal Committee Document
ADME	Absorption, disposition, metabolism, and excretion
AE	Adverse event
AL	Primary systemic amyloidosis
Allo-SCT	Allogeneic stem cell transplant
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
ASH	American Society of Hematology
AST	Aspartate aminotransferase
BPI-SF	Brief Pain Inventory – Short Form
BSA	Body surface area
BORT	Bortezomib
CDF	Cancer Drugs Fund
CR	Complete response
CRd	Carfilzomib plus Revlimid® (lenalidomide) and dexamethasone
CIs	Confidence intervals
CrCl	Creatinine clearance
DDI	Drug–drug interaction
DEX	Dexamethasone
DLT	Dose-limiting toxicity
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
ESRD	End-stage renal disease
EQ-5D	EuroQol five dimensions
FISH	Fluorescence in situ hybridisation
FLC	Free light chain
GVHD	Graft versus host disease
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Interim analysis

IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IRC	Independent Review Committee
IRd	Ixazomib plus Revlimid® (lenalidomide) and dexamethasone
ICER	Incremental cost-effectiveness ratio
ISS	International Staging System
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system
IXA	Ixazomib
KRd	Kyprolis® (carfilzomib) plus Revlimid® (lenalidomide) and dexamethasone
LEN	Lenalidomide
MM	Multiple myeloma
MRD	Minimal residual disease
mSMART	Mayo Stratification of Myeloma and Risk Adapted Therapy
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NE	Not estimable
NICE	National Institute For Health And Care Excellence
NMA	Network meta-analysis
NHS	National Health Service
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease
PFS	Progression-free survival
PI	Proteasome inhibitor
PN	Peripheral neuropathy
PR	Partial response
PRO	Patient-reported outcome
PSMB1	Proteasome subunit beta type-1
PSS	Personal social services
QALY	Quality-adjusted life years
QLQ-MY20	Quality of Life Questionnaire MM Module 20

QoL	Quality of life
RCT	Randomised controlled trial
Rd	Revlimid® (lenalidomide) and dexamethasone
RRMM	Relapsed and/or refractory multiple myeloma
SAE	Serious adverse event
SC	Subcutaneous
sCR	Stringent complete response
SCT	Stem cell transplant
SD	Standard deviation
TEAE	Treatment-emergent adverse event
ToT	Time on treatment
TRAF-3	Tumour necrosis factor receptor-associated factor-3
TTP	Time to progression
ULN	Upper limit of normal
UPS	Ubiquitin-proteasome system
US FDA	United States Food and Drug Administration
Vd	Velcade® (bortezomib) and dexamethasone
VGPR	Very good partial response

1. Executive summary

1.1 Statement of decision problem

1.1.1 Remit/appraisal objective

The remit/appraisal objective, as defined in the final NICE scope, is to appraise the clinical effectiveness and cost effectiveness of ixazomib citrate within its marketing authorisation for relapsed or refractory multiple myeloma.

On November 21st 2016, the European Commission granted conditional marketing authorisation for Ninlaro® (ixazomib), indicated in combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. Ixazomib is the first oral proteasome inhibitor to become available.

Clinical evidence regarding ixazomib is from the TOURMALINE-MM1 study, which is an ongoing Phase III, double blind randomised controlled trial (RCT), examining the efficacy and safety of ixazomib combined with lenalidomide and dexamethasone (IXA+LEN+DEX) versus placebo + lenalidomide and dexamethasone (LEN+DEX) for the treatment of adult patients with relapsed and/or refractory multiple myeloma (RRMM) who have received 1-3 prior therapies. [1]

In the NICE scope the comparators are defined based on line of therapy (Table 1). The interpretation of 'patients who have had at least one therapy' is that this relates to those with one prior therapy only – this has clinical practice relevance as the comparators in the scope are those used second line in RRMM, and this fits into the current treatment pathway as specified in NICE clinical guidelines [2] and in the recent carfilzomib ACD [3] (see Figure 2 in the ACD)This issue was discussed at the NICE/ERG decision problem meeting with agreement that this was the appropriate way to interpret the NICE scope. [3]

In the TOURMALINE-MM1 study, in addition to the analysis of the ITT population (all randomised patients who received 1-3 prior therapies), pre-specified subgroup analyses were conducted based on a number of factors including by line of therapy (i.e. patients who had received one prior line and those who had received 2 or 3 prior lines of therapy). Therefore, in addition to the ITT population, clinical and economic evidence is presented based on these subgroups to reflect the NICE scope. The recent carfilzomib ACD clearly specifies the relevant treatment pathway, with 2nd line consisting of patients having received one prior therapy, and 3rd line based on having received two prior therapies. Like carfilzomib the positioning of ixazomib in combination with lenalidomide and dexamethasone is that it will mainly be used as a 3rd line agent, but with potential use as a second line agent also, and so the relevant comparators are lenalidomide + dexamethasone in 3rd line, and bortezomib + dexamethasone in 2nd line (see figure 2 in the carfilzomib ACD, and also section 1.1.3 in this submission).[3]

1.1.2 Background to relapsed refractory multiple myeloma

Multiple myeloma (MM) is classified as an orphan (rare) disease, defined in the EU as a prevalence not exceeding 5 in 10,000 people. In 2014, there were approximately 4,652 new cases of MM in England, with 2,462 deaths. [4] It is most frequently diagnosed in older people, with 58% of people diagnosed aged 70 years and over. [4]

MM occurs when a malignant transformation results in a population of clonal plasma cells that reproduce uncontrollably [5] and produce large quantities of one antibody (monoclonal protein or M-protein) [6]. The abundance of M-protein, which eventually needs to be degraded via the ubiquitin-proteasome system within the cell, makes MM a

particularly good target for a proteasome inhibitor (PI). MM cells have a higher level of proteasome activity than normal cells, meaning that disruption of protein homeostasis by a proteasome inhibitor such as ixazomib results in apoptosis of MM cells more readily than normal cells.

Although outcomes in MM have improved significantly over the past 15 years following the introduction of the first PI Velcade (bortezomib) and immunomodulatory (IMiD) drugs, [7,8] it remains an incurable progressive disease. MM is characterised by multiple relapses; after a successful initial treatment resulting in stable disease or remission, nearly all patients will eventually relapse and will require further therapy. Such patients are difficult to treat as they tend to have more aggressive disease (and thus are less responsive to treatment) and are heavily pre-treated with more pre-existing toxicities. [9] Ultimately, the prognosis of these patients remain poor,[10] with median overall survival (OS) reducing as patients progress through lines of therapy. [11]

Prolongation of progression-free survival (PFS) and OS remain the ultimate goals of treatment, although preserving patients quality of life is also an important consideration. Due to clonal heterogeneity of myeloma, combination therapy has become the standard-of-care in many situations, with the complementary activity of a PI, an IMiD drug (e.g. lenalidomide) and a corticosteroid (dexamethasone) particularly promising. [12-14] Recent Phase III studies have demonstrated superior efficacy with triplet versus doublet combination regimens based on these agents in the frontline [15,16] and relapsed settings, [17,18] without adding any relevant additional toxicity. Additionally, to further improve long-term outcomes, there has been a shift towards a paradigm of extended treatment. [19-21]

In this submission we present evidence of the clinical- and cost-effectiveness of the all-oral triplet regimen of the PI ixazomib in combination with the IMiD lenalidomide and the corticosteroid dexamethasone (i.e. the IXA+LEN+DEX regimen, also known as IRd). Ixazomib is the first in class oral PI that can provide important efficiencies to the NHS, particularly versus parenteral treatments (i.e. intravenous or subcutaneous) that are currently available and widely used. The all-oral triplet combination of ixazomib (a convenient once-weekly, single pill dose) with lenalidomide and dexamethasone can be taken at home, and therefore has the potential to reduce the treatment burden on the NHS, patients and carers. In addition, ixazomib has a favourable toxicity profile which facilitates patient concordance.

1.1.3 Decision problem and NICE scope

The NICE scope for ixazomib issued in March 2016 (Table 1), has specified the comparators based on line of therapy to reflect clinical practice i.e. for people who have received 1 prior therapy: bortezomib (with or without dexamethasone); bortezomib retreatment (with or without dexamethasone); and lenalidomide with dexamethasone (subject to ongoing NICE appraisal [part review of Technology appraisal 171]); and for people who have received at least 2 therapies: lenalidomide with dexamethasone; and panobinostat with bortezomib and dexamethasone.

Of the comparators in the NICE scope, bortezomib monotherapy is the only current NICE recommended treatment in patients who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation. [2] Of note, both re-treatment with bortezomib, and lenalidomide for the second-line treatment of MM have recently been removed from the Cancer Drugs Fund (CDF). [22-24] The lenalidomide plus dexamethasone doublet combination is currently being appraised by NICE for adults with MM for whom thalidomide is contraindicated and whose disease has progressed after at least 1 prior treatment with bortezomib. Of relevance to this appraisal, on 11th November 2016 NICE issued a negative Appraisal Consultation Document (ACD) for lenalidomide plus dexamethasone in this setting. [25]

For those who have received two or more prior treatments, either lenalidomide in combination with dexamethasone; or panobinostat in combination with bortezomib and dexamethasone are recommended by NICE (note that for

panobinostat the NICE recommendation stipulates that the prior regimens must include bortezomib and an IMiD). [2] However, in UK clinical practice, lenalidomide plus dexamethasone is mainly used as 3rd line therapy (i.e. after 2 prior therapies), while the panobinostat plus bortezomib plus dexamethasone regimen is predominantly used as 4th line therapy (i.e. after 3 prior therapies); this has been confirmed in the recent NICE appraisal of carfilzomib and pomalidomide. Hence, we do not consider panobinostat as a relevant comparator for IXA+LEN+DEX in the 3rd line setting.

Overall, we are following the treatment pathway specified in the recent carfilzomib ACD (Figure 2 in the ACD [3], which specifies bortezomib + dexamethasone as the 2nd line placement comparator and lenalidomide + dexamethasone as the 3rd line placement comparator. This was accepted by the Appraisal Committee, and the same rationale for positioning and comparators applies for ixazomib + lenalidomide + dexamethasone. Clinical feedback has been the predominant use of ixazomib is expected to be in a 3rd line agent prior to panobinostat and other later line agents.

What this demonstrates is that for a disease characterised by multiple relapses and where the natural history is that patients will eventually become treatment refractory, there are currently relatively few NICE recommended treatment options available on the NHS in England. In addition, these treatment options have some significant limitations. IXA+LEN+DEX overcomes many of these limitations, providing patients, clinicians and the NHS with the choice and flexibility of an all-oral treatment option that is simple, efficacious and has a favourable toxicity profile.

In contrast to ixazomib, a significant limitation of treatment with the established PI bortezomib (and of the newer PI carfilzomib which is currently undergoing assessment by NICE [26]) is the requirement for parenteral administration (intravenous (IV) or subcutaneous injection (sc) for bortezomib; IV injection for carfilzomib). The licensed dosing schedule for bortezomib (either alone, with dexamethasone, or in the combination regimen of panobinostat-bortezomib-dexamethasone) requires two visits to the clinic per week for weeks 1 and 2 of a 21-day treatment cycle (i.e. 32 visits to the clinic within an 8 cycle treatment schedule) [27,28] (see Table 7). The need for healthcare professionals to administer bortezomib inevitably increases the burden on NHS resources and costs. In addition, this demanding treatment schedule may adversely affect the patient and/or caregiver financially due to travel costs, time away from work [29] as well as impacting their quality of life (e.g. the unpleasantness of having injections; time spent travelling and at the clinic/hospital, as well as the impact on daily activities). Several reports have shown that many patients with cancer prefer oral to parenteral therapy, [30-34] the reasons for which have included convenience, the place of treatment, a dislike of needles, anxiety over an IV line, feeling less ill on oral therapy and reducing the effort in coping with the disease. [30,31,34,35] Having an all-oral combination is also particularly important for patients who find it difficult to attend hospital appointments (e.g. older/frailer patients, those who live far away from hospital or those who are still in employment).[36,37]

Bortezomib is also associated with a number of adverse events; in particular peripheral neuropathy is a dose-limiting toxicity which can potentially result in permanent nerve damage to the extremities, while other common side-effects include fatigue, gastrointestinal effects, and modest cytopenias. [38] In addition, panobinostat is associated with severe diarrhoea and severe and fatal cardiac events, arrhythmias and electrocardiogram changes, [39,40] panobinostat has a “Boxed Warning” in the US, alerting patients and healthcare professionals to these risks. [39] Overall, these adverse events can lead to higher costs (i.e. to manage the adverse event), lower patient quality of life, and premature treatment discontinuation which precludes long-term efficacious treatment. By contrast, ixazomib has a favourable toxicity profile which facilitates patient concordance.

Other than the panobinostat-bortezomib-dexamethasone regimen (mainly used 4th line in the UK, as explained above), lenalidomide in combination with dexamethasone (mainly used 3rd line in the UK) is currently the only other treatment option recommended by NICE for MM patients who have had two or more prior therapies. The

TOURMALINE-MM1 Phase III randomised controlled trial (RCT), described in this submission, provides direct head-to-head evidence of the benefits of a triplet regimen of IXA+LEN+DEX (IRd) compared to a LEN+DEX (Rd) doublet. The benefits of the ixazomib regimen include improved progression-free survival and response rates, without any adverse impact on safety/tolerability or patient-reported quality of life. [1] These benefits were observed consistently across key pre-specified subgroups, including patients who generally have a poor prognosis (i.e. heavily pre-treated patients who have received 2 or 3 lines of prior therapy; patients with advanced stage disease (ISS stage III); and patients with high-risk cytogenetic abnormalities). [41]

Overall, IXA+LEN+DEX (IRd) is a simple, efficacious, well tolerated and convenient treatment regimen. Ixazomib is the first and only oral PI to be approved by the EMA, providing a much-needed, all-oral triplet option that patients can take at home, thus reducing the burden on themselves, carers and the NHS.

The final scope issued by NICE in March 2016 and the decision problem addressed in this submission is shown in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with relapsed or refractory multiple myeloma who have had at least 1 therapy.	Ixazomib is indicated for adult patients with multiple myeloma who have received at least one prior therapy, which is in-line with the NICE scope. Clinical evidence regarding ixazomib is from the TOURMALINE-MM1 study, which is an ongoing Phase III, double blind RCT, examining the efficacy and safety of ixazomib combined with lenalidomide and dexamethasone versus placebo with lenalidomide and dexamethasone for the treatment of adult patients with RRMM who have received 1-3 prior therapies.	-
Intervention	Ixazomib in combination with lenalidomide and dexamethasone.	Ixazomib in combination with lenalidomide and dexamethasone	-
Comparator (s)	For people who have had at least 1 therapy: • bortezomib (with or without dexamethasone)[a] • bortezomib retreatment (with or without dexamethasone) • lenalidomide with dexamethasone (subject to ongoing NICE appraisal [part review of technology appraisal 171]). For people who have had at least 2 therapies: • lenalidomide with dexamethasone • panobinostat with bortezomib and dexamethasone.	For people who have had 1 prior therapy: • bortezomib with dexamethasone For people who have had at least 2 therapies: • lenalidomide with dexamethasone Evidence of the cost-effectiveness of IXA+LEN+DEX vs LEN+DEX is derived from the head-to-head TOURMALINE-MM1 trial. Evidence vs bortezomib with dexamethasone is from a systematic review and NMA of treatments for RRMM.	The interpretation of 'patients who have had at least 1 therapy' is that this relates to those with 1 prior therapy only – this has clinical practice relevance as the comparators in the scope are those used second line in RRMM, and this fits into the current treatment pathway as specified in NICE clinical guidelines. [2] This issue was discussed at the NICE/ERG decision problem meeting with agreement that this was the appropriate way to interpret the NICE scope. For people who have had 1 therapy: • We have excluded bortezomib monotherapy as this is rarely used in UK practice; • bortezomib retreatment is excluded as it is not funded by NHS England. • LEN+DEX is excluded as it is not NICE approved is not on the CDF and has recently had a negative ACD from NICE. In addition to second line usage as above, the company proposes to also position IXA+LEN+DEX as a third line treatment (i.e. for people who have had 2 prior therapies). The relevant comparator at third line is LEN+DEX For people who have had 2 therapies:

			• We have excluded panobinostat with bortezomib and dexamethasone as this is predominantly used as a 4th line therapy in the UK (i.e.it is not a relevant comparator at 3rd line).
Outcomes	The outcome measures to be considered include: • progression-free survival (PFS) • overall survival (OS) • response rates • time to next treatment • adverse effects of treatment • health-related quality of life.	The submission will present the PFS, OS, best overall response and EQ-5D endpoints using TOURMALINE-MM1 effectiveness results for IXA+LEN+DEX. The results from an NMA will be used as a source of evidence for the comparison with bortezomib and dexamethasone. In the cost-effectiveness analysis, extrapolation of PFS and OS beyond the TOURMALINE-MM1 and NMA based clinical trial follow-up will be performed to estimate mean life-years and QALYs for ixazomib and the comparator regimens.	All of the outcomes in the NICE scope have been reported in the TOURMALINE-MM1 Phase III study, except for *time to next treatment*. However, the TOURMALINE-MM1 trial does collect data on the following parameters that may be useful surrogates for *time to next treatment*: *time to progression; time to response; and duration of response*. The clinical results for these will be presented. NMA and cost-effectiveness results incorporating these outcomes will be presented.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes (PASs) for the intervention or comparator technologies should be taken into account.	The cost-effectiveness analysis will reflect the reference case, although no PSS costs are considered. Patient Access Schemes (PAS) are considered for both ixazomib and comparator treatments where relevant.	
Subgroups to be considered	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by	Clinical and economic evidence from the subgroups of relevance to the indicated population are the focus of this submission. These include: • Patients who have received 1 prior therapy • Patients who have received 2-3 prior therapies.	As explained above, the company proposes to position IXA+LEN+DEX as a second-line and third-line treatment only.

	the regulator. If the evidence allows, subgroup analyses based on number of lines of previous therapy will be considered.		
Special considerations including issues related to equity or equality	-	The TOURMALINE-MM1 trial has included adult (age ≥18 years) male and female patients of different ethnic backgrounds.	

Abbreviations: EMA = European Medicines Agency; EQ-5D = EuroQol five dimensions; ITT = intent-to-treat; ISS = international staging system; NHS = National Health Service; NMA = network meta-analysis; NMA = network meta-analysis; OS = overall survival; PAS = patient access scheme; PFS = progression-free survival; PSS = personal social services; RCT = randomised controlled trial; RRMM = relapsed and/or refractory multiple myeloma; QALY = quality-adjusted life year

[a] The NICE scope for ixazomib states the following: “NICE recommends bortezomib monotherapy as an option for treating multiple myeloma at first relapse. In clinical practice, bortezomib is often given in combination with dexamethasone.”

1.2 Description of the technology being appraised

Ixazomib is the first oral PI to be approved in multiple myeloma. A description of ixazomib is shown in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Ixazomib citrate (Ninlaro®)
Marketing authorisation/CE mark status	On November 21st 2016, the European Commission granted a conditional marketing authorisation for Ninlaro® (ixazomib).
Indications and any restriction(s) as described in the summary of product characteristics	Ixazomib 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. Restrictions/contraindications include patients with hypersensitivity to the active substance or to any of the excipients. In addition, women should avoid becoming pregnant while being treated with ixazomib. Ixazomib is used in combination with lenalidomide and dexamethasone.
Method of administration and dosage	The intervention consists of an all-oral triplet regimen with a once weekly single capsule dose of ixazomib combined with lenalidomide and dexamethasone. The recommended dose of ixazomib is 4 mg taken once on days 1, 8 and 15 of a 28-day treatment cycle. The recommended dose for lenalidomide is 25 mg taken daily on days 1 through 21 of a 28-day treatment cycle, whilst dexamethasone 40 mg is taken on days 1, 8, 15 and 22 of a 28-day treatment cycle.
Abbreviations: CHMP = Committee for Medicinal Products for Human Use Source: SmPC (Appendix 1)	

1.3 Summary of the clinical effectiveness analysis

1.3.1 Identification of studies

A systematic literature review was undertaken to evaluate the relative efficacy and safety of IXA+LEN+DEX versus other selected regimens for the treatment of RRMM.

One randomised clinical trial (RCT) of IXA+LEN+DEX in adult patients with RRMM was identified (TOURMALINE MM-1). [1,42] Evidence versus the other relevant comparators in the NICE scope (i.e. bortezomib with dexamethasone) is derived from a network meta-analysis (NMA) using studies identified in the systematic literature review.

1.3.2 TOURMALINE-MM1 study design

Clinical evidence regarding ixazomib is from the TOURMALINE-MM1 study, which is an ongoing Phase III, double blind RCT, examining the efficacy and safety of IXA+LEN+DEX versus LEN+DEX for the treatment of adult patients with RRMM who have received 1-3 prior therapies.[1] The double-blind design is a particular strength of the TOURMALINE-MM1 study and one that differentiates it from other trials of new agents for RRMM, most of which have an open label design.

Patients were randomly assigned in a 1:1 ratio to receive either oral ixazomib 4 mg or matching placebo capsule on days 1, 8, and 15, plus oral lenalidomide 25 mg on days 1-21 and oral dexamethasone 40 mg on days 1, 8, 15, and 22, in 28-day cycles. Randomisation was stratified by number of prior therapies (1 vs. 2 or 3), previous proteasome inhibitor exposure (naïve vs. exposed), and International Staging System (ISS) disease stage (I or II vs. III). [1] Treatment continued until disease progression or unacceptable toxicity.

In addition to the outcomes from the entire ITT population (i.e. all patients who were randomised [n=722]), the study also analysed outcomes in pre-specified subgroups according to baseline demographics and disease characteristics, including patients who had received 1 prior therapy (n=425) and who had received 2 or 3 prior lines (n=297). Therefore, the study reports evidence in the patient populations that are of interest for the NICE scope.

The outcomes of interest in the NICE scope (Table 1) that were assessed in this study i.e. *progression free survival, overall survival, response rates, adverse effects of treatment and health-related quality of life* are presented. However, because the TOURMALINE-MM1 study does not collect data on *time to next treatment,* the following parameters that may be useful surrogates have been reported: *time to progression; time to response;* and *duration of response.*

To date there have been two interim analyses. At the data cut-off for the first interim analysis (30 October 2014), median follow-up was 14.8 months and 14.6 months in the IXA+LEN+DEX and LEN+DEX groups, respectively. As the primary endpoint of improved PFS was met at the first analysis, this was the final statistical analysis of the primary endpoint (primary analysis). Data from the second pre-planned interim analysis (cut-off date: 12th July 2015, median follow-up of ~23 months) is also presented – a non-inferential PFS analysis was also conducted at the second interim analysis. Adverse events are reported from the longer duration second interim analysis.

1.3.3 Clinical effectiveness of IXA+LEN+DEX vs. LEN+DEX

The TOURMALINE-MM1 study has shown that the addition of IXA to LEN+DEX significantly improves outcomes including PFS and response rates, with limited additional toxicity. [1]

A statistically significant PFS improvement was demonstrated with IXA+LEN+DEX vs LEN+DEX in patients with RRMM (ITT population at the primary analysis of PFS: median, 20.6 months vs. 14.7 months; hazard ratio (HR) 0.74, p=0.012; median follow-up ~15 months), showing a clinically meaningful ~6 month improvement in median PFS. In addition, median PFS in the 2 or 3 prior therapies stratified subgroup was not estimable (NE) for IXA+LEN+DEX versus 12.9 months for LEN + DEX (HR 0.58; p=0.0033). PFS benefit was also observed consistently across other key pre-specified subgroups, including in poor-prognosis subgroups such as elderly patients, patients with advanced stage disease, and patients with high-risk cytogenetic abnormalities (for whom the LEN+DEX doublet is emerging as sub-optimal treatment) [41]

With median follow-up of ~23 months, overall survival was not yet mature. Follow-up is ongoing, with OS data from the third interim analysis (IA3) expected in Q2 2017 and final OS analysis expected in Q3 2019.

Overall response rates (ORR) in the ITT population were 78.3% in the IXA+LEN+DEX group and 71.5% in the LEN+DEX group (p=0.04). Responses were rapid and durable and deepening responses were noted with increasing treatment duration; median time to response was 1.1 months vs. 1.9 months, and median duration of

response was 20.5 months vs. 15.0 months, in the IXA+LEN+DEX and LEN+DEX arms, respectively. ORRs were also 80.4% vs. 67.1% in patients who had received 2 or 3 prior lines of therapy, respectively.

Reflecting the findings of the primary endpoint of PFS, time to progression (TTP) was also significantly longer in the IXA+LEN+DEX vs. LEN+DEX arm (ITT population: median 21.4 months vs. 15.7 months: HR: 0.71, p=0.007). In patients who had received 2 or 3 prior lines of therapy, the median TTP was not estimable vs. 12.9 months at the first interim analysis (median follow-up of 15 months) and was 28.8 months vs. 14.1 months at the second interim analysis (median follow-up of 23 months).

There was no adverse impact on patient-reported quality of life (EORTC-QLQ-C30 and MY-20 questionnaires) from the addition of IXA to LEN+DEX in this double-blind study. This is particularly noteworthy given the tendency to overestimate quality of life benefit in open-label studies.

1.3.4 Safety and tolerability of IXA+LEN+DEX vs. LEN+DEX [1]

Ixazomib triple therapy had a manageable tolerability profile. The frequencies of serious adverse events (47% vs. 49%), discontinuations due to adverse events (17% vs. 14%) and on-study deaths (4% vs. 6%) were similar in both the IXA+LEN+DEX and LEN+DEX groups. Overall, 74% and 69% of patients experienced grade ≥3 adverse events. The only grade ≥3 adverse event for which there was a ≥5% difference between the IXA+LEN+DEX and LEN+DEX groups was thrombocytopenia, a known side effect of bortezomib and carfilzomib [43,44] and for which there were no apparent clinical sequelae. Addition of IXA to LEN+DEX resulted in a slightly increased rate of peripheral neuropathy (27% vs. 22%), with only 2% being grade 3 events (compared with 6% with subcutaneous bortezomib [45] and 3% with carfilzomib in other clinical trials). [18]

Duration of therapy with the IXA+LEN+DEX regimen was prolonged, with half of the patients having received at least 18 cycles at the 23-month analysis. Treatment compliance appeared high and similar between the groups, consistent with the observed tolerability of ixazomib, and suggesting that the all-oral ixazomib triplet regimen was as simple and convenient for patients to take as the lenalidomide-dexamethasone doublet regimen.

The safety data was consistent across the subgroups by prior line of therapy and the overall safety population; despite having received more prior therapy, patients in the subgroup who received 2 or 3 prior therapies did not experience more AEs than patients with 1 prior therapy.

Overall, the favourable tolerability profile of IXA+LEN+DEX is important in RRMM patients who are typically older and less fit. Taken together with its efficacy and convenient oral dosing schedule, the favourable tolerability profile of ixazomib represents a therapeutic innovation and offers a significant benefit for patients with RRMM.

1.3.5 Network meta-analysis: Clinical effectiveness of IXA+LEN+DEX vs BORT+DEX in 1 prior therapy

The results from the NMA show the relative efficacy benefits of IXA+LEN+DEX vs BORT+DEX, the main comparator for a positioning of one prior line of therapy:

- For PFS, a hazard ratio of 0.72 (95% credible interval (CrI) 0.41, 1.19) was estimated, showing a numerical benefit for IXA+LEN+DEX
- For OS, there was a significant benefit estimated for IXA+LEN+DEX with a HR of 0.31 (95%CrI:0.13, 0.65)

- For ORR an odds ratio of 0.88 (95%CrI: 0.35, 1.88) was estimated, showing a numerical benefit for LEN+DEX, although not significant and in a scenario analysis was favourable for IXA+LEN+DEX.
- For BoR there was a significant benefit for IXA+LEN+DEX with an OR of 3.82 (95%CrI: 1.32, 8.93)
- Treatment discontinuations due to AEs (safety measure) showed a difference vs BORT+DEX, which was numerically worse for IXA+LEN+DEX but which was not statistically significant (OR= 2.58, 95%CrI: 0.81, 6.32).

There are some limitations to the NMA to support the relative clinical effectiveness of IXA+LEN+DEX vs BORT+DEX in RRMM patients who have received one prior therapy, in particular there is not specific comparator data published or available with which to form a network for this comparison, hence 1+ prior therapy evidence had to be used as a proxy. However, the advantage of this data is that is relatively robust as it is based on a larger dataset and can be considered generalisable for a specific 1 prior treatment RRMM patient population.

Other limits of the NMA were that only fixed effects modelling was possible for each of the networks, and there were limited studies with the approved doses for the comparator. Therefore, for some outcomes (such as PFS), dose specific studies had to be combined with studies with other doses or where none were specified. In general there were no heterogeneity issues in the networks, with the exception of the ORR network. In the base case, evidence networks were based on all evidence, both RCT and observational, and used specific approved doses and evidence from study primary publications. However, in general scenario analysis demonstrated low sensitivity in the HRs and ORs to using only RCT evidence, combining all dose studies, or using later datacuts/evidence (with the exception of the ORR analysis).

Although there is head to head data for IXA+LEN+DEX vs. LEN+DEX from the TOURMALINE MM-1 study, this comparison is still included in the NMA; however, because each patient population and outcome is only really informed by this study, the results from the NMA do not differ from those in this study as reported Section 4.

1.4 Summary of the cost-effectiveness analysis

The cost-effectiveness of IXA+LEN+DEX in RRMM has been evaluated compared with BORT+DEX for 2nd line use, and compared with LEN+DEX for 3rd line use. The ICERs presented in this submission are above the conventional thresholds of cost-effectiveness adopted by NICE, but are highly uncertain due primarily to the immaturity of the OS and ToT data. There is reason to believe that the ICERs could be much more favourable for IXA, but the economic argument requires further trial follow-up and real world data collection to establish this (see Section 5.11). Clinical opinion received has indicated that the most feasible positioning and area of greatest unmet need is for the use of IXA+LEN+DEX as a 3rd line regimen.

The economic model used a partitioned survival model approach based upon progression status and survival to model movement between three independent health states: pre-progression, post-progression and death. Time on treatment was modelled independently and could surpass progression, in line with observed data from the pivotal TOURMALINE-MM1 clinical trial. The comparison of IXA+LEN+DEX with BORT+DEX at a second line positioning used data from the TOURMALINE-MM1 clinical trial for IXA+LEN+DEX and data obtained from an NMA for BORT+DEX relative to LEN+DEX. Due to scarcity of data for a specific one prior therapy population for the comparator from the NMA, hazard/odds ratios for OS, PFS and ORR were obtained from a 1+ prior therapies population instead and assumed generalisable. The comparison of IXA+LEN+DEX with LEN+DEX at a third line positioning used data directly from the TOURMALINE-MM1 clinical trial, with the outcomes from the 2+ prior therapies population used as representative for the outcomes associated with this positioning. This consisted of patients who had received either 2 or 3 prior treatments, and combined represented a pre-specified sub-group in the TOURMALINE MM1 study, hence was robust evidence to use in the model.

Health related quality of life was captured within the economic model using a regression equation fit to the patient level data from the TOURMALINE-MM1 (TMM1) clinical trial. Explanatory variables included in the regression equation were: response, hospitalisation, adverse events grade 3 or 4 (including new primary malignancies) and whether a patient was in Grade 3 or 4 (including new primary malignancies) and whether a patient was in the final stages of life (≤3 months to death). Therefore, disutilities associated with adverse events were incorporated in the regression equation. To avoid double counting, hospitalisations associated with adverse events were not included. Costs and resource use were included for treatment, administration, adverse events, concomitant mediations, hospitalisations, post-progression therapies and terminal care costs. Estimates of resource use were sourced from the International Myeloma Foundation Patient Handbook or clinical advice. All costs were costed using UK specific sources.

In line with NICE process, results are presented (Table 3 and Table 4) including the PAS for lenalidomide (treatment beyond 26 treatment cycles is refunded). Full incremental analysis was not presented for IXA+LEN+DEX, BORT+DEX and LEN+DEX as the comparators for IXA+LEN+DEX differ depending on positioning (2nd or 3rd line).

Table 3: Base case results, IXA+LEN+DEX compared with BORT+DEX at a second line positioning (without PAS – see separate PAS template for with PAS results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
BORT+DEX	£38,770	2.452	1.596	-	-	-	-
IXA+LEN+DEX	[redacted]	5.943	3.932	[redacted]	3.491	2.336	[redacted]

Key: BORT, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; LYG, life years gained; QALYs, quality-adjusted life years

Table 4: Base case results, IXA+LEN+DEX compared with LEN+DEX at a third line positioning (without PAS – see separate PAS template for with PAS results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
LEN+DEX	£91,428	3.324	2.2041	-	-	-	-
IXA+LEN+DEX	[redacted]	4.708	3.1736	[redacted]	1.385	0.9694	[redacted]

Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; LYG, life years gained; QALYs, quality-adjusted life years

Treatment with IXA+LEN+DEX is shown to increase the life years and QALYs compared with current UK treatment in both the 1 prior therapy and 2+ prior therapies populations (3.49 and 2.34 for the 1 prior therapy population and 1.39 and 0.97 for the 2+ prior therapies population). Probabilistic analysis found that IXA+LEN+DEX was associated with a QALY gain in 99.0% and 96.6% of the simulations in the 1 prior therapy and 2+ prior therapies populations.

However, clinically effective and relatively safe treatments often result in patients continuing on treatment for longer. This is shown in the economic analysis as IXA+LEN+DEX is shown to accrue additional costs from treatment, resource use whilst on treatment and TRAEs. Furthermore, increases in survival were associated with increased post-progression costs (+£140 in the 1 prior therapy population and +£10,682 in the 2+ prior therapies population).

Sensitivity and scenario analyses demonstrated that the results were sensitive to key parameters, with the main areas of uncertainty associated with:

- Estimates of relative survival between IXA+LEN+DEX and BORT+DEX in the 1 prior therapies population and between IXA+LEN+DEX and LEN+DEX in the 2+ prior therapies population.
- Absolute and relative duration of treatment estimates for all comparators

The results from this submission provide the first economic analysis using the initial data set from the randomised controlled trial: TMM1. These data show an improvement in progression free survival. However, due to the immaturity of the survival data the impact on overall survival is inconclusive. Ixazomib is the first and currently the only approved oral proteasome inhibitor, offering a convenient, fixed dose, once-weekly, single capsule administration with benefits for patients, carers and the NHS. Ixazomib also has a favourable safety profile compared to some other new RRMM therapies. The impact of AEs on costs and QALYs has been included in the economic analysis. However, the full benefits to clinicians and patients of a favourable AE profile are hard to fully capture within the QALY framework. Alongside being an oral treatment, the favourable AE profile is an important attribute of ixazomib when compared to other therapies that are being considered for a 3rd line positioning in the treatment pathway such as carfilzomib (which has a resource intensive IV administration schedule and is associated with rare but serious CV adverse events.)

In performing the economic analysis, a paradox has been identified due to the combination of ixazomib with lenalidomide (+DEX). The high cost of the latter therapy means that only with a very low (or almost zero) price of ixazomib is it possible for ixazomib with lenalidomide (+DEX) to meet conventional thresholds of cost-effectiveness; a cost of £6 per capsule and £175 per capsule to achieve a £30,000 WTP threshold for the 1 prior therapy and the 2+ prior therapies populations respectivly. This is a paradox that needs to be considered in this appraisal when interpreting the cost-effectiveness of ixazomib.

Within the 2+ prior therapies population analysis, another scenario considered only costing the additional LEN+DEX in the IXA+LEN+DEX regimen, over and above what was received in the LEN+DEX regimen; this reduced the ICER from [redacted] to [redacted]. Whilst exploratory for the 2+ prior line population this ICER is potentially more representative of the cost-effectiveness of IXA+LEN+DEX compared to current UK standard of care, as without the introduction of IXA to the UK market LEN+DEX would still be administered. Therefore, tt should be considered that the consequences of introducing IXA+LEN+DEX should only include the costs associated with IXA and the additional LEN+DEX for a fair assessment of the cost-effectiveness of IXA+LEN+DEX vs LEN+DEX.

The current base case ICERs (presented in this submission without a PAS) are not sufficient for IXA+LEN+DEX to be considered as a cost-effective use of resources based on conventional cost-effectiveness thresholds used by NICE. However, we believe the high uncertainty and the potential for improved cost-effectiveness makes IXA a candidate for funding via the CDF alongside a data collection plan (see Section 1.5 and Section 5.11.1).

A PAS consisting of a simple price discount on the list price of ixazomib has been submitted to PASLU, and the results are presented with PAS in the separate PAS template. This PAS is designed to give a price of ixazomib similar to other treatments routinely used in clinical practice for RRMM. The PAS improves the cost-effectiveness of IXA+LEN+DEX vs. the comparators considered.

1.4.1 Incremental cost-effectiveness results

Incremental analysis was not applicable as there was only one comparator for each of the two patient populations of interest.

1.5 Consideration for Cancer Drugs Fund (CDF)

As of July 2016, NICE is able to recommend a medicine for use within the CDF when it considers there to be plausible potential for the medicine to satisfy the criteria for routine commissioning but there remains uncertainty surrounding the clinical data. Takeda believes ixazomib is a potentially suitable candidate to be recommended for inclusion within the CDF for two years (up to Q3 2019), as this would enable the collection of key clinical data such as more mature overall survival and time on treatment data which would better inform the cost-effectiveness of the IXA+LEN+DEX regimen (see also section 5.11.1).

The TOURMALINE MM-1 study was designed with three sequential interim analyses plus a final analysis for OS. At the first interim analysis (~15 months median follow up), the PFS results crossed the pre-specified O'Brien-Fleming boundary demonstrating a statistically significant benefit of the IXA+LEN+DEX regimen versus LEN+DEX (HR 0.74, 95% CI 0.59-0.94, p=0.012). As per the statistical plan, this was the final statistical analysis of PFS and the study has continued in a double-blind manner in order to obtain more mature OS data.

At time of this NICE submission, there have been two interim analyses (IA1 and IA2 at ~15 months and ~23 months follow up, respectively). At IA1, only 107 (22%) of the pre-specified 486 deaths required for the final OS analysis had occurred (51 in the IXA+LEN+DEX arm and 56 in the LEN+DEX arm). At the second interim analysis, there were 171 deaths (81 in the IXA+LEN+DEX group, 90 in the LEN+DEX group), which represents only 35% of the pre-specified number of deaths required for final OS analysis. Both interim analyses have indicated a trend for an OS advantage with IXA+LEN+DEX versus LEN-DEX. This trend is present within both the ITT population (HRs 0.9 and 0.87) and the stratified 2-3 prior line subgroup (HRs 0.62 and 0.65; see Table 5). Therefore, due to the short follow up and limited number of deaths, OS results are immature and likely underestimate the true OS benefit with IXA+LEN+DEX. The third interim and final OS analyses are due in Q2 2017 and Q3 2019, respectively. With this additional follow up, a statistically significant OS benefit may emerge.

In addition, more mature data would provide increased certainty related to duration of treatment. This would better inform time on treatment, as the current short follow up may result in an overestimation in the modelled duration of time on treatment. Inclusion of ixazomib on the CDF would therefore allow RRMM patients to benefit from interim access to the all oral triplet IXA+LEN+DEX regimen, while OS and time on treatment results mature within the TOURMALINE MM-1 study.

Table 5: Summary of OS Results at the First and Second Interim Analyses

Variable	Entire ITT population			Subgroup: 2-3 prior lines		
	IRd (N=360)	Rd (N=362)	Statistical analysis: HR (95% CI)	IRd (N=148)	Rd (N=149)	Statistical analysis: HR (95% CI)
First interim analysis: median follow-up of ~15 months						
OS: median, months	NE	NE	HR: 0.90 (0.62, 1.32)	NE	NE	HR: 0.62 (0.35, 1.09)
Second interim analysis: median follow-up of ~23 months						
OS: median, months	NE	NE	HR: 0.87 (0.64, 1.18) p=0.359	NE	NE	HR: 0.65 (0.41, 1.02)
Abbreviations: AE = adverse event; IRd = ixazomib + lenalidomide + dexamethasone; Rd = placebo + lenalidomide + dexamethasone; NE: not estimable						

In addition to more mature OS results and more data on time on treatment from the TOURMALINE MM1 pivotal trial, inclusion in the CDF would allow real-world evidence to be collected on the effectiveness and safety of ixazomib in the UK setting. Since January 2016, ixazomib (for use in combination with LEN and DEX) has been available through a global compassionate use, named patient program (NPP). As of December 2016, a significant number of UK patients have been enrolled into the NPP and have received treatment with IXA+LEN+DEX. Inclusion in the NPP has been restricted to RRMM patients who fulfil the inclusion criteria for TOURMALINE-MM1 and therefore the licenced indication for ixazomib (see Section 2.2.5 for further details). At a recent advisory board, UK clinicians with experience of managing patients on IXA+LEN+DEX within the NPP have confirmed that it would be feasible to retrospectively collect data for PFS, OS, time to next treatment, dose reductions and toxicities. Initiation of a retrospective, non-interventional study using data collected from the NPP could be used to confirm the efficacy and safety of IXA+LEN+DEX in routine UK clinical practice in a population that is reflective of the reimbursed population. However, with a current maximum of only 1 year of follow up, efficacy results will currently be immature and so further, prospective follow-up will be required.

In conclusion, ixazomib is a suitable candidate to be considered for the CDF as the additional two years would allow for data collection to increase the certainty of key clinical parameters with the prospect of more robust overall survival benefit estimates and clarity on the usual duration of treatment that would be expected to lead to improved ICER estimates for IXA+LEN+DEX (see also Section 5.11.1) while allowing timely access to a novel, effective therapy for patients with this incurable disease.

2. The technology

2.1 Description of the technology

2.1.1 Name and therapeutic class

Brand name: Ninlaro®

Approved name: Ixazomib (formulated as ixazomib citrate)

Takeda research compound name: MLN9708

Chemical name: 1,3,2-dioxaborolane-4,4-diacetic acid, 2-[(1R)-1-[[2-[(2,5-dichlorobenzoyl)amino]acetyl]amino]-3-methylbutyl]-5-oxo-

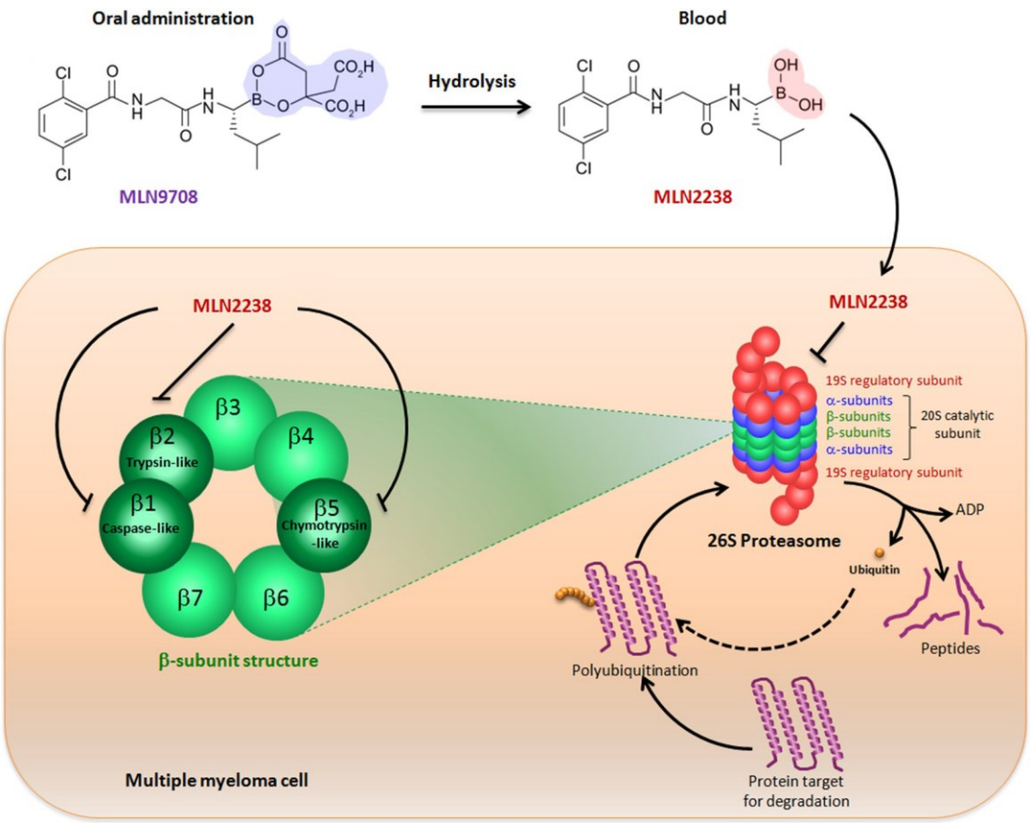
Therapeutic class: Other Antineoplastic Agents, ATC code: L01XX50

2.1.2 Mechanism of action

Ixazomib is a small-molecule, proteasome inhibitor (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. The 26S proteasome is composed of a catalytic proteolytic core (20S) flanked by two regulatory subunits (19S) (Figure 1). Inhibition of the 20S proteasome pathway has been proven important in the treatment of multiple myeloma (MM). Bortezomib, a drug administered intravenously or subcutaneously, was the first PI in class and has validated the proteasome as an effective anti-cancer target in MM. [46] The rationale for targeting the proteasome in MM is that malignant plasma cells produce large amounts of immunoglobulin that eventually has to be degraded, leading to a higher level of proteasome activity than in normal cells [47] When protein homeostasis is disrupted by a PI, the MM cells undergo apoptosis more readily than normal cells, [46] thus conferring selectivity to these agents.

Ixazomib refers to the biologically active, boronic acid form of the drug substance (MLN2238) (Figure 1). The drug substance is administered as a stable citrate ester, ixazomib citrate, a prodrug of ixazomib (MLN9708). In physiological conditions, ixazomib citrate rapidly hydrolyses to the biologically active boronic acid, ixazomib, which potently, reversibly, and selectively inhibits the proteasome (Figure 1). Ixazomib (like bortezomib and another PI, carfilzomib) preferentially binds to and inhibits chymotrypsin-like activity of the β5 subunit of the 20S proteasome and, at higher concentrations, inhibits the activity of the β1 and β2 sites (Figure 1). Whereas carfilzomib is an irreversible inhibitor of the 20S proteasome, ixazomib and bortezomib are both reversible inhibitors, and ixazomib has a shorter proteasome dissociation half-life than bortezomib (i.e inhibition is more rapidly reversible). Ixazomib is the first oral PI to be approved for the treatment of MM. [48]

Figure 1: Mechanism of action of ixazomib



Ixazomib citrate (MLN9708) administered orally as a capsule is rapidly absorbed and hydrolysed to the biologically active form (MLN2238) when it comes in contact with aqueous plasma. Ixazomib blocks protein degradation by inhibiting the 20S catalytic subunit of the 26S proteasome. More specifically, at lower concentrations, MLN2238 inhibits the β5 chymotrypsin-like subunit, which cleaves proteins after hydrophobic residues. At high concentrations, MLN2238 inhibits the β1 caspase-like subunit and β2 trypsin-like subunit, which cleave proteins after acidic and basic residues, respectively. Source: Muz et al 2016 [38]

Cell-based studies have shown ixazomib to result in the anticipated downstream pathway inhibition arising from proteasome inhibition in MM cells, including increased levels of ubiquitinated proteins and apoptotic markers, activation of the endoplasmic reticulum stress response, and up-regulation of proteins degraded by the proteasome such as the tumour suppressor p53 and the cell cycle inhibitor p21. [49] Effects on the nuclear factor-κB pathway have also been demonstrated. [49] In MM cell lines, ixazomib has been shown to reduce cell viability and to have cytotoxicity, and synergistic activity has been demonstrated with lenalidomide. [49] Additionally, disruption of the bone marrow microenvironment has been seen, with ixazomib inhibiting bone marrow stromal cell-induced proliferation, along with promotion of osteoblastogenesis and inhibition of osteoclast activity. [50] In mouse xenograft models of MM, ixazomib resulted in tumour growth inhibition and prolonged survival. [49] and showed inhibition of bone resorption and alleviation of osteolytic bone disease. [50,51] Marketing authorisation/CE marking and health technology assessment.

2.1.3 UK marketing authorisation

On November 21st 2016, the European Commission granted a conditional marketing authorisation for Ninlaro® (ixazomib).

2.1.4 Indication

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*."

The SmPC posology indicates that ixazomib is used in combination with lenalidomide and dexamethasone. The SmPC is shown in Appendix 1.

2.1.5 Restrictions and contraindications

The SmPC for ixazomib states the following contraindications, and special warnings and precautions for use.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in

Table 6.

Table 6: Excipents in ixazomib (NINLARO)

Components	NINLARO 4 mg hard capsules	NINLARO 3 mg hard capsules	NINLARO 2.3 mg hard capsules
Capsules contents	Microcrystalline cellulose Magnesium stearate Talc	Microcrystalline cellulose Magnesium stearate Talc	Microcrystalline cellulose Magnesium stearate Talc
Capsules shell	Gelatin Titanium dioxide (E171) Yellow iron oxide (E172) Red iron oxide (E172)	Gelatin Titanium dioxide (E171) Black iron oxide (E172)	Gelatin Titanium dioxide (E171) Red iron oxide (E172)
Printing ink	Shellac Propylene glycol Potassium hydroxide Black iron oxide (E172)	Shellac Propylene glycol Potassium hydroxide Black iron oxide (E172)	Shellac Propylene glycol Potassium hydroxide Black iron oxide (E172)

Special warnings and precautions for use

Thrombocytopenia
Thrombocytopenia has been reported with ixazomib with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next
cycle.

Platelet counts should be monitored at least monthly during ixazomib treatment. More frequent monitoring should be considered during the first three cycles as per the lenalidomide SmPC. [52] Thrombocytopenia can be managed with dose modifications and platelet transfusions as per standard medical guidelines.

Gastrointestinal toxicities
Diarrhoea, constipation, nausea and vomiting have been reported with ixazomib, occasionally requiring use of antiemetic and antidiarrhoeal medicinal products and supportive care. The dose should be adjusted for severe

(Grade 3–4) symptoms. In case of severe gastrointestinal events, monitoring of serum potassium level is recommended.

Peripheral neuropathy
Peripheral neuropathy has been reported with ixazomib. The patient should be monitored for symptoms of peripheral neuropathy. Patients experiencing new or worsening peripheral neuropathy may require dose modification.

Peripheral oedema
Peripheral oedema has been reported with ixazomib. The patient should be evaluated for underlying causes and provide supportive care, as necessary. The dose of dexamethasone should be adjusted per its prescribing information or ixazomib for Grade 3 or 4 symptoms.

Cutaneous reactions
Rash has been reported with ixazomib. Rash should be managed with supportive care or with dose modification if Grade 2 or higher.

Hepatotoxicity
Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have been uncommonly reported with ixazomib. Hepatic enzymes should be monitored regularly and the dose should be adjusted for Grade 3 or 4 symptoms.

Pregnancy
Women should avoid becoming pregnant while being treated with ixazomib. If ixazomib is used during pregnancy or if the patient becomes pregnant while taking ixazomib, the patient should be apprised of the potential hazard to the foetus.

Women of childbearing potential must use highly effective contraception while taking ixazomib and for 90 days after stopping treatment. Women using hormonal contraceptives should additionally use a barrier method of contraception.

Posterior reversible encephalopathy syndrome
Posterior reversible encephalopathy syndrome (PRES) has occurred in patients receiving ixazomib. PRES is a rare, reversible, neurological disorder, which can present with seizure, hypertension, headache, altered consciousness, and visual disturbances. Brain imaging, preferably Magnetic Resonance Imaging, is used to confirm the diagnosis. In patients developing PRES, discontinue ixazomib.

Strong CYP3A inducers
Strong inducers may reduce the efficacy of ixazomib, therefore the concomitant use of strong CYP3A inducers such as carbamazepine, phenytoin, rifampicin and St. John's Wort (Hypericum perforatum), should be avoided. Closely monitor patients for disease control
if co-administration with a strong CYP3A inducer cannot be avoided.

2.1.6 Regulatory process and timelines

On 30th July 2015, Takeda applied for marketing authorisation for ixazomib to the European Medicines Agency (EMA), using the centralised procedure. The Committee for Medicinal Products for Human Use (CHMP) of the EMA

granted an accelerated assessment to ixazomib; this is awarded to medicines deemed to be of major public health interest and, in particular, therapeutic innovation.

The EMA dossier was based on the same dataset utilised for the US FDA submission, which led to FDA approval in November 2015. Following data submissions and scientific discussions, the CHMP acknowledged that the TOURMALINE-MM1 study had met its primary endpoint at the first pre-planned interim analysis with a clinically significant median increase of PFS with the ixazomib regimen (IXA+LEN+DEX) versus control (LEN+DEX) (HR 0.74; p=0.012), especially as it showed a consistent benefit in patients with high-risk cytogenetic abnormalities, across subgroups, and other endpoints. In addition, no important uncertainties were identified in relation to ixazomib's safety profile. As the primary endpoint had been achieved this became the final statistical analysis for PFS. In accordance with the study protocol plan all future statistical analyses (pre-specified interim analyses 2, 3 and Final) would be assessing overall survival. At the time of the second interim analysis (data cut July 2015; ~23 months follow up) an analysis on overall survival was conducted in line with the study protocol. In addition, there was a non-inferential analysis of PFS, overall response rates and TTP for the ITT population and this showed a reduced difference in effect between arms compared to the first interim analysis (hazard ratio for PFS of 0.82 (95% CI 0.67, 1.0; p=0.054). As the p-value for the primary endpoint was higher than that usually required by the EMA for a medicine with a single pivotal trial the CHMP requested that Takeda look to identify a subgroup of patients with a poor prognosis where the risk-benefit of ixazomib was more certain. Takeda and the CHMP were unable agree on such a subgroup within the constraints of the regulatory timeframe. The CHMP therefore issued a negative opinion for ixazomib on 26th May 2016.

Following the negative CHMP opinion, Takeda submitted an appeal for a re-examination. As part of the appeal, on September 5th 2016, the CHMP consulted with an independent Scientific Advisory Group (SAG) for Oncology which included multiple myeloma experts. The SAG reached the following conclusions:

- The SAG considered unanimously that the data submitted on the basis of the primary ITT analysis of PFS of TOURMALINE-MM1 (HR=0.742; p=0.012), and, importantly, the favourable toxicity profile, established a clear positive benefit-risk balance in the ITT population.
- The SAG discussed the results of the second interim analysis and concerns on data maturity. The SAG considered that on the basis of the primary PFS analysis (i.e. the first interim analysis), which was conducted according to the pre-specified statistical considerations, the trial had met its objective of showing a statistically and clinically significant improvement in PFS.
- The maturity of the dataset was considered adequate and consistent with that of other pivotal trials in this setting. The number of events was considered to be in line with what is generally expected in the field for trials of this size in this patient population. Hence, the ITT analysis was therefore considered mature and the observed effect (an approximate 6-month improvement in median PFS) as clinically relevant. The SAG concluded that the fact that a subsequent exploratory interim analysis showed some uncertainty about the level of statistical significance was not enough to change their conclusions about a clear beneficial effect in terms of PFS on the basis of the pre-planned (and, for PFS, the final) analysis.
- The supportive data from the China Continuation Study (a Phase III, randomised, double-blind, multicentre study comparing oral IXA+LEN+DEX versus LEN+DEX in adult patients with RRMM) provided corroborative findings in terms of a statistical and clinically significant effect in terms of PFS (HR=0.598; p=0.035). The robustness of this conclusion is also supported by internal consistency; namely, the favourable trends in terms of OS in the pivotal and supportive studies (HR=0.868, p=0.36, and HR=0.323, p=0.013, respectively).
- Concerning the benefit-risk balance, given the favourable toxicity profile of ixazomib, the SAG was confident that a positive benefit-risk balance has been established for ixazomib.

- The SAG also considered that ixazomib is the first agent to allow oral triple combination therapy, which represents a therapeutic innovation in terms of convenience for patients.
- The fact that the results are based on a single pivotal trial is not considered an issue in view of the convincing results, the supportive evidence from the China Continuation Study and the entirety of the evidence.

Following the advice from the SAG and considering all of the detailed grounds for re-examination, including review of data on quality, safety and efficacy, the CHMP concluded that the delay in disease progression observed with ixazomib in the TOURMALINE-MM1 study was clinically relevant. Any remaining uncertainty seemed acceptable given the favourable toxicity profile, and that ixazomib is the first agent to allow oral triple combination therapy in this patient population, which represents a therapeutic innovation in terms of convenience for patients. Therefore, on 15th September 2016 the CHMP re-examined its initial opinion and, in its final and binding opinion, recommended the granting of a conditional marketing authorisation for Ninlaro (ixazomib) in the following indication:

''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''

The CHMP considered that ixazomib fell within the scope of European Commission regulations concerning the granting of a conditional marketing authorisation and fulfilled this on the basis that:

a) The benefit/risk balance of ixazomib is positive:

The 5.9 months gain in PFS data observed in the final statistical analysis of PFS in the ITT population in TOURMALINE-MM1 is significant and clinically relevant in RRMM (as part of its analysis the CHMP concluded that recently approved drugs for the treatment of MM have shown improvements in median in PFS in the range of 4 to 6 months). Together with the low toxicity of ixazomib and the benefit of the oral dosing regimen, the benefit-risk balance is considered positive.

b) As part of the conditional marketing authorisation, Takeda will provide additional data to confirm efficacy and safety of ixazomib from ongoing studies, including:

- The 3rd interim analysis and final OS report from the TOURMALINE-MM1 study.
- Final OS results from C16010 China Continuation study (a Phase III, randomised, double-blind, multicentre study comparing oral ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with RRMM).
- Primary endpoint PFS results from study C16014 (a Phase III, randomised, double-blind, multicentre study comparing oral ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with newly diagnosed MM not eligible for ASCT).
- Primary endpoint PFS results from study C16019 (a Phase III, randomised, placebo-controlled, double-blind study of oral ixazomib maintenance therapy in patients with MM following ASCT).
- Descriptive data from study NSMM-5001 (a global, prospective, non-interventional, observational study of presentation, treatment patterns, and outcomes in MM patients).

Data is expected to be provided by Takeda to the EMA for the China Continuation study by December 2016, for the study C16014 by December 2017, for the study C16019 by December 2018, and for study NSMM-5001 and TOURMALINE-MM1 by December 2019.

c) Ixazomib fulfils an unmet medical need:

The efficacy benefit of ixazomib is comparable with other therapies, but due to the significantly lower toxicity and the additional benefits of an oral dosing regimen, this product provides a major therapeutic advantage in comparison with available treatments and an important contribution to the care of patients with MM. The oral delivery of the ixazomib regimen addresses multiple myeloma patient needs and overcomes some of the significant burdens they face with currently available intravenous/ injectable therapies.

d) The benefits to the public health of the immediate availability of ixazomib outweighs the risks inherent in the fact that additional data are still required

Considering that ixazomib has favourable safety profile that is superior to that of the available alternatives, and that it is the first agent to allow oral therapy in this patient population (considerably improving convenience for patients), the immediate availability of ixazomib outweighs the risk inherent in the fact that additional data are still required.

Subsequently, on November 21st 2016 the European Commission granted conditional marketing authorisation for Ninlaro (ixazomib), indicated in combination with lenalidomide and dexamethasone for adult patients with multiple myeloma who have received at least one prior therapy. In addition at its meeting held on 4-6th October 2016 the EMA's Committee for Orphan Medicinal Products (COMP) concluded that ixazomib's designation as an orphan medicinal product should be maintained for the treatment of multiple myeloma (Orphan decision number EU/3/11/899, originally granted on 27th September 2011).

The EPAR is publically available. [53]

2.1.7 Expected date of availability in the UK

Takeda UK will not launch commercial stock until confirmed availability of NHS funding, either on receipt of a NICE positive recommendation or via the new Cancer Drugs Fund (CDF). During the period between EC approval (November 2016) and commercial stock availability, ixazomib (for use in combination with lenalidomide and dexamethasone) will continue to remain available through a global compassionate use, named patient program (NPP). This NPP has been open since January 2016 and access has been restricted to RRMM patients who fulfil the inclusion criteria for TOURMALINE-MM1. This is consistent with the European Marketing Authorisation where the positive risk-benefit of IXA+LEN+DEX has been demonstrated. When a final reimbursement decision is made, the NPP will immediately cease to include new patients. At this time, should ongoing therapy for existing patients already enrolled in the NPP not be covered by the reimbursement decision, then ixazomib will continue to be provided to such patients through the existing NPP process.

The availability of ixazomib through the NPP has not been promoted by Takeda and therefore enrolment has been solely restricted to unsolicited, compassionate use requests from physicians. As of 2nd December 2016, a substantial number of RRMM patients in the UK and Ireland have been enrolled across 51 sites. The significant uptake of the NPP highlights the unmet need for effective RRMM treatments and also shows the level of clinician demand for ixazomib. The decision to continue the NPP after receipt of Marketing Authorisation shows Takeda's commitment to support the clinical community and ensure the best outcomes for myeloma patients.

2.1.8 Regulatory approval outside the UK

In November 2015, the US Food and Drug Administration (FDA) approved ixazomib in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least

one prior therapy. [54] The FDA granted ixazomib priority review (given to drugs that, if approved, would be a significant improvement in safety or effectiveness in the treatment of a serious condition) and orphan drug designation for ixazomib. [55] Ixazomib is also licenced in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy in in a number of other countries (Table 7).

Table 7: Ixazomib Worldwide Marketing Authorization Status - APPROVED

Country	MAH	Trade Name	Submission Date	Approval date
United States	Millennium Pharmaceuticals, Inc.	NINLARO®	10-Jul-2015	20-Nov-2015
EU	Takeda Pharma A/S	NINLARO®	30-Jul-2015	21-Nov-2016
Australia	Takeda Pharmaceuticals Australia Pty Ltd.	NINLARO®	28-Sep-2015	15-Nov-2016
Canada	Takeda Canada Inc.	NINLARO™	11-Dec-2015	04-Aug-2016
Israel	Takeda Israel Ltd.	NINLARO®	07-Sep-2015	14-Aug-2016
Venezuela (MSP)	Takeda S.R.L.	NINLARO® 2.3 mg capsule	30-Mar-2016	15-Jun-2016
Venezuela (MSP)	Takeda S.R.L.	NINLARO® 3 mg capsule	30-Mar-2016	12-May-2016
Venezuela (MSP)	Takeda S.R.L.	NINLARO® 4 mg capsule	30-Mar-2016	13-Jun-2016
South Africa	Takeda (Pty) Ltd.	NINLARO®	30-Oct-2015	Under Review
Switzerland	Takeda Pharma AG	NINLARO®	24-Sep-2015	Under Review
Taiwan	Takeda Pharmaceuticals Taiwan, Ltd	NINLARO	28-Oct-2016	Under Review
Turkey	Takeda İlaç Sağlık Sanayi Ticaret Limited Şirketi (Takeda Turkey)	NINLARO®	19-Oct-2016	Under Review
Venezuela	Takeda S.R.L.	NINLARO® 2.3 mg capsule	10-Nov-2016	Under Review
Venezuela	Takeda S.R.L.	NINLARO® 3 mg capsule	16-Nov-2016	Under Review
Venezuela	Takeda S.R.L.	NINLARO® 4 mg capsule	17-Nov-2016	Under Review
Abbreviations: MAH = marketing authorisation holders; MSP = Medical Service Product				

2.1.9 Other health technology assessments in the UK

Ixazomib is expected to be appraised by the Scottish Medicines Consortium (SMC), with submission currently scheduled for Q1 2017.

2.2 Administration and costs of the technology

2.2.1 Administration and costs of ixazomib

Details of the ixazomib treatment regimen and costs are shown in Table 8.

Table 8: Treatment details and costs of ixazomib

	Administration and Cost	Source
Pharmaceutical formulation	4 mg hard capsules 3 mg hard capsules 2.3 mg hard capsules	SmPC
Acquisition cost (excluding VAT) *	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 lenalidomide and dexamethasone. The acquisition costs of lenalidomide and dexamethasone are: • lenalidomide: £4,368 per 21-tablet (25mg) pack (£208 per tablet) • dexamethasone: £49.00 per 50-tablet (2mg) pack (£0.98 per tablet)	Takeda BNF BNF
Method of administration	Oral	SmPC
Doses	The recommended starting dose of ixazomib is 4 mg (one capsule)[a]	SmPC
Dosing frequency	Once a week on Days 1, 8, and 15 of a 28-day treatment cycle[a]	SmPC
Average length of a course of treatment (i.e. cycle)	Each 28-day period is considered one treatment cycle for ixazomib + lenalidomide + dexamethasone.	SmPC
Average cost of a course of treatment (i.e. cycle)	In combination with lenalidomide and dexamethasone: Ixazomib: £6,336 per cycle Lenalidomide: £4,368 per cycle Dexamethasone: £74.48 per cycle Total: £10.778.48 per cycle	Takeda
Anticipated average interval between courses of treatments	None	
Anticipated number of repeat courses of treatments	Treatment should be continued until disease progression or unacceptable toxicity. Treatment for longer than 24 cycles should be based on an individual benefit risk assessment, as the data on the tolerability and toxicity beyond 24 cycles is limited.	SmPC
Dose adjustments	Dose reductions due to adverse events: first reduction to 3 mg and second reduction to 2.3 mg. An alternating dose modification approach is recommended for ixazomib and lenalidomide for overlapping toxicities of thrombocytopenia and rash. For these toxicities, the first dose modification step is to withhold/reduce lenalidomide. The reduced dose of 3 mg is recommended in patients with moderate (total bilirubin > 1.5-3 x ULN) or severe (total bilirubin > 3 x ULN) hepatic impairment and severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease requiring dialysis.	SmPC
Anticipated care setting	Secondary care (oncology/haematology); potential to explore home care delivery initiated by secondary care.	Takeda

Abbreviations: ULN = upper limit of normal

[a] 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.

Sources: SmPC in Appendix 1; BNF

2.2.2 Patient Access Scheme (PAS)

Takeda UK has submitted a proposed Patient Access Scheme (PAS) for Ninlaro® (ixazomib) to PASLU. The proposed PAS would offer a reduction from the basic NHS list price through a discount applied to all original invoices for Ninlaro. The proposed PAS would be made available to all NHS providers including homecare providers, secondary care, NHS patients in a private hospital, outsourced hospital pharmacies, and primary care via homecare arrangements.

2.3 Changes in service provision and management

2.3.1 Additional tests or investigations

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 lenalidomide and dexamethasone, other than those that are already required for the lenalidomide-dexamethasone regimen.

2.3.2 Resource implications for the NHS

Ixazomib is a convenient fixed-dose once-weekly capsule, and the all-oral combination of IXA+LEN+DEX is expected to have a beneficial impact on healthcare resource use within the NHS, in addition to reducing the treatment burden for both patients and caregivers.

The most relevant comparators in the NICE scope are:

- for people who have had at least 1 prior therapy: bortezomib with dexamethasone
- for people who have had 2 prior therapies: lenalidomide with dexamethasone

The PI bortezomib requires parenteral administration (i.e. subcutaneous [SC] or intravenous [IV]) in a clinic/hospital; the approved dosing schedule (invariably given with dexamethasone) requires two patient visits to the clinic per week for weeks 1 and 2 of the 21-day treatment cycle for cycles 1-8 (i.e. 32 visits over 8 cycles) [27,28] In the UK, it is common practice for bortezomib to be given once weekly and by subcutaneous injection, because this is associated with fewer adverse reactions, and therefore patients are able to receive the full 32 doses. [3]

The need for healthcare professionals to administer SC or IV bortezomib inevitably increases the burden on NHS resources and costs. In addition, this demanding treatment schedule may adversely affect the patient and/or caregiver financially (e.g. travel costs, time away from work [29]) as well as impacting on their quality of life (e.g. the unpleasantness of having injections; time spent travelling and at the clinic/hospital) [30-35] This is particularly relevant for multiple myeloma patients as bone degradation, fractures and fatigue are common symptoms of the disease, thereby compromising patients' mobility and increasing the importance of minimising travel. In contrast, the completely oral IXA+LEN+DEX regimen can be taken at home (Table 9), giving patients greater control over their treatment and their lives.

Table 9: Recommended dosing schedule of BORT+DEX, LEN+DEX, and IXA+LEN+DEX

BORT+DEX[a]															
Treatment schedule (Day taken)	**Week 1**							**Week 2**							**Week 3**
Cycles 1-8															
BORT (SC or IV)[b,c]	1			4				8			11				Rest period
DEX (oral)	1	2		4	5			8	9		11	12			Rest period
Cycles 9-16															
BORT (SC or IV)[b]	1							8							Rest period
DEX (oral)	1	2						8	9						Rest period
LEN+DEX															
Treatment schedule (Day)	**Week 1**							**Week 2**							**Week 3**	**Week 4**
LEN (oral)	Daily							Daily							Daily	
DEX (oral)	1							8							15	22
IXA+LEN+DEX															
Treatment schedule (Day)	**Week 1**							**Week 2**							**Week 3**	**Week 4**
IXA (oral)	1							8							15	
LEN (oral)	Daily							Daily							Daily	
DEX (oral)	1							8							15	22

Abbreviations: BORT = bortezomib; DEX = dexamethasone; IV = intravenous; IXA = ixazomib; LEN = lenalidomide; SC = subcutaneous

[a] The approved dosing schedule is shown; however in clinical practice in the UK BORT is commonly given once weekly by SC injection for up to 32 doses

[b] BORT requires parenteral administration in a clinic/hospital

[c] For the approved schedule is for BORT administered twice weekly for two weeks on days 1, 4, 8, and 11 in a 21-day treatment cycle. This 3-week period is considered a treatment cycle. It is recommended that patients receive 2 cycles of BORT following a confirmation of a complete response. It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of bortezomib therapy

Source: Velcade SmPC [27]; Revlimid SmPC [52], Ixazomib SmPC (Appendix 1)

The IXA+LEN+DEX triplet regimen is not expected to have a significant impact on NHS resource utilisation compared to the existing LEN+DEX doublet regimen. In the TOURMALINE-MM1 study (the pivotal Phase III RCT assessing the efficacy and safety of IXA+LEN+DEX compared to LEN+DEX), an exploratory analysis at the first interim analysis (median follow-up of ~15-months) suggested that healthcare resource utilisation was lower with IXA+LEN+DEX versus LEN+DEX, based on rates per 100-patient-years of treatment exposure, which may potentially translate into lower costs of disease management [42] Rates of hospitalisations (56.0 vs. 63.4), acute care unit stays (45.5 vs. 51.8), outpatient visits (299.3 vs. 343.8), study physician/site visits (72.7 vs. 99.4), other physician/clinic visits (146.7 vs. 168.2), and palliative care unit stays (4.4 vs. 7.2) were lower with IXA+LEN+DEX, whereas the rate of emergency room stays (18.7 vs. 12.1) was higher and the rate of intensive care unit (ICU) stays (3.4 vs. 2.5) was similar. A second interim analysis with a median follow-up of ~23-months also demonstrated that, compared to patients in the LEN+DEX regimen, patients in the IXA+LEN+DEX regimen had lower numbers of hospitalisations (53.0 vs. 56.4), acute care unit stays (41.1 vs. 46.3), study physician/site visits (88.9 vs. 93.9), and other physician/clinic visits (167.7 vs. 181.0); a higher number of emergency room stays (14.3 vs. 10.9); and similarly low numbers of palliative care unit stays 6.9 vs. 6.2) and ICU stays (3.4 vs. 2.4). Because the 95% CIs

overlapped, health care utilisation in the two treatment groups would be assessed as similar overall, despite the addition of a third active agent.

2.3.3 Concomitant therapies

Ixazomib is indicated in combination with lenalidomide and dexamethasone (as the IXA+LEN+DEX regimen; see SmPC [Appendix 1]).

Anti-viral prophylaxis should be considered in patients being treated with ixazomib to decrease the risk of herpes zoster reactivation. Patients included in studies with ixazomib who received anti-viral prophylaxis had a lower incidence of herpes zoster infection compared to patients who did not receive prophylaxis. As for the existing LEN+DEX regimen, thromboprophylaxis is recommended in patients being treated with IXA+LEN+DEX (based on the know side-effect profile of lenalidomide), and should be based on an assessment of the patient's underlying risk and clinical status (see SmPC).

2.4 Innovation

Ixazomib is the first and currently the only approved oral PI. This is a step-change in the management of MM, providing the benefits of a triplet regimen of a PI, an immunomodulatory drug (lenalidomide) and a corticosteroid (dexamethasone) but in an all-oral regimen that can be taken at home. Ixazomib offers a convenient, fixed dose, once-weekly, single capsule administration. The all-oral IXA+LEN+DEX triplet regimen represents a therapeutic innovation by offering practical and logistical benefits to patients, caregivers, healthcare professionals and the broader NHS, particularly versus the parenteral treatments that are currently available and widely used.

The IXA+LEN+DEX triplet is well tolerated and it offers the efficacy benefits of a triplet regimen, without significant increased toxicity versus the doublet LEN+DEX regimen. This favourable toxicity profile is predicted to enable continuation of treatment, leading to a durable response. These factors have been included in the QALY.

However, one factor that has not been included in the QALY is the unmet need for such a regimen. MM is characterised by multiple relapses and, at present, there are relatively few treatment options that are funded in England and Wales in the second and third line setting (see Section 3.3). Therefore, ixazomib would be a welcome addition to the therapeutic armamentarium, with the added advantage of a convenient all-oral regimen that is efficacious with a good tolerability profile. In May 2016,a letter in support of ixazomib was sent to the CHMP by the following organisations: Myeloma UK, the British Society of Haematology, the UK Myeloma Forum, as well as Myeloma Patients Europe and other European organisations. The letter documents the strong clinical support for using ixazomib in RRMM, as evidenced by the widespread uptake of ixazomib through the EMA approved compassionate use programme. [36]

Another factor which is not included in the QALY is the benefit that ixazomib can offer to a patient's carer by reducing the burden of treatment on them (e.g. reduced need to accompany the patient to hospital visits, freeing up time for other activities). For patients who are still in employment there are potential benefits for the economy/society, for example by allowing patients to continue working or reducing the amount of time they need to take off work for clinic visits to receive injectable therapies.

3. Health condition and position of the technology in the treatment pathway

3.1 Overview of multiple myeloma and its course

3.1.1 Disease course of MM and relapsed or refractory multiple myeloma (RRMM)

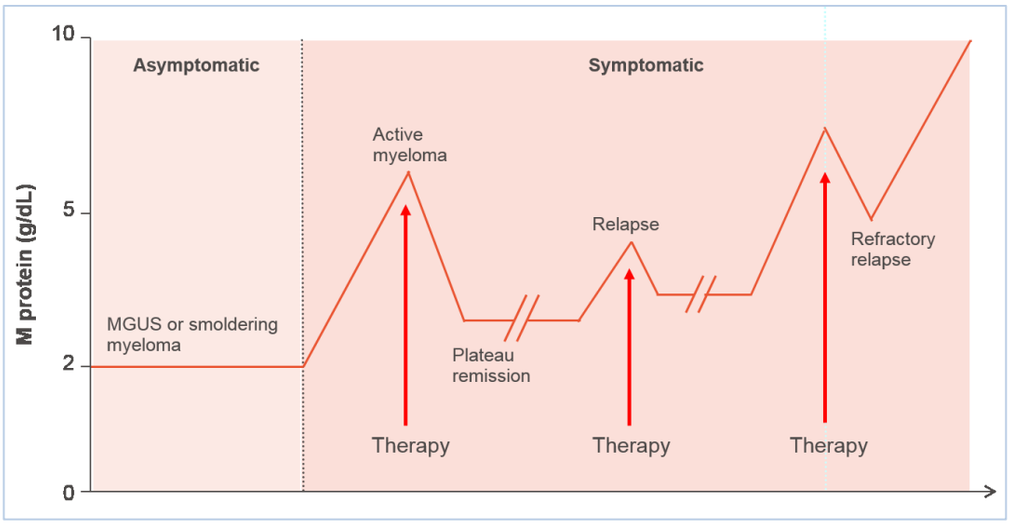
Multiple myeloma (MM) is a malignant plasma cell disorder that accounts for approximately 1.6% of all neoplasms and 16.6% of haematologic malignancies. [56] It is classified as an orphan (rare) disease (defined in the EU as a prevalence not exceeding 5 in 10,000 people), primarily affecting elderly patients (see Section 3.4.1). Ixazomib was granted orphan drug designation in MM in both the U.S. and Europe in 2011.

Plasma cells are an important part of the immune system and are responsible for producing specific antibodies to fight infections. [6] Different clones of plasma cells make numerous types of antibodies (immunoglobulins); MM occurs when a malignant transformation results in a population of clonal plasma cells that divide uncontrollably [5] and produce large quantities of one antibody (monoclonal Ig protein or M-protein) [6] The malignant myeloma cells most commonly produce IgG or IgA, or rarely IgD, IgM, or IgE, M-protein; in approximately a fifth of cases, there is no heavy chain, only the overproduction of κ and λ light chains. [57] The production of large quantities of antibody leads to unfolded immunoglobulins within the myeloma cells, which eventually needs to be degraded via the ubiquitin-proteasome system (UPS). MM cells have a higher level of proteasome activity than normal cells to deal with these unfolded proteins, and disruption of protein homeostasis by a proteasome inhibitor (PI) such as ixazomib results in apoptosis of the MM cells more readily than normal cells.

MM is an incurable progressive disease, characterised by multiple relapses; after a successful initial treatment resulting in stable disease or remission, nearly all patients will eventually relapse and will require further therapy. It typically recurs with a more aggressive disease course after each remission, resulting in shorter duration of response with each successive line of therapy and eventually treatment-refractory disease. [9]

Figure 2 is a schematic representation of the typical disease course in MM. Patients who have relapsed after treatment or who have refractory MM (i.e. RRMM) represent the population of interest in this submission.

Figure 2: Typical MM disease course

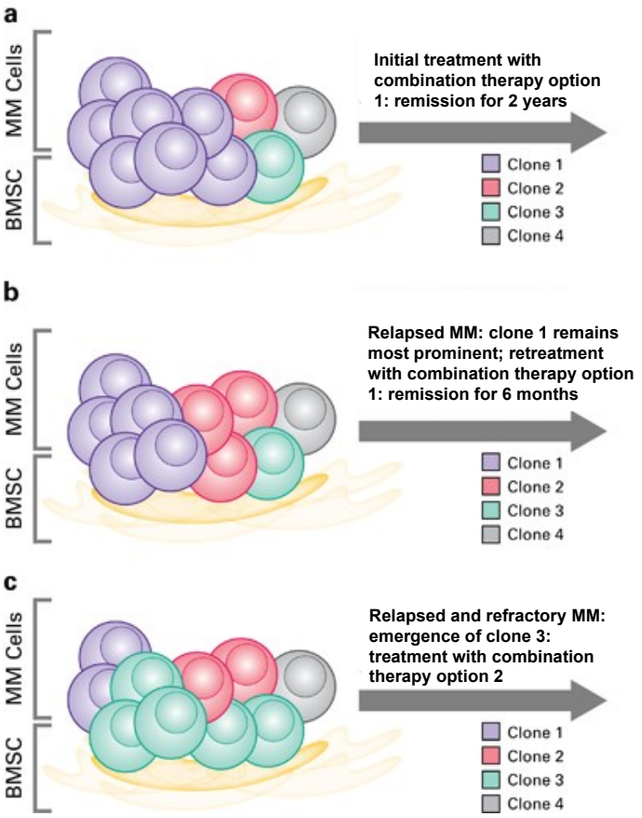


Abbreviations: M = monoclonal; MGUS = monoclonal gammopathy of undetermined significance
Source: Adapted from Durie, 2011 [58]

Recent advances in genome sequencing have provided evidence of both clonal heterogeneity and shifting clonal dominance over time in MM, [13] which are thought to contribute to drug resistance and relapse over the course of treatment (Figure 3) [13] The clonal evolution occurs over time because of selective pressures from treatment and the bone marrow microenvironment, [13,59] involving either the re-emergence of the dominant clone, linearly acquired mutations within the dominant clone or evolution of a prediagnostic clone with newly acquired mutations. Clonal heterogeneity may at least partly explain the high level of heterogeneity that is observed clinically among RRMM patients, both in terms of disease presentation and their response to treatment.

Combination therapy regimens are frequently used to treat patients with MM; clonal heterogeneity may, at least in part, explain the success of combination therapy in MM as the different therapies can target coexisting sub-clones. [13] The heterogeneity of MM also emphasises the need for physicans to have access to a range of different treatment options so that combination regimens can be tailored to the needs of individual patients.

Figure 3: Hypothetical and illustrative example of clonal evolution and heterogeneity in patients with MM over the disease course



Abbreviations: BMSC = bone marrow stromal cells; MM = multiple myeloma
Source: Adapted from Cornell and Kassim, 2016 [13]

3.1.2 Risk assessment: Staging and cytogenetics

The clinical course of MM is highly heterogeneous with survival times ranging from a few weeks in some patients to >20 years for others. [60,61] Many studies have identified prognostic factors capable of predicting at least some of this heterogeneity in survival. For example, the International Staging System (ISS) is a powerful tool that defines 3 risk categories based on the serum concentration of β2-microglobulin and albumin. [60,61]

In addition, certain cytogenetic and molecular genetic abnormalities have been shown to predict outcome in MM. Immunoglobulin heavy chain gene translocations including t(4;14), t(14;16) and t(14;20), as well as copy number changes such as gain of chromosome 1q or deletion of chromosome 17p13 (del[17p]) demonstrated by fluorescence in situ hybridisation (FISH), are associated with adverse outcomes such as more aggressive disease and shorter survival. [37,60,61] The identification of these high-risk subgroups by FISH is recommended by NICE Clinical Guidelines (NG35) [62] and other clinical practice guidelines. [37,60-62]

The International Myeloma Working Group (IMWG) has recently published consensus guidelines on risk categories for MM that incorporate the ISS together with best available data on cytogenetics. [63] In addition, the Mayo Clinic

(US) has also published a risk stratification system for MM —the Mayo Stratification of Myeloma and Risk Adapted Therapy (mSMART) [64] (Table 10). As can been seen in Table 10 patients in the high-risk categories have a particularly poor prognosis, with a median overall survival of 2–3 years despite best available treatments, and are therefore in need of new treatments.

Although not a specific focus of this submission, the benefits of IXA+LEN+DEX have been demonstrated consistently across key pre-specified subgroups, including patients with high-risk cytogenetic abnormalities; there is a high unmet need in these patients for whom LEN+DEX is emerging as a sub-optimal treatment. [41]

Table 10: IMWG and Mayo Clinic (mSMART) risk stratification of MM

IMWG risk stratification in MM			
	High-risk	**Standard-risk**	**Low-risk**
Parameters	ISS II or III; and t(4;14) or 17p13 del	Others	ISS I or II; and absence of t(4;14), 17p13 del and +1q21; and age <55yrs
Median OS	2 years	7 years	>10 years
% patients	20%	60%	20%
Mayo Clinic (mSMART) risk stratification of MM			
	High-risk	**Intermediate-risk**	**Standard-risk**
Parameters	• FISH: del 17p, t(14;16), t(14;20) • GEP: high-risk signature	• FISH: t(4;14) • Cytogenic del 13 • Hypodiploidy • PCLI ≥3%	All others including: FISH: t(11;14), t(6;14)
Median OS	3 years	4–5 years	8–10 years
% patients	20%	20%	60%
Mayo Clinic (mSMART) risk stratification of RRMM			
	High-risk	**Intermediate-risk**	**Standard-risk**
Parameters	• Relapse <12 months from transplant or progression within first year of diagnosis • FISH: del 17p, t(14;16), t(14;20) • High-risk GEP	• FISH: t(4;14), 1q gain • Complex karyotype • Metaphase deletion 13 or hypodiploidy • High PC S-phase	All others including: • Trisomies • t(11;14) • t(6;14)
Abbreviations: FISH = fluorescence in situ hybridisation; GEP = gene expression profiling; ISS = International Staging System; PC = plasma cell; PCLI = plasma cell labeling index Source: Chng et al., 2014 [63] Mikhael et al., 2013 [64] Mayo Clinic, 2015 [65]			

3.1.3 Symptoms of MM

MM is associated with anaemia, bruising or bleeding (caused by platelet deficiency), and increased risk of infection due to overcrowding of the bone marrow and overproduction of one type of unwanted antibody. [6] These arise as a result of the expanding myeloma cell population in the bone marrow compartment preventing normal reproduction of other blood cell types.[6]

Other features, such as kidney and other end-organ damage, as well as hyperviscosity of the blood, result from the overproduction of M-protein and light chains in particular. The classic diagnostic symptoms of bone pain and the presence of lytic bone lesions are caused by the malignant plasma cells stimulating osteoclasts and suppressing

osteoblasts, thereby leading to increased bone resorption. Furthermore, in the bone marrow microenvironment, myeloma cells create a pro-survival supportive signalling network with the stromal cells, producing cytokines and angiogenic factors that promote blood vessel formation and facilitate the survival of the malignant cells. These effects give rise to the classical 'CRAB' diagnostic criteria for active MM: hypercalcemia, renal impairment, anaemia, and bone lesions. [57] Patients typically present with at least one of these criteria at diagnosis, as well as a number of associated symptoms such as fatigue, bone pain, and fractures. [66,67]

3.2 The effects of multiple myeloma on patients, carers and society

3.2.1 Impact of symptoms on quality of life

The main signs and symptoms of MM including pain and bone disease, anaemia, fatigue, hypercalcaemia, renal impairment and recurring infections, heavily impact on the quality of life (QoL) of patients, as described in Table 11.

Table 11: Clinical signs and symptoms of MM, causal factor(s), clinical manifestation and frequency, and impact/burden on patients

Clinical feature	Causal factor(s)	Manifestation	Impact/ burden	
Hypercalcaemia	• Release of calcium from damaged bone into bloodstream.	• ~13% of patients have hypercalcaemia at diagnosis but it may develop at any time over the course of the disease.	• Weakness • Fatigue • Polydipsia • Polyuria • Constipation • Anorexia	• Nausea • Vomiting • Mental confusion • Coma • Chronic renal failure (if not recognised and treated)
Renal impairment	• Cast nephropathy (plugs of secreted monoclonal light chains in renal tubules). • High blood calcium and infections can also induce or increase severity of kidney damage.	• 30% to 40% of patients have a serum creatinine concentration above the upper limit of normal at diagnosis.	• Contributes to early death in 28% of patients. • Associated with increased all-cause mortality.	
Anaemia	• Decrease in both number and activity of cells that produce red blood cells in the bone marrow.	• Fatigue • Weakness • Bleeding (from thrombocytopenia)	• Approximately 70% of patients have anaemia at diagnosis.	
Bone lesions	• Myeloma cells activate osteoclasts, which destroy bone and block osteoblasts, which normally repair damaged bone.	• ~70% of patients have osteolytic bone lesions at diagnosis; almost all patients will develop bone lesions. • Pathologic fractures are present in 26% of patients at diagnosis of MM. • Pathological fracture is associated with a 20% increased risk of death.	• Bone pain • Bone swelling • Fracture or collapse of a bone • Nerve or spinal cord damage • Loss of height (up to 6 inches).	
Infection	• Impaired immune function resulting from accumulation of myeloma cells in the bone marrow, which reduces the number and activity of normal plasma cells that produce antibodies against infection.	• Common in patients with MM.	• Pneumonia, septicaemia, or meningitis.	

Clinical feature	Causal factor(s)	Manifestation	Impact/ burden	
Neurologic involvement	• Radiculopathy (nerve pain caused by pressure on nerve roots) is the most frequently observed neurological complication of MM. • Usually result of compression of a nerve by a vertebral plasma cell tumor (rarely by the collapsed bone itself). • Up to 20% of patients have symptoms of peripheral neuropathy at diagnosis.	• Spinal cord compression occurs in ~5% of patients with MM.	• Back pain • Paresthesia (tingling) or weakness in legs, or bladder or bowel dysfunction (spinal cord compression) • Numbness, burning, tingling, sharp stabbing pain, muscle weakness and paralysis, lack of coordination (peripheral neuropathy).	
Leptomeningeal MM	• Cerebrospinal fluid contains monoclonal plasma cells. • Most often associated with chromosome 17p 13.1(p53) deletions.	• Uncommon, but is observed more frequently in advanced MM.	• Cranial nerve palsies • Spinal radiculopathies • Headache • Disorientation • Mental status changes	• Weakness • Sensory disturbances • Abnormal myotactic stretch reflexes • Seizures • Coma
Organ infiltration	• Caused by plasmacytoma or infiltration of plasma cells.	• Organs that may be infiltrated by plasma cells: • Ribs and sternum (frequent) • Stomach (occasionally) • Gallbladder, bile ducts, pancreas, and large and small bowel (rare). • Mediastinum, mediastinal lymph nodes, or lung (occasionally) • Pleura (may occur late in the disease) • Pericardium (rare) • Orbit (occasionally)	• Bleeding and pain (stomach) • Localised, painless swelling (ribs and sternum) • Diplopia, vision loss (orbit).	
Sources: Dimopoulos et al., 2010 [68] Durie, 2011 [58] ; Kyle and Rajkumar, 2014 [69]; Kyle et al., 2003 [66]; Yellu et al., 2014 [70]; Abbott and Agodoa, 2001 [71]; Augustson et al., 2005 [72] ; Richardson et al., 2009 [73]; Saad et al., 2007 [74]				

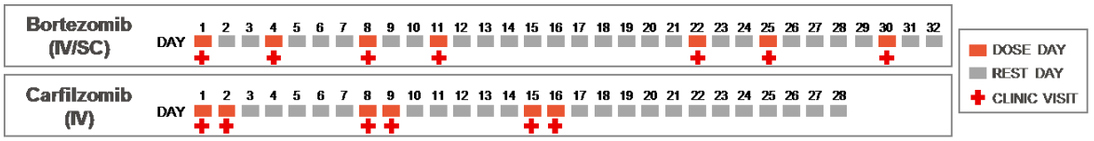
Studies have reported that patients with MM experience a very high symptom burden and low QoL compared with the general population, as assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the Quality of Life Questionnaire MM Module 20 (QLQ-MY20). [75] For example pain has been shown to have a significant impact on the QoL of patients with MM. [76,77] Pain can limit mobility, restricting the distance that patients can walk, or walk independently. It can also disrupt sleep and everyday activities, including leisure pursuits and job-related functions. Since pain greatly affects MM patients, dependence on analgesics is high and the side-effects of pain medication also add to the negative QoL of these patients. [78] Likewise, fatigue, which is a common symptom of MM mainly caused by anaemia, is associated with sleep and mood disturbances, reduced ability to complete simple physical activities, and elevated pain levels. [79]

3.2.2 Quality of life burden of treatment administration and adverse events

IV and SC administration of drugs is associated with frequent clinic visits for treatment administration, in addition to routine visits for diagnosis and monitoring. For example, a recently approved PI, carfilzomib, requires 6 clinic visits per month, including visits on consecutive days (i.e. it is given on days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period every 28 days. [80] Bortezomib's approved dosing schedule is by IV or SC injection twice weekly for 2 weeks on days 1, 4, 8, and 11 [27] (in clinical practice in the UK bortezomib is commonly given once weekly subcutaneously for up to 32 doses [3]). These treatment schedules are illustrated in Figure 4. Due to the impact on

patients' mobility from pain, fatigue, bone degradation and bone fractures, which are symptoms of multiple meyloma, the frequency of travel including hospital visits for treatments is of great relevance.

Figure 4: Administration schedules for bortezomib and carfilzomib



A recent study by Baz et al., 2015 [76] developed a conceptual model to illustrate the impact of MM and its treatment on QoL. The authors of the study reported that therapies often cause adverse effects and can have demanding administration and monitoring schedules (Table 12). Based on feedback from the interviewees, the study authors reported that clinic visits ranged from 'very quick' to up to 2 hours. While most patients did not find clinic visits to be inconvenient, one participant had an 80-mile journey to get to the clinic for treatment, which was reported to be the biggest impact on their QoL; others who were receiving bisphosphonates felt that a monthly intravenous treatment had the biggest impact on their life. Participants receiving oral regimens did not report any inconvenience associated with their treatment. [76]

Feedback from clinicians indicates that in many parts of the UK there is significant pressure on hospital infusion capacity and this frequently leads to lengthy waiting times for patients who are being treated with injectable therapies. This has an adverse impact on QoL for patients as it means they must spend additional time at the hospital, thus limiting their time for other life activities. The availability of an all-oral treatment regimen would offer significant QoL benefits for such patients, as well as lessening the pressure on the hospital system.

Table 12: Selected examples of the negative impact of MM treatment on patients' QoL

Impact on QoL	Example participant quotation
Impact of clinic visits	"…the biggest thing is the fact that it's a full two hour drive to get to the cancer center and back each way. So, today we left at 5:30, and luckily, the lab was on time and the pharmacy was on time, and we got back by noon. There's been other days where we go over there and…we don't get back until four or five in the afternoon." [1 year since diagnosis; first-line therapy]
Mode of treatment administration	"I don't think anybody likes getting an IV every month…time-wise… I don't work or anything, so that doesn't bother me so much. It's more or less the actual IV, because they don't always get it the first time, so it's a couple of sticks. The process is not fun." [4.5 years since diagnosis; first-line therapy]
Mode of treatment administration	"Well, if they miss the IV, number one, and number two, I always have these marks every time I leave there. I always have marks on my arms. Looks like I'm a drug user." [4.5 years since diagnosis; first-line therapy]
Mode of treatment administration	"…anything other than an infusion deal where you've got to run down there all the time, that's great" [20 years since diagnosis; third-line therapy or more]
Impact of clinic visits	"The interruption to my lifestyle is the fact that I've got to go down there and get my new stuff…wherever I am. It wouldn't matter what part of the country I'm in, I've got to go to find a lab and go over there and get my blood drawn; get them then to fax the results to [clinic name] and [clinic name] calls me and says, "Okay, your results are okay, you go ahead and take your dosage."" [20 years since diagnosis; third-line therapy or more]

These were selected by the study authors as typical responses that best illustrate the impact on each area of HRQoL.
Source: Baz et al., 2015 [76]

3.2.3 Quality of life impact on caregivers

The diagnosis of MM can also be a life-changing event for informal caregivers who must face the fear of losing a family member or friend while at the same time providing emotional support to the patient. [81] In addition to emotional support, caregivers often need to provide direct skilled care such as administering medicines (the authors did not specify types of medication, but that the proportion of care-givers who report administering medication as part of their role is 34%), monitoring for AEs and coordinating care between the patient and healthcare providers (e.g. transportation of patients to medical appointments). Increased stress has been observed in caregivers who do not feel adequately prepared for this responsibility (e.g. because of lack of knowledge). [82] A summary of the key elements of the caregiver role is presented in Table 13.

Table 13: Key elements of the caregiver role

Direct care	Care co-ordination and life management	Emotional support
• Monitoring and reporting or recording treatment side effects • Administering medications • Deciding whether to call a healthcare provider • Deciding whether medicine is needed • Performing technical procedures: dressing changes, line care • Communicating with healthcare providers	• Transportation • Accompanying the patient to appointments • Communication to other family members, friends; being a gatekeeper and advocate • Household maintenance, financial management, shopping, cooking • Availability for emergencies • Completing medical forms, keeping track of bills, applications for assistance • Engaging the healthcare system	• Balancing medical expectations while maintaining hope • Listening • Providing reassurance
Source: Kurtin et al., 2013 [82](ref)		

A qualitative study by Molassiotis and colleagues found that MM significantly impacts patients' and caregivers' emotional, social, and work-related areas of life. [83] Moreover, caregivers often neglect their own needs in order to support patients. In a survey of 132 patients with MM and 93 of their partners, one-third of partners reported unmet supportive care needs; almost half reported signs of anxiety (48.8%) and 13.6% reported signs of depression. [84]

As MM is increasingly experienced as a chronic condition, Stephens and colleagues performed a qualitative study on 10 long-term survivors and their primary carers to understand the experience of long-term survival in MM patients and their caregivers. The carers of these patients had to be mindful of managing the risk to their own well-being and balance their own needs along with those of the family and the MM sufferer. Further to this, carers also had to manage their own emotional responses including the feelings of anxiety, loss and uncertainty, particularly when dealing with the patient. [85]

Time commitments, resulting in lost work productivity, can also be considerable for caregivers. Although MM treatment protocols vary between treatment centres, they all require a large time commitment from patients and their caregivers. [86]

3.2.4 Years of potential life lost and indirect costs

The average years of life lost with MM ranges from 36 years in patients younger than 40 years to less than 5 years in patients aged 80 years and older. [87] Using a commonly applied standard value of US$150,000 for 1 year of life

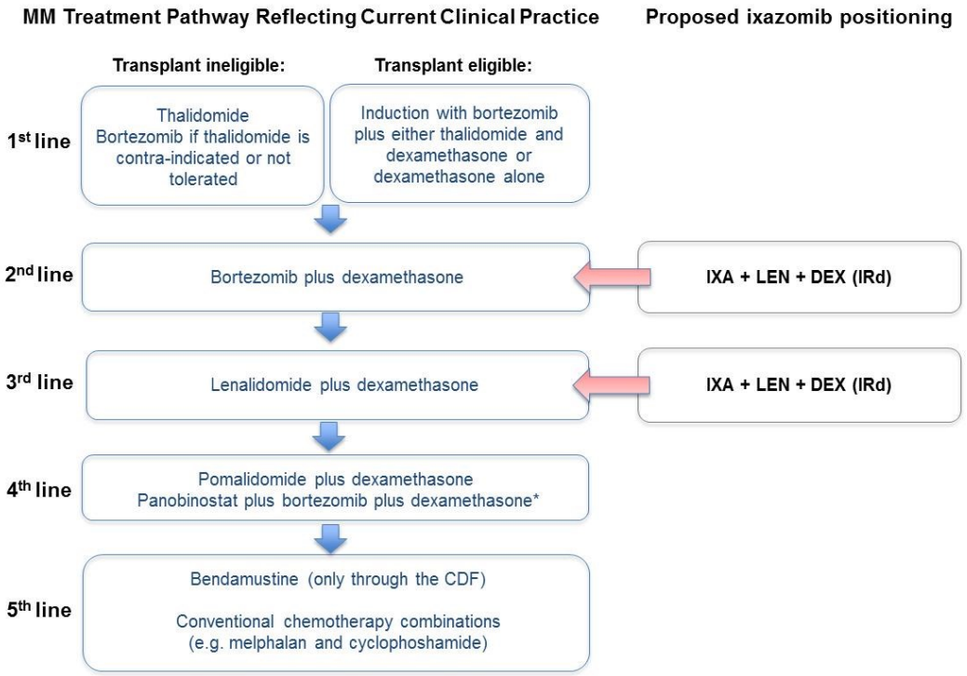
for both sexes and all ages, [88,89] Ludwig et al. estimated that the value of life-years lost in a MM patient diagnosed at age 50 amounts to $4,035,000 (= approximately £2,835,700). [87] This figure highlights the significant economic burden that MM places on society.

MM can result in significant lost work productivity because of patients leaving the workforce. This places a considerable financial burden on patients, families and society as a whole. A survey of MM patients (n=762) who had received treatment at a single US centre reported that of 500 (66%) respondents who were employed at the time of diagnosis and treatment onset, only 33% were currently employed, including 41% of patients aged 54 years or younger. [86] The primary explanation given by patients (35%) for why their employment had ended was a physical inability to carry out job-related functions, mainly due to fatigue and/or pain. Additionally, 21% of patients were no longer employed because of the amount of time and/or travel required for treatment (e.g. frequent physician appointments or prolonged treatment stays). Peripheral neuropathy and the potential for exposure to infection in the workplace were other reasons given by patients (14%). Only 11% of patients had retired. Furthermore, some of the patients who were still in employment had reduced their work hours or had used medical leave (paid and/or unpaid). Ensuring the optimal and efficient treatment of patients with MM and improving outcomes for this disease may reduce the personal and wider economic impact of MM.

3.3 Clinical pathway of care and the impact of ixazomib

The current MM treatment pathway in England, reflecting both the current funding position of the different treatment options and their use in clinical practice, along with the proposed positioning of the IXA+LEN+DEX regimen, is shown in Figure 5

Figure 5: Current treatment pathway for multiple myeloma in England and the proposed positioning of the ixazomib regimen



*Panobinostat-bortezomib-dexamethasone is funded in 3rd line onwards; however, in clinical practice, patients tend to receive LEN+DEX prior to the panobinostat regimen, meaning that panobinostat is predominantly used as a 4th line therapy.

First line: In newly diagnosed, transplant-eligible patients, the recommended first-line treatment is induction with bortezomib plus either thalidomide and dexamethasone (VTd) or dexamethasone alone (Vd), followed by an autologous stem cell transplant (ASCT). [90] Although ASCT is recommended in newly diagnosed MM patients, with a second transplant recommended for some patients with relapsed myeloma, it should be noted that only a small number of patients are suitable for this treatment, [90] highlighting the importance of systemic drug treatment for the majority of patients. In transplant-ineligible patients, the first-line treatment option is thalidomide in combination with an alkylating agent and a corticosteroid; when thalidomide is unsuitable (due to contraindications or intolerance) bortezomib in combination with an alkylating agent and a corticosteroid is recommended (Figure 5).

First relapse (2nd line): The NICE scope has specified a number of potential comparators, including bortezomib ± dexamethasone, bortezomib retreatment and lenalidomide plus dexamethasone. These comparators are based on the NICE clinical pathway and other treatments thought to be of potential relevance in clinical practice in England and Wales. Although bortezomib monotherapy is reimbursed by NICE, in practice bortezomib is usually given in combination with dexamethasone (as agreed in the scope). In the latest multiple myeloma IMS therapy tracker market research (from Oct 2016, based on 37 specialists and 347 patient records across all lines of therapy), bortezomib has a 68% market share at 2nd line, as shown in Table 14 and is by far the dominant therapy. Bortezomib plus dexamethasone is therefore the appropriate comparator for the ixazomib regimen at 2nd line. According to expert clinical opinion, some of the other comparators in the NICE scope are unlikely to be displaced by the ixazomib regimen in clinical practice for the following reasons:

- Bortezomib retreatment (with or without dexamethasone): this treatment option is not recommended by NICE and is no longer available on the CDF
- Lenalidomide with dexamethasone (subject to ongoing NICE appraisal [part review of Technology appraisal 171]): this treatment option is not currently recommended by NICE, is not available on the CDF and recently received a negative draft opinion from NICE at the appraisal consultation stage (ACD published on 11th November 2016). [25]

Second relapse onwards (3rd line +): For patients who have received two or more prior treatments, LEN+DEX is recommended by NICE. In addition, in January 2016, panobinostat in combination with bortezomib and dexamethasone received a positive recommendation by NICE within its marketing authorisation, that is, for 'adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent'. As thalidomide (immunomodulatory agent) and bortezomib are typically used first and second line in England and Wales, this potentially places the panobinostat regimen at 3rd line onwards. However, the predominant use of the panobinostat regimen in England and Wales is at 4th line, after LEN+DEX; this was confirmed by the clinical experts during the carfilzomib and pomalidomide NICE Appraisal Committee meetings in October 2016 (Figure 5).

Consistent with this proposed care pathway, the latest multiple myeloma IMS therapy tracker market research shows that lenalidomide is dominant in 3rd line with a 69% market share. The panobinostat regimen has a low market share at both 3rd and 4th line (currently 7% and 19% respectively; Table 14)

Table 14: IMS multiple myeloma therapy tracker market share data of therapies by line of treatment

Line of treatment	Market share by line of therapy (>5% market share only)
2nd line (1 prior therapy)	68% bortezomib 26% lenalidomide 19% thalidomide
3rd line (2 prior therapies)	69% lenalidomide 12% bortezomib 7% panobinostat
4th line (3+ prior therapies)	39% pomalidomide 25% lenalidomide 25% bortezomib 19% panobinostat

In November 2016, pomalidomide in combination with low-dose dexamethasone received a positive recommendation from NICE as an option for treating MM at third or subsequent relapse; that is, after 3 previous treatments including both lenalidomide and bortezomib. [91] As pomalidomide can only be prescribed in routine practice after lenalidomide, the ixazomib regimen will be positioned in an earlier treatment line, excluding pomalidomide as a relevant comparator. For patients who have had four or more relapses, bendamustine is available as a treatment option only through the CDF or otherwise patients are treated with conventional chemotherapy combinations (e.g. melphalan and cyclophosphamide). Of note, and supporting our rationale here, the NICE scope for ixazomib did not include either pomalidomide, bendamustine nor conventional chemotherapy.

Conclusion: Based on the above rationale, the proposed positioning of the ixazomib regimen is as either a 2nd or 3rd line treatment option. Given where lenalidomide is currently most used we would expect the predominant use of the ixazomib regimen to be in the 3rd line setting. Based on the current treatment pathway, the relevant comparator for the ixazomib regimen in patients who have received 1 prior therapy is bortezomib plus dexamethasone, while for patients who have received 2 prior therapies it is lenalidomide plus dexamethasone.

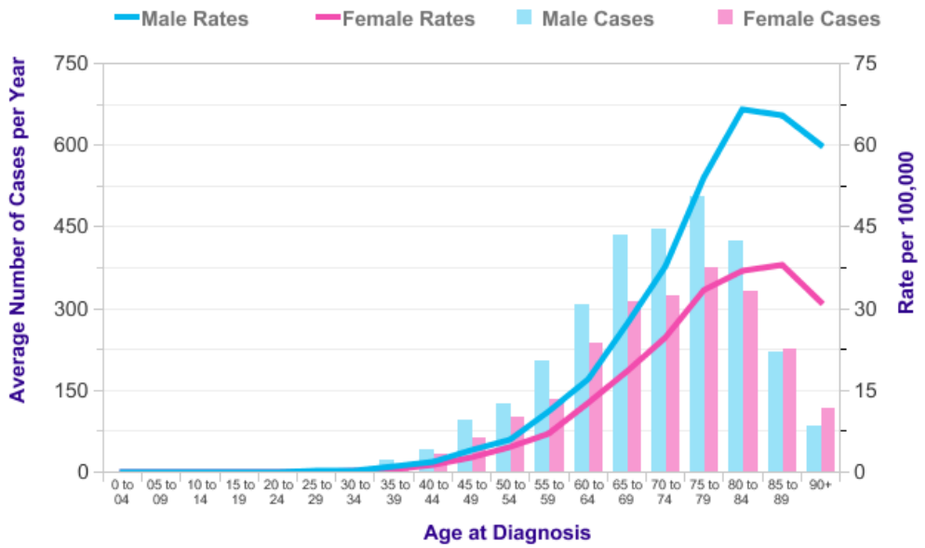
3.4 Epidemiology of multiple myeloma and relapsed/refractory multiple myeloma in the UK

The epidemiology of MM from Cancer Research UK (CRUK), which provides a comprehensive overview of national cancer statistics in the UK using data provided by members of the (UK) and Ireland Association of Cancer Registries, is presented in the following sections. [4] There are no epidemiology data in the published literature on the number of patients with RRMM. Therefore, a study was conducted by Lin and colleagues (Global Outcomes Research, Takeda Oncology, Cambridge, USA) to estimate the number of patients with RRMM (Section 3.4.3).

3.4.1 Incidence and mortality data for MM in the UK

MM is predominantly a disease of the elderly. Incidence rates increase suddenly between ages 55 and 59 with approximately 58% of MM cases being diagnosed in patients aged 70 and over (Figure 6).

Figure 6: Average number of new cases of MM per year and age-specific incidence rates per 100,000 population, UK (2012-2014)



Source: CRUK 2016 [4]

In 2014, there were approximately 5,501 new cases of MM in the UK, approximately 3,072 (56%) male and 2,429 female (44%) (Table 15) accounting for 2% of all new cancers. Data shows that MM is more common in men than in women and twice as common in black people compared to white and Asian people.

In 2014, there were 2,928 deaths from MM (Table 15), accounting for 2% of all cancer deaths in the UK. Around 6 in 10 (59%) MM deaths in the UK each year are in people aged 75 and over (2012-2014).

Table 15: Incidence and mortality data for MM in the UK (2014)

	England	Wales	UK[a]
Incidence			
Number of new cases per year, total (male, female)	4652 (2598, 1054)	228 (114, 114)	5501 (3072, 2429)
ASR per 100,000, total (male, female)	9.5 (11.7, 7.7)	8.6 (10.6, 7.2)	9.3 (11.6, 7.6)
Mortality			
Number of deaths per year, total (male, female)	2462 (1335, 1107)	144 (76, 68)	2928 (1596, 1332)
ASR per 100,000, total (male, female)	5 (6.4, 4.0)	4.6 (5.6, 3.8)	5.0 (6.3, 4.0)

Abbreviations: ASR = age-standardised rate
[a] England, Wales, Scotland and Northern Ireland
Source: CRUK 2016 [4]

3.4.2 Survival data for MM in the UK

For MM, the 1-year net survival is 76.6% in England and Wales, decreasing to 47%, and 32.5% for 5, and 10 years, respectively (Table 16). Survival for men is slightly higher than women (Table 16). Around three quarters of people in England diagnosed with MM aged 15-49 survive their disease for five years or more, compared with a quarter of people diagnosed aged 80 and over (2009-2013).

Table 16 shows that, at the end of 2006, there were 12,465 people alive in the UK who had been diagnosed with MM within the previous 10 years. Again, a slight gender bias can be seen.

Table 16: Survival (2010–2011) and prevalence (at end of 2006) data for MM in the UK

	Males	Females	Total
Prevalence as at the end of 2006			
1-year prevalence	1,595	1,294	2,889
5-year prevalence	5,247	4,175	9,422
10-year prevalence	6,921	5,544	12,465
Age-standardised net survival for patients diagnosed in 2010–2011 (England and Wales only)			
1-year net survival, % (95% CI)	77.9 (77.9–78)	75.1 (75.1-75.2)	76.6 (76.6-76.6)
5-year net survival, % (95% CI)	49.8 (49.3-50.3)	43.8 (43-44.5)	47 (46.5-47.4)
10-year net survival, % (95% CI)	36.6 (34.8-384)	28.1 (25.3-30.9)	32.5 (31-34.1)
Source: CRUK 2016 [4]			

3.4.3 Estimated incidence of RRMM in the UK

A study was conducted by Lin and colleagues (Global Outcomes Research, Takeda Oncology, Cambridge, USA) to estimate the number of patients with RRMM. [92] This involved a systematic review of MM epidemiology data (the search included electronic databases and online sources) to determine the country-specific incidence of MM and a systematic review of randomised controlled clinical trials in newly diagnosed MM to determine the proportion of patients whose disease progressed after first-line treatment. This is not a country-specific RRMM rate, as response to treatment is assumed to be applicable globally. The results of these two systematic reviews were used to calculate estimates of the incidence (per 100,000 person-years) of RRMM in the UK:

UK-specific incidence of MM × relapse/ refractory rate = number of RRMM in the UK

The relapsed and/ or refractory rate used was either the overall proportion of MM patients estimated to relapse from or be refractory to first-line treatment (65.7%), a 1-year rate (48.6%), or a 2-year rate (63.9%). The detailed methodology is described in Lin et al., [92] and a summary of the results are reported below .

The sources identified in the systematic review and the incidence rates for MM are shown Table 17.

Table 17: UK MM incidence – sources and rates/100,000 of the general population

	Year	Crude			Country ASR			Regional ASR			World ASR		
Source		**M**	**F**	**total**	**M**	**F**	**total**	**M**	**F**	**total**	**M**	**F**	**total**
Benson (2013)	1999-2009	-	**12.79**	-	-	-	-	-	-	-	-	-	-
Ferlay (2013)	2012	-	-	-	-	-	-	**6.5**	**4.1**	-	-	-	-
HMRN	2004-2012	**8**	**5.5**	**6.7**	-	-	-	6.8	3.7	5	-	-	-
IARC	2012	-	-	-	-	-	-	**6.5**	**4.1**	**5.2**	-	-	-
Reeves (2007)	1996-2001	-	**7.65**	-	-	-	-	-	-	-	-	-	-
Phekoo (2004)	1999-2000	-	-	-	**10.45**	**6.73**	**7.79**	-	-	4.82	-	-	3.29
GLOBOCAN	2012	**8.4**	**6.4**	**7.4**	-	-	-	-	-	-	4.3	2.8	3.5
Abbreviations: HMRN = Haematological Malignancy Research Network; IARC = International Association for Cancer Research Source: Lin et al., 2015 [92]													

The UK population size for 2013 (ONS 2013: total: 64,105,654; male: 31,532,900; female: 32,572,800) was used to estimate the number of incident cases of MM in the UK according to incident rates reported in Table 17. Estimated incident cases of MM in the UK are reported in Table 18.

Table 18: UK: MM incidence –rates/100,000 of the general population

	Annual incident cases		Annual incidence/100,000	
	Average	**Range**	**Average**	**Range**
Male	2,513	2,050 – 3,295	7.97	6.50 - 10.45
Female	2,200	1,335 – 4,167	6.75	4.10 - 12.79
Total	4,342	3,333 – 4,994	6.77	5.20 - 7.79
Source: Lin et al., 2015 [92]				

The incidence of RRMM in the UK was calculated by applying the proportion of RRMM (global) to the number of incident cases in the UK (Table 18). [92]

Table 19 summarises the estimated number of RRMM patients in the UK. Applying the total rate (65.7%) to the total MM population in the UK indicates that there are approximately 2,854 new cases of RRMM each year, which represents an incidence rate of 4.45 per 100,000 people.

Table 19: Estimated incident cases and incidence rate (cases per 100,000 population) of RRMM in the UK

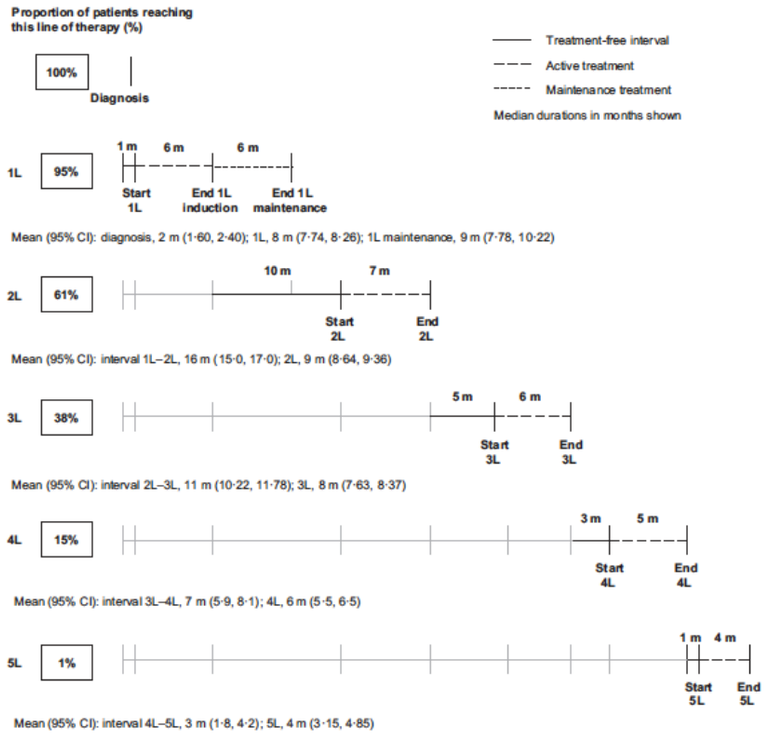
	Total (65.7%)		1 year (48.6%)		2 year (63.9%)	
	Number	**Incidence / 100,000 population**	**Number**	**Incidence / 100,000 population**	**Number**	**Incidence / 100,000 population**
	Average	**Average**	**Average**	**Average**	**Average**	**Average**
Male	1,652	5.24	1,220	3.87	1,606	5.09
Female	1,446	4.44	1,068	3.28	1,406	4.32
Total	2,854	4.45	2,108	3.29	2,774	4.33
Source: Lin et al., 2015 [92]						

3.4.4 Real-world data: patients by line of therapy

Two recent publications have reported on a pan-European (Belgium, France, Germany, Italy, Spain, Switzerland and the UK) real-world study based on an audit of MM patient charts. [93,94] The chart review consisted of a cross-sectional audit (a total of 435 physicians completed 7635 cross-sectional chart reviews [94]) and a retrospective component (435 physicians retrospectively reviewed 4997 patient charts [93]).

Figure 7 shows the proportion of patients reaching each subsequent line of therapy (these data were derived partly from the cross-sectional part of the study), together with the duration of treatment and length of the treatment-free interval. Overall, 95% of patients diagnosed with symptomatic MM who were treated by haematologists received at least one line of anti-tumour drug treatment, 61% received ≥2 lines of therapy and 38% received ≥3 lines. Median duration of therapy and median treatment-free interval decreased with increasing lines of therapy, as did time to progression.

Figure 7: Proportion of patients by line of therapy, treatment duration and treatment-free intervals



Source: Yong et al,. 2016 [93]

In addition, the depth of response, as assessed by the treating physician, also decreased with each additional line of therapy, with 74% of patients achieving at least a very good partial response at first line, compared with only 11% at fifth line. Deeper responses were associated with longer time to progression, although these were physician-judged. Toxicities and comorbidities increased with later treatment lines, and were more likely to have led to discontinuation of treatment. Overall, the authors concluded that there was an unmet need for better-tolerated, efficacious treatments in later treatment lines.

3.5 Clinical guidance

3.5.1 Completed NICE technology appraisal guidance for RRMM

NICE recommendations for technologies in patients with RRMM are shown in Table 20 (see Section 3.3.1 for their position in the clinical pathway).

Table 20: NICE technology appraisals of relevance for patients with RRMM

NICE guidance number & date	Title	Guidance
TA129 October 2007 [95]	Bortezomib monotherapy for relapsed multiple myeloma	Bortezomib monotherapy **is recommended** as a possible treatment for progressive multiple myeloma for people: • whose multiple myeloma has relapsed for the first time after having one treatment, and • who have had a bone marrow transplant, unless it is not suitable for them. • After not more than four cycles of treatment, a blood or urine test should be done to check how well the cancer has responded to bortezomib. • Treatment should be continued only if there has been at least a partial response to the drug.
TA171 June 2009 [96]	Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy	Lenalidomide (used together with a medicine called dexamethasone) **is recommended** as a possible treatment for people with multiple myeloma who have already had at least two other treatments. The manufacturer of lenalidomide has agreed to cover the cost of the drug for people who stay on treatment for more than 26 cycles (normally a period of 2 years).
TA338 March 2015 [97]	Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib	Pomalidomide (Imnovid), given with a drug called dexamethasone, **is not recommended** for treating relapsed and refractory multiple myeloma in people whose disease has gotten worse despite having had both lenalidomide and bortezomib.
TA380 January 2016 [98]	Panobinostat for treating multiple myeloma after at least 2 previous treatments	Panobinostat in combination with bortezomib and dexamethasone **is recommended**, within its marketing authorisation, as an option for treating multiple myeloma, that is, for 'adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent' when the company provides panobinostat with the discount agreed in the patient access scheme.

Other therapies currently under consideration by NICE for patients with RRMM are shown in Table 21. Of note, carfilzomib [ID934] and lenalidomide (post bortezomib) (part rev TA171) [ID667] have recently received initial negative recommendations at the ACD stage by the NICE Appraisal Committee.

Regarding the upcoming NICE appraisals, of interest is the fact that carfilzomib and daratumumab are both administered intravenously. If recommended by NICE, both of these agents have administration schedules that would present logistical challenges to patients and the NHS. In the case of carfilzomib this relates to the frequency of the IV injections while for daratumumab the challenge is the lengthy IV infusion times. By contrast, if recommended by NICE, the IXA+LEN+DEX regimen would be the only all-oral triplet available on the NHS for RRMM, fulfilling an unmet need for additional efficacious treatment options for RRMM patients with a favourable

toxicity profile and the added advantages of a regimen that can be taken at home, minimising the travel burden and impact on the daily life of patients and caregivers.

Table 21: Technologies under NICE review

NICE guidance number & date	Title	Final scope	Appraisal committee recommendation/ status
GID-TAG452 [25]	Lenalidomide (post bortezomib) (part rev TA171) [ID667]	Lenalidomide in combination with dexamethasone for treating multiple myeloma in people: • whose condition has relapsed for the first time and • who have had 1 prior treatment with bortezomib and • for whom thalidomide is contraindicated or cannot be tolerated, and • for whom stem cell transplantation is not appropriate.	**Not recommended** (ACD on 11/11/16) Status: in progress Anticipated publication date: TBC
GID-TA10005 [26]	Carfilzomib [ID934]	• Carfilzomib in combination with lenalidomide and dexamethasone • Carfilzomib in combination with dexamethasone Adults with multiple myeloma who have received at least 1 prior therapy	**Not recommended** (ACD on 9/11/16) Status: in progress Anticipated publication date: May 2017
GID-TA10038 [99]	Pomalidomide (with dexamethasone) for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib (review of TA338) [1D985]	Pomalidomide, in combination with low-dose dexamethasone, is recommended as an option for treating multiple myeloma in adults at third or subsequent relapse; that is, after 3 previous treatments including both lenalidomide and bortezomib, only when the company provides pomalidomide with the discount agreed in the patient access scheme	**Recommended** (4th line only. FAD on 23/11/16) Status: in progress Anticipated publication date: January 2017
GID-TA10076 [100]	Daratumumab for multiple myeloma [ID933]	Not available	Status: in progress Anticipated publication date: July 2017

3.5.2 Cancer Drugs Fund

The Cancer Drugs Fund (CDF) within NHS England is designed to improve the availability of cancer drugs on the NHS. Table 22 shows the therapies for the treatment of RRMM that are available through the CDF (version 1.13; 23rd November 2016).

Table 22: Medicines for the treatment of relapsed multiple myeloma available through the CDF

Drug	CDF approved criteria
Bendamustine (from 29th July 2016)	The treatment of relapsed multiple myeloma where all the following criteria are met: • Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy • Multiple myeloma • Relapsed disease where other treatments contraindicated or inappropriate • To be used within the treating Trust's governance framework, as bendamustine is not licensed in this indication
Bortezomib (from 29th July 2016)	The treatment of bortezomib-naive relapsed multiple myeloma where all the following criteria are met: • Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy • Relapsed myeloma • No previous bortezomib
Pomalidomide (from 23rd Nov 2016)	The treatment, with dexamethasone, of relapsed and refractory multiple myeloma after at least three regimens including lenalidomide and bortezomib where all the following criteria are met: • Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy • Multiple myeloma • PS 0-2 • Previously received 3 lines of treatment with adequate trials of at least all of the following options of therapy: bortezomib, lenalidomide and alkylating agents • Refractory disease to previous line of treatment
Abbreviations: CDF = Cancer Drugs Fund Source: NHS England [22]	

Table 23 shows the indications that were removed from the CDF in 2015. As a result of these delistings, there are now fewer treatment options available for MM patients in England in the relapsed setting.

Table 23: Medicines for the treatment of relapsed multiple myeloma removed from the NDCF

Drug	Indication removed (as of 12th March 2015 and 4th November 2015)
Bortezomib[a]	Re-treatment in patients with relapsed myeloma
Lenalidomide[b]	2nd line treatment of multiple myeloma in patients who have received prior treatment with bortezomib
Pomalidomide[b]	Treatment of relapsed and refractory multiple myeloma in patients who have received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy

Abbreviations: CDF = Cancer Drugs Fund
[a] Removed as of 12th March 2015
[b] Removed as of 4th November 2015
Source: NHS England [101] Myeloma UK September 2015 [23] Myeloma UK January 2015[24]

3.5.3 UK clinical guidelines for RRMM

The NICE guidelines and clinical pathway for MM are described in Section 3.1. In addition, the British Committee for Standards in Haematology (BCSH) guidelines for the diagnosis and management of MM were published in 2011 [102] and updated in 2014. [61] Table 24 summarises the BCSH clinical practice guidelines for the management of RRMM.

For patients at second and subsequent relapse the BCSH recommended lenalidomide, with patients presenting in renal failure being recommended a bortezomib-containing regimen. They also noted that many new drugs were in development at the time of the guidelines in 2014. The BCSH also stated that "decisions regarding treatment at relapse should be made according to a number of factors including the timing of relapse, efficacy and toxicity of drugs used in prior therapy (e.g. peripheral neuropathy), age, bone marrow and renal function, co-morbidities (e.g. diabetes) and patient preference".

Table 24: British Committee for Standards in Haematology (BCSH) guidelines for RRMM

	Recommendations
Refractory myeloma	• Patients should be entered into clinical trials where possible • A bortezomib-based salvage regimen is recommended for patients refractory to first-line therapy or intolerant of thalidomide • A lenalidomide-based regimen should be given to patients with ≥ grade 2 peripheral neuropathy
Relapsed myeloma	• Most suitable management should be decided on an individual basis, taking into account age, timing of relapse, previous therapies, bone marrow function, comorbidities and patient preference • Thalidomide, bortezomib and lenaliomide based regimens are recommended for patients suffering from their first or subsequent relapse • The number or type of previous therapy does not alter the clinical effectiveness of thalidomide, bortezomib and lenalidomide • Dexamethasone with or without chemotherapy should be administrated alongside thalidomide, bortezomib or lenalidomide treatment, unless contraindicated. • Consider a 2nd ASCT for patients showing a good response to the initial transplant procedure (≥18 months to disease progression) • Patients should be entered into clinical trials where possible. Phase I or II trials are suitable for RRMM patients • Good supportive therapy is essential
Patients at second relapse	• Patients at second and subsequent relapse (or patients at first relapse intolerant of thalidomide or bortezomib) should be considered for lenalidomide. • Patients presenting in renal failure should be treated on a bortezomib-containing regimen, to achieve rapid reduction in light chain load to the kidneys, and maximize chances of regaining renal function.

Abbreviations: ASCT = autologous stem cell transplantation
Source: Bird et al., 2014 [61]

3.5.4 International and European guidelines

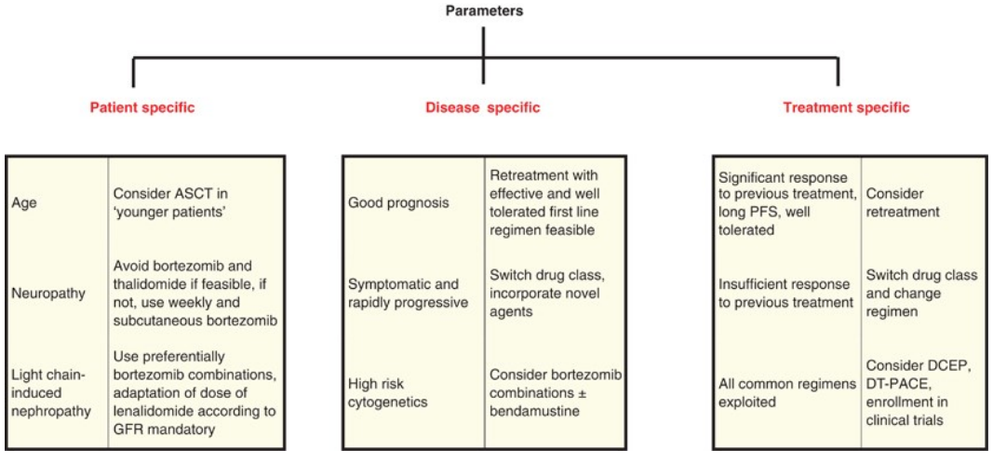
International and European clinical practice guidelines for RRMM are described in Table 25 As described, various factors need to be considered in order to make the optimal treatment choice, including patient-specific factors, tumour characteristics, such as cytogenetics, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options and the interval from the last therapy. [37]
Of note, in the 2016 National Comprehensive Cancer Network (NCCN) guidelines from the US, the IXA+LEN+DEX regimen is a preferred treatment option for MM patients who have received at least one prior therapy, with category 1 evidence (i.e. based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate), and it is also recommended by the US Mayo Clinic guidelines. In addition, the International Myeloma Working Group (IMWG) suggests that an oral regimen may be preferred in patients living far away from their treatment centre (Figure 8).

Table 25: International and European clinical practice guidelines for RRMM

Organisation	Recommendations for RRMM
IMWG 2014 [37]	• Selection of therapy depends on patient-specific factors, tumour characteristics, such as cytogenetics, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options and the interval from the last therapy • Drugs with potential neurotoxicity, such as bortezomib or thalidomide, should be avoided in patients with polyneuropathy, whereas less myelotoxic drugs should be preferred in those with compromised bone marrow function • An oral regimen may be preferred in patients living far away from their myeloma treatment centre. • Changing the treatment regimen and drug class (if possible) for second or further lines of therapy is recommended in patients with an insufficient response, a rapid relapse and poor tolerance. • Treatment should be continued until best possible response, provided tolerance is adequate.
NCCN 2016 [103]	Preferred treatment options for previously treated MM (category 1 evidence[a]): • Bortezomib • Bortezomib/liposomal doxorubicin • Carfilzomib/lenalidomide/dexamethasone • Elotuzumab[b]/lenalidomide/dexamethasone • Ixazomib[c]/lenalidomide/dexamethasone • Lenalidomide/dexamethasone[d] • Panobinostat/bortezomib/dexamethasone[e] • Pomalidomide[f]/dexamethasone[d]
US Mayo Clinic July 2016 [104]	• Depending on factors such as first or second relapse, being refractory to prior drugs and status of the patient (fit or frail) treatment options include: • Carfilzomib, lenalidomide, dexamethasone • Carfilzomib, pomalidomide, dexamethasone • Cyclophosphamide, bortezomib, dexamethasone • Ixazomib, lenalidomide, dexamethasone • Ixazomib, cyclophosphamide, dexamethasone • Lenalidomide, dexamethasone, elotuzumab • Pomalidomide, dexamethasone, daratumumab • Pomalidomide, cyclophosphamide, dexamethasone, daratumumab • Pomalidomide, bortezomib, dexamethasone • Daratumumab, bortezomib, dexamethasone • Daratumumab, lenalidomide, dexamethasone
ESMO 2013 [60]	• The choice of therapy in the relapse setting depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options and the interval since the last therapy.
N.B.: Not all of the above treatment combinations are approved in the UK. Abbreviations: ESMO, European Society for Medical Oncology; IMWG, International Myeloma Working Group; NCCN = National Comprehensive Cancer Network; RRMM = relapsed/refractory multiple myeloma; [a] Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.	

Organisation	Recommendations for RRMM
[b] Indicated in combination with lenalidomide and dexamethasone for the treatment of patients who have received one to three prior therapies. [c] Indicated for the treatment of patients who have received at least one prior therapy. [d] Consider single-agent lenalidomide, pomalidomide, or thalidomide for steroid intolerant individuals. [e] Indicated for the treatment of patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent. [f] Indicated for the treatment of patients who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.	

Figure 8: Parameters relevant for treatment selection in patients with relapsed/refractory multiple myeloma (IMWG recommendations 2014)



Source: Ludwig et al 2014 [37]

3.6 Issues relating to current clinical practice

There is currently no cure for MM and thus prolongation of PFS and OS remain the ultimate goals of treatment. The discovery of novel agents such as immunomodulatory drugs (IMiD) (e.g. thalidomide and lenalidomide) and proteasome inhibitors (PI) (e.g. bortezomib) have contributed to a doubling of survival in MM patients as compared to the 1990s when only conventional chemotherapy was used. [105] However, despite such advances, most patients ultimately relapse. [9] Such patients are difficult to treat as they tend to have more aggressive disease (and thus are less responsive to treatment) and have been heavily pre-treated, thereby having more pre-existing toxicities. [9]

There are several issues relating to current clinical practice, particularly in relation to the logistical burden that existing treatments place on patients and the NHS. The IXA+LEN+DEX regimen overcomes many of these limitations, with the potential to offer meaningful benefits to patients, caregivers and the wider healthcare system, as follows:

Improved treatment choice

For a disease that is characterised by multiple relapses, there are relatively few treatment options available on the NHS in England, especially in light of the recent delistings from the CDF (Section 3.5.2), and negative recommendations from NICE (Section 3.5.1). It is vital for MM patients to have access to a range of treatments and treatment combinations at each stage of the disease pathway, so that their treatment can be tailored to their needs and circumstances. [36]

Improved long-term outcomes

Combination therapy has become the standard-of-care in many situations, with the complementary activity of a PI, an IMiD and a corticosteroid (dexamethasone) particularly promising. [12,14] Recent Phase III studies have demonstrated superior efficacy with triplet versus doublet combination regimens based on these agents in the frontline [15,16,106] and relapsed settings. [17,18]

In addition, to further improve long-term outcomes, there has been a shift towards a paradigm of extended treatment. [19-21] However, treatment-related adverse events plus the demanding administration and monitoring schedules of treatments such as bortezomib impose a substantial burden on patients over time, leading to treatment discontinuation in many cases. [38,107]

The triple combination of IXA+LEN+DEX significantly improves progression free survival (PFS) by an average of 6 months compared to LEN+DEX alone, representing a significant and prolonged period for patients and families. In some groups of patients, including third line and high-risk patients, the PFS gain was greater than this; given that these patients currently have very poor outcomes this is a major area of unmet need. [36] In addition, the favourable toxicity profile of ixazomib is predicted to enable continuation of treatment, leading to a durable response.

Improved quality of life

Improving the quality of life of patients is an important treatment goal in MM. [108] In particular, treatment tolerability is important in RRMM patients who are typically older and less fit. Ixazomib is not associated with the troublesome severe peripheral neuropathy or cardiopulmonary toxicities seen with other PIs, such as bortezomib and carfilzomib respectively. [1,18,45] No increase in serious adverse events (SAEs) has been reported with IXA+LEN+DEX compared to LEN+DEX alone. [1]

Furthermore, several reports have shown that many patients with cancer prefer oral to parenteral administration of chemotherapy. The reasons for this are many and include convenience, the place of treatment, a dislike of needles, anxiety over an IV line, feeling less ill and reducing the effort in coping with the disease. [30-35] Oral treatment options can help patients feel more “in control” of their treatment and also to carry on with their everyday lives without having to attend regular hospital appointments. [36] This is particularly important for patients who find it difficult to attend hospital appointments (e.g. if they are older/frailer, live far away from hospital or are still in employment). The all-oral combination of IXA+LEN+DEX can be taken at home, thereby reducing the burden on patients and caregivers (and the NHS – see below).

Reduced burden on the NHS

The need for healthcare professionals to administer bortezomib, either subcutaneously or intravenously, inevitably increases the burden on NHS resources and costs, and the management of treatment toxicity and side-effects also adds to this burden. Given the rising demand for cancer services as a whole (due to the ageing population and increased survival rates), together with limited resources and budgets, [109] the option of an oral PI/ all oral triplet regimen with a favourable toxicity profile could help reduce the burden on the NHS.

Overall, IXA+LEN+DEX would provide patients, clinicians and the NHS with the choice and flexibility of an all-oral treatment option that is efficacious with a favourable toxicity profile, which is predicted to reduce burden on the patient and the NHS. This is particualraly important for future sustainability as the arrival of new injectable

treatments, such as carfilzomib and daratumumab, seems set to increase the logistical burden on the NHS even further. In this context, a simple oral product like ixazomib looks like a particularly attractive treatment option for an increasingly resource constrained NHS.

3.7 Equality

We foresee no equality issues with ixazomib.

4. Clinical effectiveness

4.1 Identification and selection of relevant studies

4.1.1 Systematic literature review

A systematic literature review (SLR) of the clinical evidence relating directly to the appraisal decision problem in Section 1.1 was undertaken in order to perform a decision-focused network meta-analysis (NMA) that is relevant for a NICE single technology appraisal (STA), as well as future submissions to other UK HTA bodies. The primary objective of the SLR was to address the following decision problem:

> "What is the clinical efficacy and safety of ixazomib citrate in combination with lenalidomide and dexamethasone (LenDex) for the treatment of patients with relapsed or refractory multiple myeloma (RRMM) who have received at least one prior therapy?"

In line with this, data on the clinical efficacy and safety of ixazomib or comparators were obtained by a systematic literature search and review of published research evidence and conference abstracts (with supporting poster presentations), supplemented by unpublished trial data for ixazomib supplied by Takeda UK.

The search terms were developed specifically for each database. Searches took into account generic and other product names including variations in different countries. Specific search filters for randomised controlled trials were used to retrieve studies of clinical effectiveness. Each abstract was assessed by two independent reviewers.

The search strategy used is reported in Appendix 2. In addition, separate ixazomib SLR reports (firstly an interim analysis utilising the first data-cut date of 30th October 2014 [IA1]; followed by an updated analysis by means of the second data of 12th July 2015 [IA2]) provide further details. [110,111] The search strategy was executed on 1st June 2015 and repeated firstly on the 10th April 2016, and then more recently on the 7th October 2016 to update the search and fill in gaps in the evidence from the first systematic search in the following databases:

- MEDLINE® with Daily Update
- MEDLINE® In-Process & Other Non-Indexed Citations
- Embase
- The Cochrane library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials)
- The Centre for reviews and Dissemination (CRD) Databases: Database of Abstracts of Reviews of Effect (DARE), Health Technology Assessment Database (HTA), NHS Economic Evaluation Database (NHSEED)
- PubMed (for E-publications ahead of print)

Search strategies combined free-text and controlled vocabulary terms (MeSH terms in MEDLINE and CENTRAL and EMTREE terms in EMBASE) for multiple myeloma (MM). To identify relevant studies, the search strategies were designed to identify a MM population that was relapsed or refractory; hence they represent a combination of the terms for the disease of interest –'Multiple myeloma' and 'relapsed or refractory.'

In addition, manual searches of the following conferences were performed to identify relevant abstracts, not yet available as full publications:

- American Society of Haematology (ASH)
- American Society of Clinical Oncology (ASCO)
- European Haematology Association (EHA)
- European Society for Medical Oncology (ESMO)

Furthermore, the Clinical trials website (www.clinicaltrials.gov) was searched to identify ongoing studies with interim results not yet published in an abstract/ poster; and lastly references from systematic reviews, indirect comparisons, and network meta-analyses were searched.

4.1.2 Eligibility criteria

The following eligibility criteria were used to determine articles to be included in the systematic review. Eligibility criteria are specified in the table below in terms of patients, interventions, comparators, outcome and study design (PICOS). The same criteria were applied for both the 2016 updates as for the original search carried out in 2015.

Table 26: Eligibility criteria for search strategies conducted in 2015 and 2016

Patients	**Adult patients (≥18 years) with diagnosed relapsed or refractory multiple myeloma (RRMM) who have received at least one prior therapy**
Interventions	Patients in the active treatment group receiving at least one of the following treatments for RRMM were eligible: • Chemotherapy including regimens based on melphalan, vincristine, cyclophosphamide, or doxorubicin • Thalidomide containing regimens • Bortezomib containing regimens • Lenalidomide containing regimens • Pomalidomide containing regimens • Bendamustine containing regimens • Carfilzomib containing regimens • Daratumumab containing regimens • Elotuzumab containing regimens • Panobinostat containing regimens
Comparators	Patients in the control group receiving placebo or dexamethasone were eligible. Studies without a control group but with two interventions of interest were also eligible for inclusion
Outcomes	The following list of outcomes was considered. This list was compiled after reviewing the NICE draft scoping documents for similar regimens (i.e., carfilzomib and panobinostat) for treatment of MM in patients with at least 1 prior therapy: • Progression Free Survival (PFS) • Overall survival (OS) • Overall response rate (ORR) • Treatment discontinuation • Adverse events (grades 3-4) • Time to progression (TTP) • Duration of response (DOR)

	• Time to next treatment (TTNT) • Duration of treatment • Health-related quality of life (HRQoL)
Study design	Peer-reviewed RCTs, observational studies and conference abstracts (both RCTs and observational studies) were eligible. Post-hoc analysis studies were examined only if an updated or new data of an original study was presented. All other types of literature, such as letters, editorials or reviews were not considered for inclusion

4.1.3 Study selection

The process of study selection was made according to specifications in the Protocol.[112] Thus, studies were selected based on the comparators and outcomes listed in the Final NICE scope for ixazomib, [113] as well as for HTA purposes and future submissions. Thus, studies involving comparators bendamustine, chemotherapy, daratumumab, and elotuzumab were not selected from the systematic review for data extraction as they were not to be included in the NMA (see Section 4.10). For the purpose of this STA submission, which has been previously agreed by the NICE Appraisal Committee following the publication of the carfilzomib appraisal consultation document (ACD) [3] the following studies will be reported only:

- Ixazomib + lenalidomide + dexamethasone compared with bortezomib + dexamethasone at second line (i.e. patients that have received 1 prior therapy)

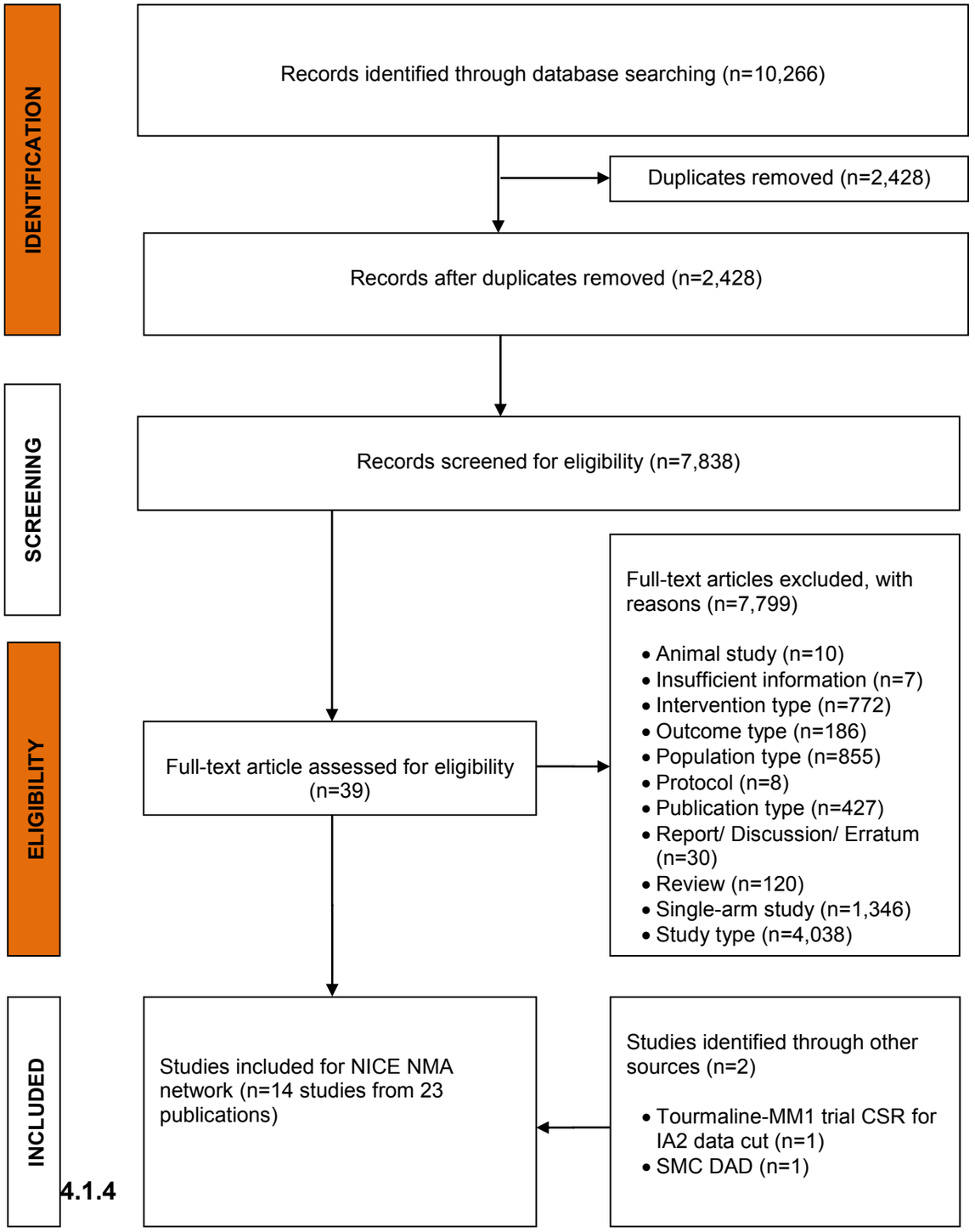
- Ixazomib + lenalidomide + dexamethasone compared with lenalidomide + dexamethasone at third line (i.e. patients that have received 2+ prior therapies)

Due to the limited availability of randomised evidence for RRMM patients who have received 1 or 2+ prior therapies (for the comparators of interest shown above), non-randomised study designs such as prospective interventional studies, prospective observational studies, as well as retrospective studies were considered in this systematic review.

All abstracts were reviewed by two experienced systematic reviewers according to the eligibility criteria outlined in Section 4.1.2; any difference in opinion regarding eligibility was resolved through discussion with a third reviewer. The same process was applied to the subsequent review of full papers.

A PRISMA flow diagram indicating the numbers of studies included and excluded at each stage of the review is provided below (Figure 9). The PRISMA flow diagram from indication includes combined results from the original systematic review (2015) and updates in April 2016 and October 2016.

Figure 9: PRISMA flow diagram of the study selection process for relapsed or refractory multiple myeloma patients (June 2015 original review, April and October 2016 updates)



4.1.4

A systematic review of electronic databases was conducted on the 1st June 2015. An updated systematic review was conducted on 10th April 2016, and more recently on 7th October 2016. The search strategies used for each database are described in Appendix 2. References were downloaded into dedicated Reference Manager® databases. After de-duplication a total of 7,838 articles were identified specifically from these searches. These

abstracts were double reviewed for eligibility and 39 full-text articles were ordered for assessment (Figure 9). Following full paper review, 23 of these articles were identified as being eligible for inclusion into an NMA (Figure 8). Two articles (TOURMALINE-MM1 trial CSR [114] and the SMC detailed advice document for panobinostat [3]) were identified from other sources that were subsequently obtained for full review, met our eligibility criteria and were also included (Figure 8). Reviewing of reference lists is a process which is recommended by the Cochrane Handbook for Systematic Reviews to ensure all relevant studies are identified. [115] In total, 23 full text articles reporting on 14 individual studies were identified for inclusion into the NICE NMA network (Figure 8). In the April 2016 update we identified the abstract from the Tourmaline-MM1 trial (Moreau et al., 2015), [116] along with the full publication (Moreau et al., 2016) [1] which was associated with the first data cut of the TOURMALINE-MM1 trial data (IA1). [42] We identified Hou et al., 2016 [117] from the October 2016 update which was a regional expansion of the Tourmaline-MM1 trial conducted in China. As this study relates directly to ixazomib further details of methods and results are provided in Appendix 4. All three articles were included in the review.

Of the 23 articles from 14 individual studies to be included in the NMA, 18 articles were RCTs from 11 individual studies, 3 were observational studies, 1 study was a systematic literature review with 2 analyses (Pano + Bort + Dex versus either Len + Dex or Pom + Dex), and 1 study used data from the ixazomib CSR.

The 23 data sources from 14 studies are listed in Table 27 below.

A complete list of all excluded studies from the systematic review are also included in the systematic review reports.

Table 27: Data sources of identified RCTs for ixazomib plus lenalidomide – dexamethasone and other treatments for the treatment of RRMM

Study ID	Study type (RCT or Observational)	Primary data source	Location	Comparator 1	Comparator 2
Tourmaline-MM1*	**RCT**	***Data cut IA1 (30th October 2014)*** **Publication: Moreau et al., 2016a**	**International, including UK**	**Ixazomib + LenDex**	**Placebo + LenDex**
Tourmaline-MM1	RCT	*Data cut IA2 (12th July 2015)* CSR ixazomib 2015	International, including UK	Ixazomib + LenDex	Placebo + LenDex
Tourmaline-MM1	RCT	Hou et al., 2016 (*Data cut 12th July 2015)*	China	Ixazomib + LenDex	Placebo + LenDex
Matched-pairs of patients from 3 clinical trials: MMY-2045, APEX, and DOXIL-MMY-3001	Observational (retrospective analysis)	Dimopoulos et al., 2015	North America, Canada, and Europe (including the UK)	Bortezomib + Dex	Bortezomib
eVOBS	Observational	Dimopoulos et al., 2010	Belgium, France, Greece, Spain, Sweden, Turkey, and Brazil	Bortezomib + Dex	Bortezomib
Phase III	RCT	Montefusco et al.,	Italy	Bortezomib + Dex + cyclophosphamide	Len + Dex + cyclophosphamide
APEX	RCT	Richardson et al., 2005	North America, Canada, and Europe (including the UK)	Bortezomib	Dexamethasone
APEX	RCT	Richardson et al., 2007a	North America, Canada, and Europe (including the UK)	Bortezomib	Dexamethasone
ENDEAVOR*	**RCT**	**Dimopoulos et al., 2016**	**North and South America, Canada, Europe (including the UK), and the Asia-Pacific region**	**Carfilzomib + Dex**	**Bort + Dex**
ENDEAVOR	RCT	Moreau et al., 2015c	North and South America, Canada, Europe (including the UK), and the Asia-Pacific region	Carfilzomib + Dex	Bort + Dex
ASPIRE	**RCT**	**Stewart et al., 2015a**	**North America, Canada, and Europe (including the UK)**	**Carfilzomib + Len + Dex**	**Len + Dex**
ASPIRE	RCT	Dimopoulos et al., 2015b	North America, Canada, and Europe (including the UK)	Carfilzomib + Len + Dex	Len + Dex
MM-010	RCT	Dimopoulos et al., 2007	Europe (including the UK), and Asia-Pacific region	Len + Dex	Placebo + Dex
MM-009	RCT	Weber et al., 2007	North America and Canada	Len + Dex	Placebo + Dex
–	Observational (retrospective analysis)	Zagouri et al., 2016	–	Len + intermediate dose Dex	Len + low dose Dex
Match-adjusted indirect analysis of patients from 3 clinical trials: PANORAMA-1, MM009/010, MM-003	Systematic review	Majer et al., 2016	–	Pano + Bort + Dex Pano + Bort+ Dex	Len + Dex Pom + Dex
PANORAMA-1	RCT	Richardson et al., 2016	North and South America, Canada, Europe (including the UK), and the Asia-Pacific region	Pano + Bort + Dex	Bort + Dex

Study ID	Study type (RCT or Observational)	Primary data source	Location	Comparator 1	Comparator 2
PANORAMA-1*	**RCT**	**San-Miguel et al., 2014**	**North and South America, Canada, Europe (including the UK), and the Asia-Pacific region**	**Pano + Bort + Dex**	**Bort + Dex**
MM-002	RCT	Richardson et al., 2014	North America and Canada	Pom + Dex	Pom
MM-003	RCT	San-Miguel et al., 2013	North America, Canada, Europe (including the UK), and the Asia-Pacific region	Pom + Dex	High dose Dex
MM-003	RCT	San-Miguel et al., 2015d	North America, Canada, Europe (including the UK), and the Asia-Pacific region	Pom + Dex	High dose Dex

Abbreviations: CSR = clinical study report; LenDex = lenalidomide + dexamethasone; Bort = bortezomib; Dex = dexamethasone; Len = lenalidomide; Cyclo = cyclophosphamide; Pano = panobinostat; Pom = pomalidomide

* Studies in **bold** font indicate the primary publication

4.1.5 Data sources

Table 28 presents the bibliographic details of the references for the one identified study of ixazomib in patients with RRMM. The SLR identified the Clinical Study Report (CSR), an abstract presented at the American Society of Hematology (ASH) in 2015, and a manuscript published in 2016. The study design, procedures and results described in the following sections are from the publication by Moreau et al, 2016, [1] supplemented using the CSR [42] where needed (data from the abstract was not used as it was more comprehensively reported in the manuscript; it was also not included in the NMA to prevent double counting).

Table 28: Bibliographic details of the ixazomib RCT in patients with RRMM

Clinical Trial Records	
NCT01564537 (TOURMALINE-MM1 [C16010]) [42]	A Phase III, Randomised, Double-Blind, Multicenter Study Comparing Oral MLN9708 Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma
Published articles	
Moreau et al, 2016 [1]	Oral Ixazomib, Lenalidomide and Dexamethasone for Multiple Myeloma
Conference posters and abstracts	
Moreau, 2015Abstract: American Society of Hematology 57th Annual Meeting [116]	Ixazomib, an investigational oral proteasome inhibitor (PI), in combination with lenalidomide and dexamethasone (IRD), significantly extends progression-free survival (PFS) for patients (PTS) with relapsed and/or refractory multiple myeloma (RRMM): The Phase III TOURMALINE-MM1 study (NCT01564537).
Hou, 2016 [117] Abstract: ASCO annual meeting	Ixazomib plus lenalidomide-dexamethasone (IRd) vs placebo-Rd in patients (pts) with relapsed/refractory multiple myeloma (RRMM): China continuation of TOURMALINE-MM1
Richardson, 2016 [118] Abstract: ASCO annual meeting	Efficacy and safety of ixazomib plus lenalidomide-dexamethasone (IRd) vs placebo-Rd in patients (pts) with relapsed/refractory multiple myeloma (RRMM) by cytogenetic risk status in the global phase III TOURMALINE-MM1 study
Mateos, 2016 [119] Abstract: ASCO annual meeting	Impact of prior therapy on efficacy and safety of oral ixazomib-lenalidomide-dexamethasone (IRd) vs placebo-Rd in patients (pts) with relapsed/refractory multiple myeloma (RRMM) in TOURMALINE-MM1
Mateos, 2016 [120] Abstract: European Hematology Association	Efficacy and safety of oral ixazomib-lenalidomide-dexamethasone (IRD) vs placebo-RD in relapsed/ refractory multiple myeloma patients: impact of prior therapy in the Phase III TOURMALINE-MM1 study
Avet-Loiseau, 2016 [121] Abstract: European Hematology Association	Impact of cytogenetic risk status on efficacy and safety of ixazomib-lenalidomide-dexamethasone (IRD) vs placebo-RD in relapsed/refractory multiple myeloma patients in the global TOURMALINE-MM1 study
Leleu, 2016 [122] Abstract: European Hematology Association	Patient-reported quality of life with ixazomib-lenalidomide-dexamethasone (IRD) vs placebo-RD in relapsed/ refractory multiple myeloma patients in the global, placebo-controlled TOURMALINE-MM1 study.
Hou, 2016 [117] Abstract: European Hematology Association	Ixazomib plus lenalidomide-dexamethasone (IRD) vs placebo-RD in patients (pts) with relapsed/refractory multiple myeloma (RRMM): China continuation of TOURMALINE-MM1.
Di Bacco, 2016 [123] American Society of Hematology 58th Annual Meeting	Higher c-MYC expression is associated with ixazomib-lenalidomide-dexamethasone)IRD) progression-free survival (PFS) benefit versus placebo-RD: biomarker analysis of the Phase III TOURMALINE-MM1 study in relapsed/refractory multiple myeloma (RRMM).
Garderet, 2016 [124] American Society of Hematology 58th Annual Meeting	Longer time to best response and depth of response are associated with improved duration of best achieved response and progression-free survival (PFS): post-hoc analysis of Phase III TOURMALINE-MM1 trial in relapsed/refractory multiple myeloma (RRMM)

4.1.6 Reference list for excluded studies

The China continuation of Study C16010 was a regional extension of the TOURMALINE-MM1 study (n=115) that evaluated the safety and efficacy of IXA+LEN+DEX versus LEN+DEX in adult RRMM patients from China.

Compared with the TOURMALINE-MM1 study, patients in the China continuation study had more advanced disease:

- more patients had Durie-Salmon stage IIIa myeloma (63% vs 38%),

- more heavily pre-treated (38% and 17% had received 2 or 3 prior lines of treatment vs 29% and 10%),
- more frequently received prior thalidomide (84% vs 45%),
- more frequently had refractory MM (53% vs 11%)
- more frequently had thalidomide-refractory MM (63% vs 12%)

These patient characteristics are consistent with a large retrospective analysis of outcomes of Chinese patients with MM [125](ref).

The efficacy and safety results seen in the China continuation study are consistent with those of the TOURMALINE-MM1 study, and therefore support the activity of IXA+LEN+DEX across different study populations.

However, due to the divergence in ethnic, disease and treatment characteristics versus the global TOURMALINE-MM1 population, the results of the China continuation study have not been used in the economic model presented in Section 5 of this submission.

An overview of the China continuation study and results is provided in Appendix 3.

4.2 List of relevant randomised controlled trials

4.2.1 List of relevant randomised controlled trials

The TOURMALINE-MM1 study identified in the SLR is presented below in Table 29.

Table 29: List of relevant RCTs

Trial name	Population	Intervention	Comparator	Primary study references
TOURMALINE-MM1	Adult (≥18 years) patients with RRMM who had received 1 to 3 prior therapies	IXA+LEN+DEX (IRd)	LEN+DEX (Rd)	Moreau et al, 2016 [1] Clinical Study Report [42]
Abbreviations: IXA+LEN+DEX (IRd) = ixazomib+lenalidomide+dexamethasone; LEN+DEX (Rd) = (placebo+)lenalidomide+dexamethasone; RRMM = relapsed and/or refractory multiple myeloma Source: Moreau, 2016 [1] ; TOURMALINE-MM1 CSR [42]				

4.3 Summary of methodology of the relevant randomised controlled trials

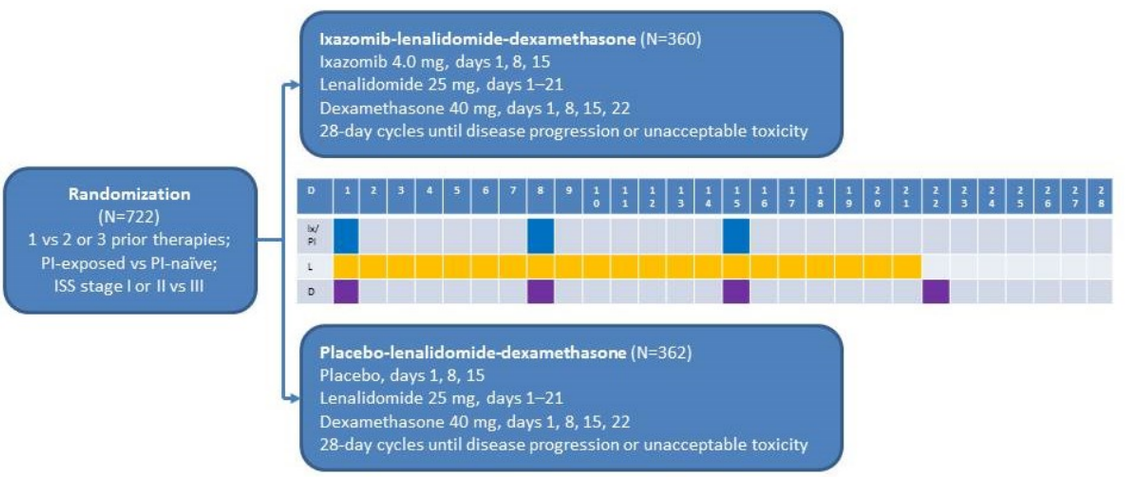
4.3.1 Trial design

The TOURMALINE-MM1 study (C16010) is an on-going global, Phase III, randomised, double-blind, multicentre clinical trial evaluating the safety and efficacy of an all-oral combination of IXA+LEN+DEX versus LEN+DEX in patients with RRMM who have had 1-3 prior therapies. [1]

Patients were randomly assigned in a 1:1 ratio to receive either oral ixazomib 4 mg or matching placebo capsule on days 1, 8, and 15, plus oral lenalidomide 25 mg on days 1-21 (10 mg for patients with creatinine clearance ≤60 or ≤50 mL/min, depending on local practice) and oral dexamethasone 40 mg on days 1, 8, 15, and 22, in 28-day cycles (Figure 10).

Randomisation was stratified by number of prior therapies (1 vs. 2 or 3), previous proteasome inhibitor exposure (naïve vs. exposed), and International Staging System disease stage (ISS I or II vs. III). [1] Treatment continued until disease progression or unacceptable toxicity.

Figure 10: TOURMALINE-MM1 study design with treatment schedule



Source: TOURMALINE-MM1 CSR [42](ref)

Patients who provided written informed consent received a country-, site-, and patient-specific enrolment code [42] Central randomisation using an interactive voice response system (IVRS) was used, with the randomisation scheme generated by an independent statistician at the sponsor, who was not on the study team. Patients were randomised strictly sequentially at each study centre as they became available for randomisation. Randomisation codes were not re-used from patients who discontinued.

In this double-blind study, all study personnel, including the investigators, site personnel, study clinicians, sponsor, and participants, were blinded to treatment assignments. [42] Only the independent statistical centre and Independent Data Monitoring Committee had, at prespecified interim analysis and interim safety review time points, access to un-blinded individual patient data.

4.3.2 Eligibility criteria

The inclusion criteria were chosen to select patients with RRMM on the basis of standard criteria and measurable disease. The exclusion criteria were chosen to remove from participation any patients who were refractory to lenalidomide or proteasome inhibitor-based therapy at any line, patients who were too ill or otherwise could not potentially benefit from the treatment, and patients with conditions that might confound assessments. The eligibility criteria are described in Table 30

Table 30: Eligibility criteria

Note: See table footnotes for abbreviations

Inclusion criteria
• **Male or female, age ≥18 years**
• **MM diagnosed per standard criteria either currently or at initial diagnosis (initial diagnosis must have been symptomatic MM; relapsed disease did not have to be symptomatic)**
• **Measurable disease, defined as at least one of: serum M-protein ≥1 g/dL, urine M-protein ≥200 mg/24 hrs, serum Free Light Chain (FLC) assay – involved FLC level ≥10 mg/dL, provided that serum FLC ratio was abnormal**
• **ECOG PS 0–2 (a scale from 0 to 5 where 0 is asymptomatic and increasing numbers indicate increasing tumour-related disability)**
• **RRMM after 1–3 prior therapies, including:** • **Patients who relapsed but were not refractory to previous treatments** • **Patients who were refractory to all lines of previous treatment (i.e. patients who had never responded)** • **Patients who relapsed from at least one previous treatment and were refractory to at least one previous treatment**
• **ANC ≥1000/mm^3, platelet count ≥75,000/mm^3**
• **Total bilirubin ≤1.5 x ULN, ALT and AST ≤3 x ULN**
• **Creatinine clearance ≥30 mL/min**
• **No active GVHD in patients with prior allo-SCT†**
• **Female patients: post-menopausal for ≥24 months prior to screening; or surgically sterile; or if they were of childbearing potential, negative pregnancy test within 10–14 days and again within 24 hours of start of cycle 1 of lenalidomide – agreed to practice true abstinence or use two reliable methods of birth control, agreed to ongoing pregnancy testing, and adhered to guidelines of RevAssist program (US) or equivalent local programme†**
• **Male patients, even if surgically sterilised: agreed to practice true abstinence; or agreed to practice effective barrier contraception during the entire study treatment period and 90 days after the last dose of study treatment if their partner was of childbearing potential, even if they had a successful vasectomy; and adhered to guidelines of RevAssist program (US) or equivalent local programme†**
• **Able to take concurrent aspirin 81–325 mg daily (or enoxaparin 40 mg subcutaneously daily [or its equivalent] if allergic to aspirin), per published standard or institutional standard of care, as prophylactic anticoagulation†** • **For patients with prior history of deep vein thrombosis (DVT), low-molecular-weight heparin (LMWH) was mandatory†**

• **Voluntary written consent; willing and able to adhere to study visit schedule and other protocol requirements**
Exclusion criteria
• **Refractory to lenalidomide or PI-based therapy at any line (refractory disease defined as disease progression on treatment or progression within 60 days after last dose)** • **Patients refractory to thalidomide-based therapy were eligible**
• **Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within 6 months before randomisation in the study**
• **Failure to have fully recovered (grade ≤1 toxicity) from effects of prior chemotherapy (except alopecia) regardless of interval since last treatment**
• **Psychiatric illness/social situation that would limit compliance with study requirements.**
• **Major surgery within 14 days before randomisation** • **Radiotherapy within 14 days before randomisation** • **Infection requiring systemic antibiotic therapy or other serious infection within 14 days before randomisation**
• **Central nervous system involvement**
• **Diagnosis of Waldenstrom's macroglobulinemia, POEMS syndrome, plasma cell leukaemia, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome†**
• **Female patients who were breast-feeding or pregnant†**
• **Ongoing or active systemic infection, active hepatitis B or C virus infection, or known human immunodeficiency virus positive**
• **Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens (e.g., peripheral neuropathy that is Grade 1 with pain or Grade 2 or higher of any cause).**
• **Systemic treatment with strong inhibitors of cytochrome P450 (CYP) 1A2 (CYP1A2) (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort within 14 days before randomisation in the study**
• **Diagnosed or treated for another malignancy within 2 years before randomisation or previously diagnosed with another malignancy and any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type were not excluded if they had undergone complete resection**
• **Inability to swallow oral medication, inability or unwillingness to comply with the drug administration requirements, or gastrointestinal condition that could interfere with the oral absorption or tolerance of treatment†**

• **Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent†**
Abbreviations: Allo-SCT = allogeneic stem cell transplant; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ECOG = Eastern Cooperative Oncology Group; FLC = free light chain; GVHD = graft-versus-host disease; PI = proteasome inhibitor; PS = performance status; RRMM = relapsed and/or refractory multiple myeloma; ULN = upper limit of normal **Source: Moreau, 2016 [1] ; † TOURMALINE-MM1 CSR [42]**

4.3.3 Settings and locations where the data were collected

The study was conducted at 147 investigative centres globally in 26 countries shown in Table 31, and included nine centres from across the UK (one was inactive), from which 21 patients were recruited and included in the study.

Table 31: TOURMALINE-MM1 study locations

Region	Countries
Europe	Austria, Belgium, Czech Republic, Denmark, France, Germany, Hungary, Italy, Israel, Netherlands, Poland, Portugal, Romania, Russian Federation, Spain, Sweden, Turkey, United Kingdom
North America	USA, Canada
Asia-Pacific	Australia, China, Japan, New Zealand, Singapore, South Korea
Source: Moreau, 2016 [1]	

4.3.4 Trial drugs and concomitant medications

4.3.4.1 Trial drugs

Patients received oral ixazomib 4 mg or matching placebo capsule on days 1, 8, and 15, plus oral lenalidomide 25 mg on days 1-21 and oral dexamethasone 40 mg on days 1, 8, 15, and 22, in 28-day cycles [1] Patients were to continue to receive treatment until disease progression or unacceptable toxicity, whichever occurred first [1] Dose adjustments for toxicities were permitted using established dose-modification guidelines per the protocol/prescribing information for each drug [1]

4.3.4.2 Permitted and disallowed concomitant medications

Permitted and disallowed concomitant medications were as follows [1]. Thromboprophylaxis according to the American Society of Clinical Oncology (ASCO) guidelines or institutional standard of care was required to prevent thromboembolic complications that may occur with lenalidomide-based regimens, e.g., aspirin (81–325 mg orally once daily) or low-molecular weight heparin (equivalent to enoxaparin 40 mg subcutaneous per day) depending on patient risk factors. Prophylactic antiviral therapy was permitted as clinically indicated.

All necessary supportive care consistent with optimal patient care per local standards was available to patients. Use of myeloid growth factors (e.g., granulocyte colony stimulating factor, granulocyte macrophage-colony stimulating factor) and erythropoietin was allowed, with use of erythropoietin to be minimised as much as possible given potential risk of deep vein thrombosis with lenalidomide. Red blood cell and platelet transfusions were given as clinically indicated. Standard anti-emetics including 5-hydroxytryptamine 3 serotonin receptor (5-HT3) antagonists were recommended for emesis if it occurred once treatment was initiated; prophylactic anti-emetics were also permitted at the physician's discretion. Topical, intravenous, or oral antihistamines or steroids were permitted to manage rash. Concomitant treatment with bisphosphonates was also permitted.

Systemic treatment with strong CYP1A2 inhibitors (fluvoxamine, enoxacin, and ciprofloxacin) or strong CYP3A inhibitors (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, and posaconazole), or use of Ginkgo biloba or St John's wort

was not permitted. Systemic treatment with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital) was to be avoided. Radiation therapy or any anti-neoplastic treatment with activity against multiple myeloma, other than the study drugs, was not permitted.

4.3.5 Primary and secondary outcomes

The primary, key secondary and other secondary outcomes in the TOURMALINE-MM1 study are described in

Table 32.

The outcomes of interest in the NICE scope include PFS, overall survival (OS), response rates, time to next treatment, adverse effects of treatment and health-related quality of life. All of these have been reported in the TOURMALINE-MM1 study (shown in bold in

Table 32) except for *time to next treatment*. However, the study did collect data on the following parameters that may be useful surrogates for *time to next treatment*: *time to progression; time to response; and duration of response.* The results of all the relevant outcomes have been presented in the clinical effectiveness results (Section 4.7) and adverse events section (Section 4.12).

Table 32: TOURMALINE-MM1 study outcomes

	Endpoint
Primary	**PFS, defined as the time from the date of randomisation to the date of first documentation of disease progression based on central laboratory results and IMWG criteria as evaluated by an IRC, or death due to any cause, whichever occurred first**
Key secondary	**OS, measured as the time from the date of randomisation to the date of death**
	OS in high-risk patients carrying del(17)
Other secondary	**Overall response rate (ORR) i.e complete response [CR] + very good partial response [VGPR] + partial response [PR])**
	CR+VGPR rate (ie, ≥ VGPR)
	Duration of response (DOR), measured as the time from the date of first documentation of response to the date of first documented progression
	Time to progression (TTP), measured as the time from randomisation to the date of first documented progression
	To determine the safety of the addition of ixazomib to lenalidomide and dexamethasone: Eastern Cooperative Oncology Group (ECOG) performance scores, adverse events (AEs), serious adverse events (SAEs), and assessments of clinical laboratory values
	Pain response rate, measured by the proportion of pain responders, as determined by Brief Pain Inventory-Short Form (BPI-SF) and analgesic use†
	Comparison of change in global health status between baseline and each post-baseline assessment, as measured by the global health scale, functioning, and symptoms of the EORTC QLQ-C30 and MY-20
	OS and PFS in high-risk cytogenetic patient groups carrying translocations t(4;14), t(14;16) or del(17) [and +1q21, del(13) †a]
	Association between response or resistance to ixazomib treatment and proteasome and NFκB-related genes, such as proteasome subunit beta type-1 (PSMB1) and tumour necrosis factor receptor-associated factor-3 (TRAF-3), in blood samples†
	Plasma concentration-time data to contribute to future population pharmacokinetic (PK) analysis†
Exploratory†	Assess health utilisation by collecting the number of medical encounters; assess health utility values per the EQ-5D questionnaire
	Time to pain progression and time to pain response, as assessed by the time from randomisation to the date of initial progression/response classification. Duration of pain response, measured as the time from randomisation to the first documented progression classification

	Endpoint
	Association between response or resistance to ixazomib treatment and tumour gene expression patterns including NFκB and protein synthesis signatures
	Mechanisms of treatment-emergent resistance, such as somatic mutations in proteasome subunits, in tumours that initially respond to therapy and then exhibit progressive disease
	Development of new or worsening of existing selected skeletal-related events, defined as new fractures (excluding vertebral compression or rib fractures), irradiation of or surgery on bone, or spinal cord compression from baseline through the development of progressive disease

Abbreviations: CR = complete response; EORTC QLQ-C30 and MY-20 = the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the Quality of Life Questionnaire MM Module 20 (MY-20); EQ-5D = EuroQol-5D; IMWG = International Myeloma Working Group; IRC = independent review committee; OS = overall survival; PFS = progression free survival; VGPR = very good partial response

BOLD black = The outcomes of interest in the NICE scope that are reported in the TOURMALINE-MM1 study

BOLD grey = The outcomes that may be useful surrogates for the outcome in the NICE scope of *time to next treatment*

[a] The final statistical analysis plan (SAP) excluded del(13) and 1q (1q21+) from the high-risk evaluations because during the course of the study, the definition of high-risk abnormalities for MM evolved and 1q21+ was considered intermediate-risk.

Source: Moreau, 2016 [1] ; [†] TOURMALINE-MM1 CSR [42]

Health-related quality of life was evaluated through patient self-reported instruments including the EORTC QLQ-C30 and MY-20 questionnaires.

Response assessments were performed every cycle (i.e. every 28 days) until disease progression. [1] Response and disease progression assessments were based on central laboratory results and International Myeloma Working Group (IMWG) 2011 criteria (Table 33) as evaluated by the independent review committee (IRC) blinded to both patient assignment and investigator assessment. All patients were followed for survival after disease progression (every 12 weeks until death or termination of the study).

Table 33: International Myeloma Working Group (IMWG) Uniform Response Criteria

Disease response	Criteria
Stringent complete response (sCR)	CR as defined below, plus: • Normal free light chain ratio, and • Absence of clonal plasma cells by immunohistochemistry or 2- to 4-colour flow cytometry
Complete response (CR)	• Negative immunofixation of serum and urine, and • Disappearance of any soft tissue plasmacytomas, and • <5% plasma cells in bone marrow Additional criterion in patients with measurable disease by serum free light chain levels only: • Normal free light chain ratio of 0.26 to 1.65
Very good partial response (VGPR)	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, or • ≥90% reduction in serum M-component plus urine M-component <100 mg/24 h Additional criterion in patients with measurable disease by serum free light chain levels only: • >90% decrease in difference between involved and uninvolved free light chain levels
Partial response (PR)	• ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 h If serum and urine M-protein are not measurable: • Decrease of ≥50% in difference between involved and uninvolved free light chain levels If serum and urine M-protein and serum free light assay are not measurable: • ≥50% reduction in bone marrow plasma cells, provided baseline percentage was ≥30% In addition to the above criteria, if present at baseline: • ≥50% reduction in size of soft tissue plasmacytomas

Disease response	Criteria
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, or PD

Progressive disease (PD) / relapse	Any one or more of the following:
	• Increase of 25% from lowest response value in any of:
	  ○ Serum M-component (absolute increase ≥0.5 g/dL), and/or
	  ○ Urine M-component (absolute increase ≥200 mg/24 h), and/or
	  ○ Difference between involved and uninvolved free light chain levels (absolute increase >10 mg/dL) (only in patients without measurable serum and urine M-protein levels), and/or
	  ○ Bone marrow plasma cell percentage (absolute percentage ≥10%) (only in patients without measurable serum and urine M-protein levels and without measurable disease by free light chain levels)
	• Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
	• Development of hypercalcaemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

All response categories and relapse require 2 consecutive assessments made at any time before the institution of any new therapy. If radiographic studies were performed, sCR, CR, VGPR, PR, and SD require no known evidence of progressive or new bone lesions. CR and VGPR require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of ≥1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL. For PD, definite increase of plasmacytoma defined as a 50% (at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion). Source: Moreau et al, 2016 [1] : Originally from Rajkumar, 2011 [126] and Durie, 2006 [127]	

4.3.6 Summary of the methodology of the TOURMALINE-MM1 RCT

A summary of the methodology of the study is shown in Table 34.

Table 34: Summary of the methodology of the TOURMALINE-MM1 study

Trial name	• TOURMALINE-MM1
Location	• 147 investigative centres globally in 26 countries in Europe, North America and Asia-Pacific
Trial design	• Phase III, randomised, double-blind, multicentre study to evaluate the efficacy and safety of IXA+LEN+DEX vs. LEN+DEX
Key Eligibility criteria for participants	• Adult patients with relapsed and/or refractory multiple myeloma, measurable disease (including by serum free light chain assay only), and ECOG performance status 0-2 who had received 1-3 prior lines of therapy, and who had adequate haematologic and hepatic function, were eligible; patients with mild-to-moderate renal function impairment (calculated creatinine clearance ≥30 mL/min) were included. • Patients with peripheral neuropathy of grade 1 with pain or grade ≥2, and patients refractory to prior lenalidomide or proteasome inhibitor-based therapy were not eligible; primary refractory patients were included
Settings and locations where the data were collected	• Secondary care - oncology
Intervention(s) (n=[x]) and comparator(s) (n=[x])	• IXA+LEN+DEX (n=360); LEN+DEX (n=362)
Permitted and disallowed concomitant medication	• Permitted: myeloid growth factors; erythropoietin; transfusions with red cells and platelets; digoxin; bisphosphonates; supportive measures. • Disallowed: Strong inhibitors of CYP1A2 and CYP3A; strong CYP3A inducers; St. John's wort and Ginkgo biloba; any antineoplastic treatment with activity against MM, other than study

	drugs; radiation therapy; platelet transfusions to help patients meet eligibility criteria were not allowed within 3 days prior to study drug dosing
Primary outcomes (including scoring methods and timings of assessments)	• PFS, defined as the time from the date of randomisation to the date of first documentation of disease progression based on central laboratory results and IMWG criteria as evaluated by an IRC, or death due to any cause, whichever occurred first
Key secondary outcomes (including scoring methods and timings of assessments)	• OS, measured as the time from the date of randomisation to the date of death • OS in high-risk patients carrying del(17)
Other secondary outcomes (including scoring methods and timings of assessments)	• Overall response rate (CR+VGPR+PR) • CR+VGPR rate • DOR, measured as the time from the date of first documentation of response to the date of first documented progression • TTP, measured as the time from randomisation to the date of first documented progression • Safety: ECOG performance scores, AEs, SAEs, and assessments of clinical laboratory values • Pain response rate, measured by the proportion of pain responders, as determined by the BPI-SF and analgesic use† • Comparison of change in global health status between baseline and each post-baseline assessment, as measured by the global health scale, functioning, and symptoms of the EORTC QLQ-C30 and MY-20 • OS and PFS in high-risk population carrying del(17), t(4;14), or t(14;16) • Association between response or resistance to ixazomib treatment and proteasome and NF-κB-related genes, such as PSMB1 and TRAF-3† • Plasma concentration-time data to contribute to future population PK analysis†
Pre-planned subgroups†	• Subgroup analyses were performed relative to baseline stratification factors, demographics, disease characteristics, and number and types of prior therapy. • They included subgroups by prior line of therapy of relevance to the NICE scope i.e those with one prior therapy and 2/3 prior therapies. • Other factors included: cytogenetic abnormalities, ISS stage, age, sex, race, region, Western country, prior therapy, relapsed (and/or) treatment refractory, ECOG performance status, and baseline CrCl.
Abbreviations: AEs = adverse events; BPI-SF = Brief Pain Inventory-Short Form; CR = complete response; CrCl = creatinine clearance; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; IMWG = International Myeloma Working Group; IRC = independent review committee;; EORTC QLQ-C30 and MY-20 = the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the Quality of Life Questionnaire MM Module 20 (MY-20); EQ-5D = EuroQol-5D;; OS = overall survival; PFS = progression free survival; PK = pharmacokinetic; PR = partial response; SAE = serious adverse event; TTP = time to progression; VGPR = very good partial response Source: Moreau, 2016 [1] † TOURMALINE-MM1 CSR [42]	

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

4.4.1 Analysis sets

The intent-to-treat (ITT) population [1] : defined as all patients who were randomised. Patients were analysed according to the treatment they were randomised to receive,

regardless of any errors in dosing. The ITT population was used for all primary and secondary efficacy analyses.

The safety population [1] : defined as all patients who received at least 1 dose of any study drug. Patients were analysed according to the treatment actually received, regardless of which treatment they were randomised to receive. Patients who received any dose of ixazomib were included in the IXA+LEN+DEX group and patients who did not receive any dose of ixazomib were included in the LEN+DEX group, regardless of their randomised treatment. The Safety population was used for all safety-related analyses such as AEs, concomitant medications, laboratory tests, and vital signs.

4.4.2 Hypotheses

The study was designed to assess the efficacy and safety of weekly IXA+LEN+DEX versus LEN+DEX in patients with RRMM. [1,42] The primary objective was to determine whether the addition of once-weekly oral ixazomib to the background therapy of lenalidomide and dexamethasone improves PFS in patients with RRMM. [1,42]

4.4.3 Sample size calculations

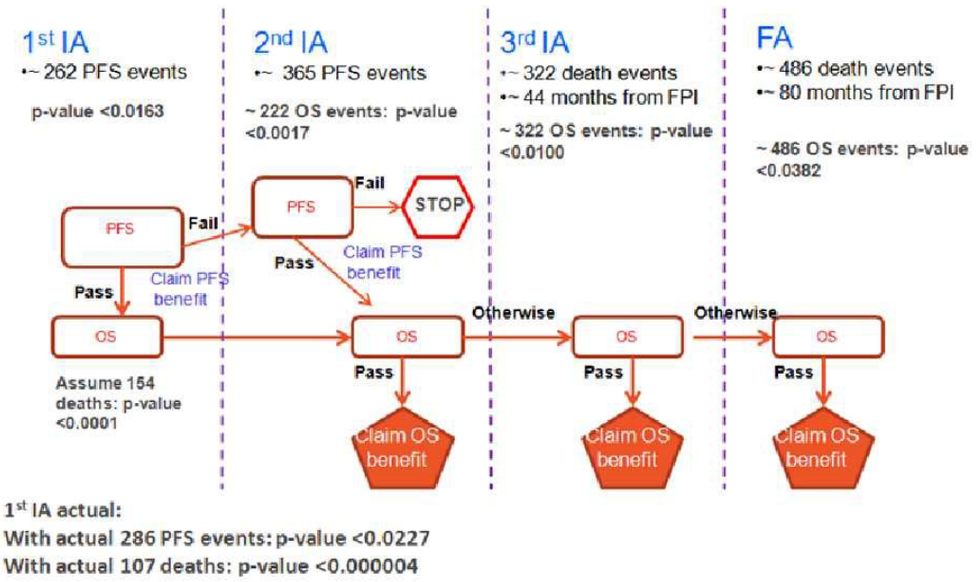
The total sample size of the study was planned to be approximately 703 patients (actual accrual: 722 patients) in order to provide sufficient power to adequately evaluate both PFS and OS. [42] Total sample size was calculated to provide 80% power (2-sided alpha 0.05) to test for a 30% improvement in OS (assumed hazard ratio of 0.77) [1]. The study was powered to demonstrate PFS superiority (hazard ratio 0.74).[1] An O'Brien-Fleming stopping boundary for efficacy was calculated using a Lan-DeMets alpha-spending function [128] based on the observed number of events at the data cut-off date. [1] An interim analysis was planned when approximately 36% of patients experienced a PFS event [1]

4.4.4 Interim analyses and stopping guidelines

Three sequential interim analyses plus a final analysis were planned (Figure 11) [1] The first interim analysis was planned when approximately 36% of patients experienced a PFS event [1] At the first, pre-planned analysis (data cut-off: 30th October 2014; median follow-up ~15 months), the PFS results crossed the pre-specified O'Brien-Fleming boundary demonstrating a statistically significant benefit of the IXA+LEN+DEX regimen versus LEN+DEX; therefore, consistent with the statistical methodology, this was the final statistical analysis of PFS. Per protocol, the study continued in a double-blind manner to gain more mature OS data; a second pre-planned interim analysis (data cut-off: 12th July 2015; median follow-up of ~23 months) was conducted for OS.

The clinical effectiveness results (Section 4.7) presents data from both these interim analyses; safety data from the second interim analysis is presented in Section 4.12. The study continues in a double-blind, placebo-controlled manner to obtain more mature OS data. A third interim analysis is expected in Q2 2017 with a final analysis to follow later.

Figure 11: Statistical assumptions in the TOURMALINE-MM1 study schedule



FPI = first patient in; IA = interim analysis; OS = overall survival; PFS = progression-free survival
Source: TOURMALINE-MM1 CSR [42]

4.4.5 Statistical methods used to compare groups

Primary and secondary outcomes

The study used a closed sequential testing procedure for the primary endpoint of PFS and the key secondary endpoints OS and OS in patients carrying del(17p) (2-sided alpha 0.05; test for overall survival conducted on its own alpha-spending functions only if PFS was significant) [1] Kaplan-Meier methodology was used to estimate time-to-event distributions, with stratified log-rank tests and Cox models (alpha=0.05, two-sided) used for inter-arm comparisons of time-to-event endpoints. [1]

Safety assessment

Adverse events (AEs) were coded using MedDRA version 16.0. [42] Treatment-emergent AEs (TEAEs) were defined as AEs that occurred after administration of the first dose of any study drug and through 30 days after the last dose of any study drug. AEs were summarised as per the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

4.4.6 Handling of missing data and withdrawals

The ITT population was used for all primary and secondary efficacy analyses. [1] The primary endpoint was PFS, defined as the time from the date of randomisation to the date of first documentation of progressive disease based on central laboratory results and International Myeloma Working Group (IMWG) criteria as evaluated by an independent review committee, or death due to any cause, whichever occurred first. Patients without documentation of progressive disease were censored at the date of the last response assessment that was stable disease or better. [42] The details regarding the handling of missing assessments and censoring for the PFS analysis are presented in Table 35

Table 35: Handling of missing assessments and censoring for PFS primary analysis based on FDA guidance

Situation	Date of Progression or Censoring	Outcome
No baseline and/or no postbaseline assessment, no subsequent anticancer therapy after study treatment, no death	Date of randomisation	Censored
Disease progression documented between scheduled visits	Date of next scheduled visit	Progressed
No documented death or disease progression	Date of last adequate assessment[a]	Censored
Lost to follow-up, withdraw consent before any documented death or disease progression	Date of last adequate assessment[a]	Censored
Treatment discontinuation for undocumented disease progression after the last adequate assessment	Date of last adequate assessment[a]	Censored
Death or progression after more than 1 missed visit	Date of last adequate assessment[a]	Censored
Alternate antineoplastic therapy started prior to disease progression	Date of last adequate assessment prior to starting alternate antineoplastic therapy	Censored
Death before first assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
[a] Adequate disease assessment was defined as sufficient data to evaluate a patient's disease status Source: TOURMALINE-MM1 CSR [42]		

4.4.7 Subgroup analyses

Pre-specified subgroup analyses of PFS and OS were conducted. Subgroup analyses were performed relative to baseline stratification factors, demographics, disease characteristics, and number and types of prior therapy. They included subgroups by prior line of therapy, which are of relevance to the NICE scope (Table 1) i.e. those with 1 versus 2 or 3 prior therapies. Other factors included: cytogenetic abnormalities, ISS stage, age, sex, race, region, Western country, prior therapy, relapsed (and/or) treatment-refractory, ECOG performance status, and baseline creatinine clearance. A stratified Cochran-Mantel-Haenszel Chi-squared test was used to assess inter-arm differences in response rates. [1]

4.4.8 Summary of the statistical analysis used in the primary analysis

A summary of the statistical analysis is shown in Table 36

Table 36: Summary of the statistical analysis

Trial name	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
TOURMALINE-MM1	The primary objective was to determine whether the addition of oral ixazomib to the background therapy lenalidomide-dexamethasone improves PFS in patients with RRMM	A closed sequential testing procedure was used for the primary endpoint of PFS and the key secondary endpoints of OS and OS in patients carrying del(17p) (2-sided alpha 0.05; test for OS conducted on its own alpha-spending functions only if PFS was significant). Kaplan-Meier methodology was used to estimate time-to-event distributions, with stratified log-rank tests and Cox models (alpha=0.05, two-sided) used for inter-arm comparisons of time-to-event endpoints	Total sample size was calculated to provide 80% power (2-sided alpha 0.05) to test for a 30% improvement in OS (assumed hazard ratio of 0.77). The study was powered to demonstrate PFS superiority (hazard ratio 0.74). An O'Brien-Fleming stopping boundary for efficacy was calculated using a Lan-DeMets alpha-spending function [128] based on the observed number of events at the data cut-off date	The ITT population was used for all primary and secondary efficacy analyses, defined as all patients who were randomised

Abbreviations: ITT = intent-to-treat; OS = overall survival; PFS = progression-free survival; RRMM = relapsed and/or refractory multiple myeloma

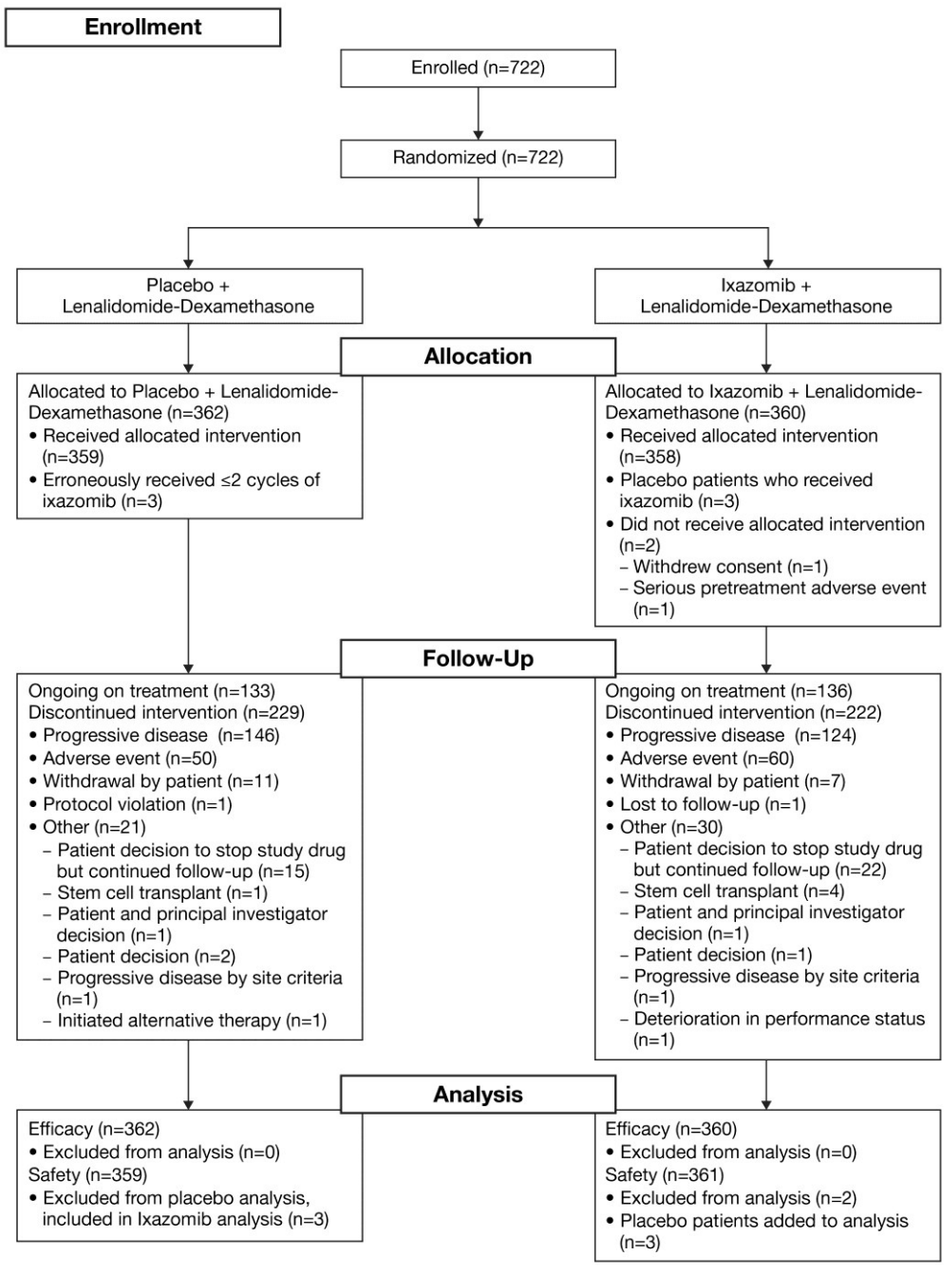
Source: Moreau, 2016.[1]

4.5 Participant flow in the relevant randomised controlled trials

4.5.1 Participant flow

Patient disposition in the TOURMALINE-MM1 study is summarised in the CONSORT diagram in Figure 12 There were no unexpected imbalances in drop-outs between treatment groups: at data cut-off for the second interim analysis (July 2015), 136 (38%) and 133 (37%) patients in the IXA+LEN+DEX and LEN+DEX arms, respectively, remained on treatment, and 222 (62%) and 229 (63%), respectively had discontinued. . [1] The two most common reasons for discontinuation were progressive disease (34% and 40% of patients) and adverse events (17% and 14%). Two of the 360 patients randomised to IXA+LEN+DEX did not receive any study treatment, and three of the 362 patients randomised to LEN+DEX accidentally received limited dosing of ixazomib, and were therefore conservatively included within the IXA+LEN+DEX group for analyses of exposure and safety. There were also no imbalances across regions and countries in terms of enrolment by treatment (Asia Pacific: 18% of IXA+LEN+DEX patients; 21% of LEN+DEX patients; Europe: 69% and 65%; North America: 13% and 14%). [42]

Figure 12: TOURMALINE-MM1 patient disposition – CONSORT diagram



Source: Moreau, 2016 [1]

4.5.2 Patient characteristics at baseline

The demographics and baseline characteristics for patients randomised to the IXA+LEN+DEX and LEN+DEX arms in TOURMALINE-MM1 are summarised in Table 37. Disease characteristics were well balanced between the two arms, notably in terms of the randomisation stratification factors, as would be expected, and other prognostic factors such as age, renal impairment (creatinine clearance of <60 mL/min), cytogenetic risk categories, and refractory disease status.

Of relevance for the NICE scope, 59% (n=425) of patients had received 1 prior line and 41% (n=297) had received 2 or 3 lines of prior therapy (based on stratification factors).Overall, 12% (87) had stage III disease and 19% (137) had high-risk cytogenetics (defined as

del[17], t[4;14], t[14;16]). In addition, 70% of the patient population had been exposed to prior PI therapy and 55% had been exposed to prior IMiD therapy. Of the 397 patients who had prior exposure to IMiD therapy, 41 of 193 IXA+LEN+DEX regimen patients (21%) and 50 of 204 LEN+DEX regimen patients (25%) were refractory to any prior IMiD therapy, with all but 1 patient noted as refractory to thalidomide. Of the 502 patients who had prior exposure to PI therapy, 4 of 249 the IXA+LEN+DEX patients (1%) and 8 of 253 the LEN+DEX patients (2%) were refractory to any prior PI therapy (the study had been designed to exclude patients who were refractory to PI-based therapy, however a few were included). Overall, 46 patients (24 in the IXA+LEN+DEX arm [7%] and 22 in the LEN+DEX arm [6%]) were primary refractory (i.e. had never responded to any prior therapy [best response of stable disease or progressive disease]).

Table 37: TOURMALINE-MM1 study baseline patient characteristics

Characteristic	IRd (N=360)	Rd (N=362)	Overall (N=722)
Age, median (range), yrs	66 (38–91)	66 (30–89)	66 (30–91)
Age >65 years, n (%)	192 (53)	186 (51)	378 (52)
Male, n (%)	207 (58)	202 (56)	409 (57)
White race, n (%)	310 (86)	301 (83)	611 (85)
Lines of prior therapy, n (%)[a]			
1	224 (62)	217 (60)	441 (61)
2	97 (27)	111 (31)	208 (29)
3	39 (11)	34 (9)	73 (10)
2 or 3	136 (38)	145 (40)	281 (39)
Stratification factors: line of therapy			
1	212 (59)	213 (59)	425 (59)
2 or 3	149 (41)	148 (41)	297 (41)
Cytogenetics[b]			
Patients with standard-risk cytogenetics, n (%)	199 (55)	216 (60)	415 (57)
Patients with high-risk cytogenetics, n (%)	75 (21)	62 (17)	137 (19)
Data not available, n (%)	86 (24)	84 (23)	170 (24)
ISS Stage at study entry, n (%)			
I	226 (63)	233 (64)	459 (64)
II	89 (25)	87 (24)	176 (24)
III	45 (13)	42 (12)	87 (12)
ECOG performance status, n (%)[c]			
0	180 (50)	170 (47)	350 (48)
1	156 (43)	164 (45)	320 (44)
2	18 (5)	24 (7)	42 (6)
Creatinine clearance, median (range), n (%)	78.4 (27–233)	78.4 (20–233)	78.4 (20– 233)
<30 mL/min	5 (1)	5 (1)	10 (1)
30-<60 mL/min	74 (21)	95 (26)	169 (23)
60-<90 mL/min	155 (43)	129 (36)	284 (39)
≥90 mL/min	126 (35)	132 (36)	258 (36)
Time since initial diagnosis of MM, median (range), months	44.2 (3–281)	42.2 (4–306)	42.8 (3–306)
Prior SCT	212 (59)	199 (55)	411 (57)
Patient category, n (%)[d]			
Relapsed	276 (77)	280 (77)	556 (77)
Refractory	42 (12)	40 (11)	82 (11)
Relapsed and refractory	41 (11)	42 (12)	83 (11)
Primary refractory	24 (7)	22 (6)	46 (6)
Prior PI therapy, n (%)	249 (69)	253 (70)	502 (70)
Bortezomib-exposed	248 (69)	250 (69)	498 (69)
Carfilzomib-exposed	1 (<1)	4 (1)	5 (<1)
Refractory to any prior PI therapy, n (%)[e]	4 (1)	8 (2)	12 (2)
Prior immunomodulatory drug therapy, n (%)	193 (54)	204 (56)	397 (55)
Lenalidomide-exposed	44 (12)	44 (12)	88 (12)
Thalidomide-exposed	157 (44)	170 (47)	327 (45)
Refractory to any prior immunomodulatory drug therapy, n (%)[f]	41 (21)	50 (25)	91 (23)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IMiD = immunomodulatory drug; IRd = ixazomib with lenalidomide and dexamethasone; Rd = placebo with lenalidomide and dexamethasone; PI = proteasome inhibitor; SCT = stem cell transplant

[a] Lines of prior therapy determined by blinded Sponsor medical review of prior therapy data. Prior therapies were defined per Rajkumar et al. 2011[126] and does not exactly match the stratification factor (lines of prior therapy: 1 versus 2 or 3).

[b] High-risk cytogenetics defined as: del(17p), t(4;14), t(14;16), detected by fluorescence in situ hybridization analysis (FISH) – 36 and 33 patients in the ixazomib and placebo groups, respectively, had del(17p) alone or in combination with either or both t(4;14) and t(14;16), 36 and 25 patients, respectively, had t(4;14) alone, and 3 and 4 patients, respectively, had t(14;16) alone; standard-risk cytogenetics defined as absence of high-risk abnormalities in evaluable samples; samples from some patients not available for testing as sample was missing or clotted, or due to other reasons. Cut-off values for defining presence of high-risk cytogenetic abnormalities were, per protocol, established by the central diagnostic laboratory based on the false-positive rates, or technical cut-offs, of the FISH probes used. These cut-offs were 5% positive cells for del(17p), 3% for t(4;14), and 3% for t(14;16).

[c] Missing data for 6 (2%) and 4 (1%) in the ixazomib and placebo groups, respectively.

[d] N=359 for ixazomib-lenalidomide-dexamethasone group.

[e] Refractoriness to any prior PI therapy as determined by blinded medical review by the Sponsor.

[f] Patients were refractory to prior thalidomide, except for one patient in the placebo- lenalidomide-dexamethasone group who, upon further blinded Sponsor medical review, was determined to be refractory to prior lenalidomide.

Source: Moreau, 2016 [1]

4.6 Quality assessment of the relevant randomised controlled trials

In order to assess the risk of bias and generalisability of the TOURMALINE-MM1 study, a quality assessment was conducted using guidance from 'Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)'. [129]

A summary of the quality assessment is provided in Table 38, showing that the TOURMALINE-MM1 study is a high quality RCT with an overall low risk of bias.

Table 38: Quality assessment of the TOURMALINE-MM1 study

Was randomisation carried out appropriately?	Yes, randomisation of patients in a 1:1 ratio to study interventions was carried out using an IVRS
Was the concealment of treatment allocation adequate?	Yes, allocation was concealed by using an IVRS for randomisation
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, baseline characteristics were well balanced between treatment groups for the ITT population and for the pre-specified subgroups
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, in this double-blind study, all study personnel, including the investigators, site personnel, study clinicians, sponsor, and participants, were blinded to treatment assignments. Only the independent statistical centre and Independent Data Monitoring Committee had, at prespecified interim analysis and interim safety review time points, access to un-blinded individual patient data.
Were there any unexpected imbalances in drop-outs between groups?	No, there were no unexpected imbalances in drop-outs between treatment groups: at data cut-off for the second interim analysis (~23-months), 136 (38%) and 133 (37%) patients in the IXA+LEN+DEX and LEN+DEX arms, respectively, remained on treatment, and 222 (62%) and 229 (63%), respectively had discontinued
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No, there is no evidence that suggests that authors measured more outcomes than they reported
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, an ITT analysis (all randomised patients) was used for analyses of efficacy The safety population, which included all patients who received ≥ 1 dose of study drug, was used for analyses of safety and tolerability.
IVRS = interactive voice response system; ITT, intent-to-treat	

4.7 Clinical effectiveness results of the relevant randomised controlled trials

In Section 4.7.1 the outcomes from the entire ITT population (i.e all patients who were randomised [n=722]) are presented. In Section 4.8 we present the results of the subgroup analysis of patients who received 2 or 3 prior lines of therapy, which is of relevance to the NICE scope. Other pre-specified subgroups based on a range of factors including age, cytogenetics, ISS stage and relapsed and/or refractory disease are shown in Section 4.8.3.

To date there have been two interim analyses from the TOURMALINE-MM1 study. At data cut-off for the first analysis (30 October 2014), median follow-up was 14.8 and 14.6 months

in the IXA+LEN+DEX and LEN+DEX groups, respectively. As the primary endpoint of improving PFS was met at the first analysis, this was the final statistical analysis of this endpoint. We have presented clinical data from both interim analyses. Adverse events from the longer duration of follow-up second interim analysis, presented for the whole safety population and the subgroups based on prior therapy are presented in Section 4.12.

4.7.1 Clinical effectiveness results in the entire ITT population

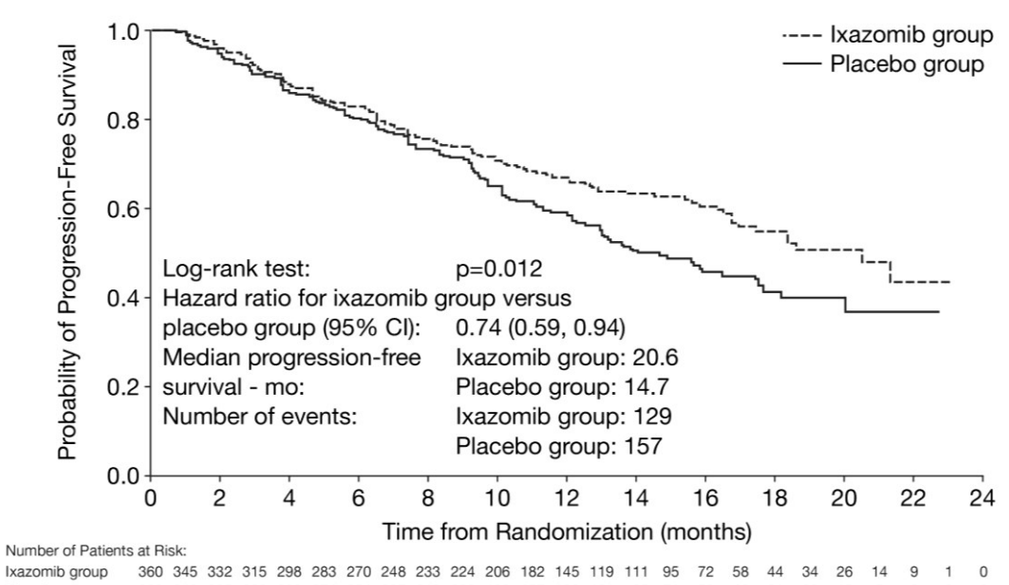
4.7.1.1 Primary endpoint: Progression-free survival (PFS)

First interim analysis

At data cut-off for the first analysis there were 129 and 157 IRC-assessed progression or death events in the IXA+LEN+DEX and LEN+DEX groups, respectively. There was a significant 35% improvement in PFS with IXA+LEN+DEX versus LEN+DEX (hazard ratio [HR] 0.74 [95% confidence interval, 0.59 to 0.94], p=0.012) (Figure 13). There was a clinically meaningful ~6 month improvement in median PFS (20.6 versus 14.7 months) in favour of the IXA+LEN+DEX arm. As the primary endpoint of improving PFS was met, this was the final statistical analysis of this endpoint.

Figure 13: Kaplan-Meier distribution of PFS with IXA+LEN+DEX versus LEN+DEX

A



Source: Moreau, 2016 [1]

Second interim analysis

A non-inferential PFS analysis was conducted at a median follow up of 23 months with 372 PFS events. The HR of PFS was 0.82 (95% confidence interval [0.67, 1.0]) for IXA+LEN+DEX versus LEN+DEX, and estimated median PFS was 20 months in the IXA+LEN+DEX group and 15.9 months in the LEN+DEX group.

4.7.1.2 Key secondary endpoints: overall survival/ overall survival in high-risk patients carrying del(17p)

At both the first and second interim analyses, OS data were not yet mature. At the first interim analysis, only 107 (22%) of the pre-specified 486 deaths required for the final OS analysis had occurred (51 in the IXA+LEN+DEX arm and 56 in the LEN+DEX arm). Early data showed a survival trend in favour of IXA+LEN+DEX (HR 0.900; 95% CI 0.62-1.32) with

18-month survival rates of 83% versus 80%, respectively. [42] At the second interim analysis, there were 171 deaths (81 in the IXA+LEN+DEX group, 90 in the LEN+DEX group), which represents 35% of the pre-specified number of deaths required for final analysis of OS. The median OS was not reached in either group. [1]

A total of 69 patients had a high-risk del(17p) chromosome abnormality. At the first interim analysis, 13 had died, including 4 of 36 (11%) patients in the IXA+LEN+DEX arm and 9 of 33 (27%) patients in the LEN+DEX arm. There was a 49% reduction in the risk of death with IXA+LEN+DEX (HR 0.506), with 18-month survival rates of 86% and 67%, respectively. At the second interim analysis, 9 of 36 IXA+LEN+DEX regimen patients (25%) and 15 of 33 LEN+DEX regimen patients (45%) had died. OS in patients with del(17p) showed a 51% reduction in the risk of death for patients treated with IXA+LEN+DEX (HR=0.487). The median OS was not reached with the IXA+LEN+DEX regimen and was 30.9 months with the LEN+DEX regimen.

In conclusion, OS data are still immature, although the current data show a survival trend in favour of the IXA+LEN+DEX regimen for both the ITT population and the high-risk subgroup of patients whose tumour harbored del(17p). The study is continuing in a double-blind, placebo-controlled fashion and OS data from the third interim analysis is expected in Q2 2017.

4.7.1.3 Response rates, duration of response and time to progression

First interim analysis
IXA+LEN+DEX resulted in a significantly higher overall response rate (78.3% versus 71.5% [p=0.04]), including significantly higher rates of ≥VGPR and CR, a significantly shorter time to response, and a longer median duration of response versus LEN+DEX (Table 39).

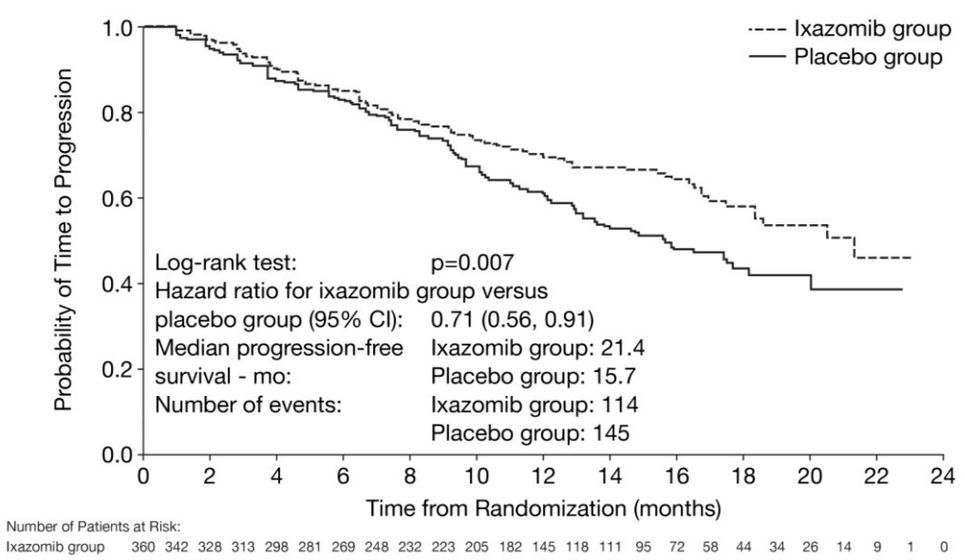
Table 39: Best confirmed treatment responses (blinded IRC assessment) and time to progression in the ITT population (15-month analysis)

Variable	IRd (N=360)	Rd (N=362)	Statistical comparison
Overall response rate, n (%) (95% CI, %)	282 (78.3) (73.7, 82.5)	259 (71.5) (66.6, 76.1)	p=0.04
≥VGPR, n (%) (95% CI, %)	173 (48.1) (42.8, 53.4)	141 (39.0) (33.9, 44.2)	p=0.01
Best response			
CR, n (%) (95% CI, %) sCR[a], n (%) (95% CI, %) PR, n (%) (95% CI, %) VGPR[a], n (%) (95% CI, %) SD, n (%) (95% CI, %)	42 (11.7) (8.5, 15.4) 9 (2.5) (1.1, 4.7) 240 (66.7) (61.5, 71.5) 131 (36.4) (31.4, 41.6) 40 (11.1) (8.1, 14.8)	24 (6.6) (4.3, 9.7) 3 (<1) (0.2, 2.4) 235 (64.9) (59.8, 69.8) 117 (32.3) (27.5, 37.4) 59 (16.3) (12.6, 20.5)	p=0.02
Median time to response, months[b]	1.1	1.9	p=0.009
Median duration of response (≥PR), months	20.5	15.0	
Median time to progression, months	21.4	15.7	HR 0.71 (95% CI 0.56, 0.91), p=0.007

Variable	IRd (N=360)	Rd (N=362)	Statistical comparison
Abbreviations: CI = confidence intervals; CR = complete response; HR = hazard ratio; IRd = ixazomib with lenalidomide and dexamethasone; Rd = placebo with lenalidomide and dexamethasone; PR =partial response; sCR = stringent complete response; SD = stable disease; VGPR = very good partial response [a] Stringent complete response is a subset of complete response, and very good partial response is a subset of partial response. [b] Median time to response in responding patients was 1.0 months vs. 1.1 months in the ixazomib vs. placebo groups. Source: Moreau, 2016 [1]			

Reflecting the findings for the primary endpoint of PFS, time to progression (TTP) was also significantly longer in the IXA+LEN+DEX versus LEN+DEX arm (Table 39; Figure 14)

Figure 14: Kaplan-Meier plot of TTP in the ITT population.
(Data from final statistical analysis for PFS)



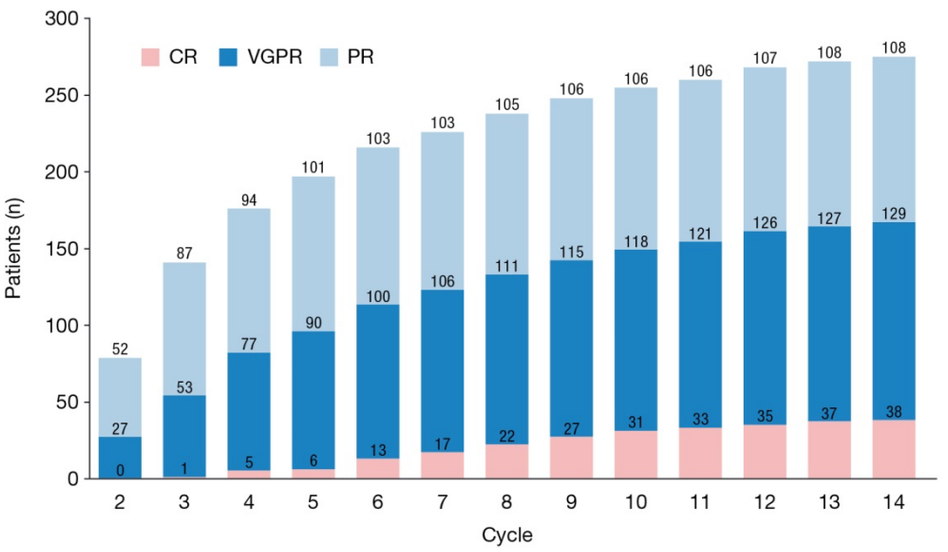
ITT = intent to treat; PFS = progression-free survival; TTP = time to progression

Source: Moreau, 2016 [1]

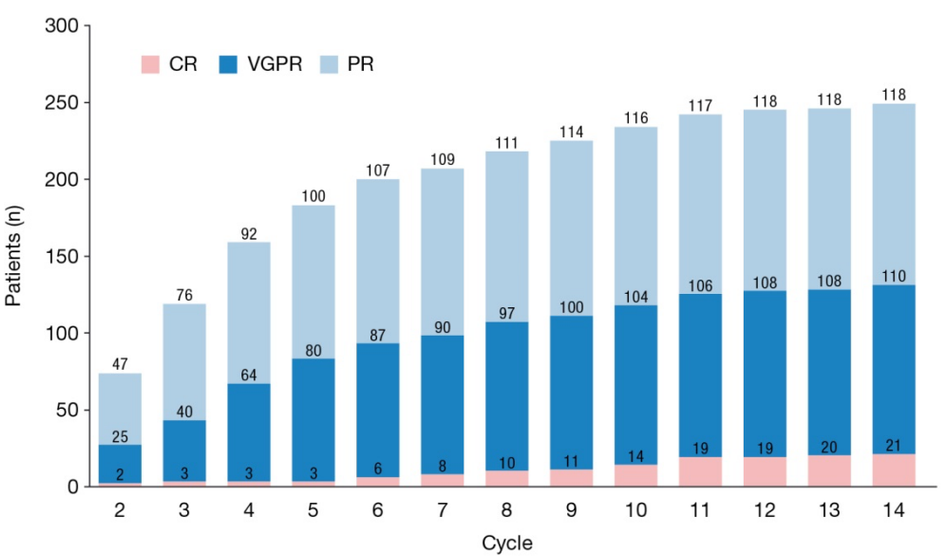
The evolution of response rates over the course of treatment is shown in, which highlights the increasing proportions of higher quality responses seen with increasing time on study treatment. Responses were rapid and durable (Table 39) and deepening responses were noted with increasing treatment duration (Figure 15).

Figure 15: Cumulative best responses over time in the ITT population. A. IXA+LEN+DEX; B. LEN+DEX

A



B



Abbreviations: CR = complete response; PR = partial response; VGPR = very good partial response

Moreau, 2016 [1]

Second interim analysis

Consistent with the first interim analysis, response rates were improved with the IXA+LEN+DEX regimen, with a shorter time to response, and a longer median duration of response and TTP. [42] The ORR was 78.6% in the IXA+LEN+DEX group and 73.2% in the LEN+DEX group. The IXA+LEN+DEX regimen delayed the median TTP by approximately 5 months, a clinically meaningful improvement (Table **40**).

Table 40: Best confirmed treatment responses (blinded IRC assessment) and TTP in the ITT population (23-month analysis)

Variable	IRd (N=360)	Rd (N=362)	Statistical comparison
Overall response rate, n (%)	283 (78.6)	265 (73.2)	OR: 1.35
≥VGPR, n (%)	185 (51.4)	159 (43.9)	OR: 1.35
Best response			
CR, n (%)	53 (14.7)	37 (10.2)	OR: 1.52
sCR[a], n (%)	12 (3.3)	4 (1.1)	
PR, n (%)	63.9 (230)	228 (63.0)	
VGPR[a] , n (%)	132 (36.7)	122 (33.7)	
SD, n (%)	37 (10.3)	53 (14.6)	
Median time to response, months[b]	1.1	1.9	HR: 1.23
Median duration of response (≥PR), months	26.0	21.7	-
Median TTP, months	22.4	17.6	HR: 0.79

Abbreviations: CI = confidence intervals; CR = complete response; HR = hazard ratio; IRd = ixazomib with lenalidomide and dexamethasone; ITT = intent to treat; Rd = placebo with lenalidomide and dexamethasone; PR = partial response; sCR = stringent complete response; SD = stable disease; TTP, time to progression; VGPR = very good partial response

[a] Stringent complete response is a subset of complete response, and very good partial response is a subset of partial response.

[b] Median time to response in responding patients was 1.0 months vs. 1.1 months in the ixazomib vs. placebo groups.

Source: TOURMALINE-MM1 CSR [42]

4.7.1.4 Quality of life

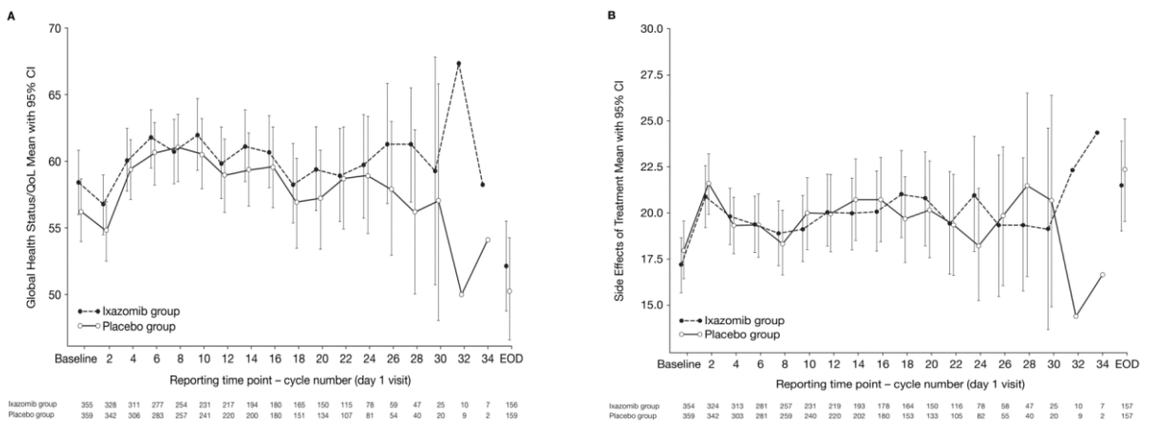
EORTC-QLQ-C30 and MY-20 questionnaires were obtained every 2 cycles until disease progression. [1] Scale scores range from 0 to 100, with higher scores representing a better health state for the functional scores and lower scores representing a better health state for the symptom scores. The EORTC QLQ-MY-20 consists of a 20-item questionnaire grouped into four scales: disease symptoms, treatment adverse effects, social support, and future perspective. Scale scores range from 0 to 100, with higher scores representing higher levels of symptomatology or problems.

In this blinded, placebo-controlled trial, patients did not know their treatment assignment and their responses on the QoL questionnaires were expected to reflect actual rather than perceived benefits of the treatment regimens. This is particularly noteworthy given the tendency to overestimate quality of life benefit in open-label studies. [130]

EORTC-QLQ-C30 and MY-20 scores over time indicated similar patient-reported quality of life in the IXA+LEN+DEX and LEN+DEX groups at both the first and second interim analysis (Figure 16), and therefore patient-reported quality of life was maintained despite the addition of a third agent to LEN+DEX. [1] Additionally, there was a trend for better physical functioning, emotional functioning, and fatigue scores for the IXA+LEN+DEX regimen compared with the LEN+DEX regimen at the first and second interim analysis; physical functioning improved over the first 6 cycles and then stabilised; while emotional functioning improved over the first 4 cycles and then stabilised (data not shown). [1]

Overall, quality of life, as measured by the EORTC QLQ-C30 and MY-20, was maintained during treatment with both regimens, and the addition of ixazomib to the LEN+DEX combination did not appear to have a negative impact.

Figure 16: (A) EORTC-QLQ-C30 mean global health status score and (B) MY-20 score for side effects of treatment over time (ITT population; median follow-up of ~23 months)



Abbreviations: EOD = end of disease treatment

(A) For the global health status score in EORTC QLQ-C30 – higher score indicates better quality of life

(B) For the MY-20 score for side effects of treatment – higher score indicates increased symptoms

Source: Moreau, 2016[1]

4.8 Subgroup analysis

As described in Section 3.3, the use of LEN+DEX in second line is subject to an ongoing NICE appraisal [part review of Technology appraisal 171] and is therefore not currently recommended by NICE in this line of treatment (ACD published on 11th November 2016). In contrast, LEN+DEX is recommended by NICE as a treatment option for MM patients who have had at least two other treatments and is the dominant therapy used in this line of therapy. Due to the LEN+DEX control arm in the TOURMALINE MM-1, the stratified subgroup of 2 or 3 prior lines of treatment from this trial is particularly relevant to UK clinical practice and is therefore presented in more detail here (Section 0). In addition, prognostically relevant pre-specified subgroups, including age, cytogenetics, ISS stage, prior therapy, and relapsed and/or refractory disease are also presented (Section 4.8.2)

4.8.1 Outcomes in the subgroup of patients who received two or three prior therapies

A total of 425 (59%) patients had received 1 prior therapy and 297 patients (41%) had received 2 or 3 prior therapies (148 in the IXA+LEN+DEX group; 149 in the LEN+DEX group) (as per the stratification factors) (Table 37). As expected from stratified randomisation principles, the subgroups were well balanced between the 2 treatment regimens with regard to baseline characteristics.

A summary of the results (PFS, OS, TTP and response rates) for the ITT population, and the subgroups based on line of therapy is shown in

Table 41, and the results are described in the following sections. There was an improvement in the response rates, TTP, and median PFS with the addition of IXA to LEN+DEX in the ITT population and the subgroups of by lines of therapy in both the first and second interim

analysis (

Table 41)

Table 41: Outcomes in the subgroup of patients with 1 prior therapy and 2-3 prior lines of therapy and in the entire ITT population (15 & 23 month analysis)

Variable	Entire ITT population			Subgroup: 1 prior line†			Subgroup: 2-3 prior lines†		
	IRd (N=360)	Rd (N=362)	Statistical analysis: HR or OR (95% CI)	IRd (N=212)	Rd (N=213)	Statistical analysis: HR or OR (95% CI)	IRd (N=148)	Rd (N=149)	Statistical analysis: HR or OR (95% CI)
First interim analysis: median follow-up of ~15 months									
PFS: n; median, months	129; 20.6	157; 14.7	HR: 0.74 (0.59, 0.94) p=0.012	80; 20.6	88; 16.6	HR: 0.88 (0.65, 1.20)	49; NE	69; 12.9	HR: 0.58 (0.40, 0.84) p<0.05
OS[a]: n ; median, months	51; NE	56; NE	HR: 0.90 (0.62, 1.32)	31; NE	26; NE	HR: 1.24 (0.74, 2.10)	20; NE	30; NE	HR: 0.62 (0.35, 1.09)
Time to progression: n; median, months	114; 21.4	145; 15.7	HR 0.71 (0.56, 0.91), p=0.007	73; 20.6	84; 16.6	HR: 0.84 (0.61, 1.16)	41; NE	61; 13.0	HR 0.55 (0.37, 0.82)
Overall response rate, n (%)	282 (78.3)	259 (71.5)	OR: 1.44 (1.03, 2.03) p=0.04	163 (76.9)	159 (74.6)	OR: 1.13 (0.72, 1.77)	119 (80.4)	100 (67.1)	OR: 2.03 (1.19, 3.45) p<0.05
VGPR+CR†, n (%)	173 (48.1)	141 (39.0)	OR: 1.45 (1.08, 1.95) p=0.014	95 (44.8)	(43.7)	OR: 1.05 (0.71, 1.54)	78 (52.7)	48 (32.2)	2.36 (1.47, 3.79) p<0.05
CR or better†,n (%)	42 (11.7)	24 (6.6)	1.87 (1.10, 3.16) p=0.019	19 (9.0)	17 (8.0)	OR: 1.13 (0.57, 2.25)	23 (15.5)	7 (4.7)	OR: 3.85 (1.58, 9.36) p<0.05
Second interim analysis: median follow-up of ~23 months									
PFS[b]: n; median, months	177†; 20	195†; 15.9	HR: 0.82 (0.67, 1.0)	109; 18.7	112; 17.6	HR: 0.99 (0.76, 1.29)	68; 22.0	83; 13.0	HR: 0.62 (0.45, 0.86)
OS[a]: n (%); median, months	81 (23); NE	90 (25); NE	HR: 0.87 (0.64, 1.18) p=0.359†	48; NE	45; NE	HR: 1.11 (0.74, 1.66)	33; NE	45; NE	HR: 0.65 (0.41, 1.02)
Time to progression: n; median, months†	158; 22.4	180; 17.6	HR: 0.79	100; 19.5	106; 18.7	HR: 0.96 (0.73, 1.26)	58; 28.8	74; 14.1	HR: 0.58 (0.41, 0.83)
Overall response rate, n (%)†	283 (78.6)	265 (73.2)	OR: 1.35	164 (77.4)	166 (77.9)	OR: 0.97 (0.61, 1.53)	119 (80.4)	99 (66.4)	OR: 2.09 (1.23, 3.56)

Variable	Entire ITT population			Subgroup: 1 prior line†			Subgroup: 2-3 prior lines†		
	IRd (N=360)	Rd (N=362)	Statistical analysis: HR or OR (95% CI)	IRd (N=212)	Rd (N=213)	Statistical analysis: HR or OR (95% CI)	IRd (N=148)	Rd (N=149)	Statistical analysis: HR or OR (95% CI)
VGPR+CR†, n (%)	185 (51.4)	159 (43.9)	OR: 1.35	105 (49.5)	105 (49.3)	-	80 (54.1)	54 (36.2)	-
CR or better†,n (%)	53 (14.7)	37 (10.2)	OR: 1.52	26 (12.3)	27 (12.7)	-	27 (18.2)	10 (6.7)	-

Abbreviations: CI = confidence intervals; CR = complete response; HR = hazard ratio; IxaLenDex = ixazomib with lenalidomide and dexamethasone; LenDex = ixazomib with lenalidomide and dexamethasone; VGPR = very good partial response

[a] OS data were not yet mature; follow-up is on-going

[b] Post hoc analyses revealed that a regional difference in PFS was observed in patients from North Asia who were enrolled later into the study and who had a disproportionate effect on the second analysis compared with the first analysis. In the study population excluding patients from North Asia ("non-North Asia"), the median PFS in the ixazomib and placebo regimens was 20.5 and 15.6 months, respectively (HR=0.785)

Source: Moreau, 2016 [1]; † TOURMALINE-MM1 CSR [42]

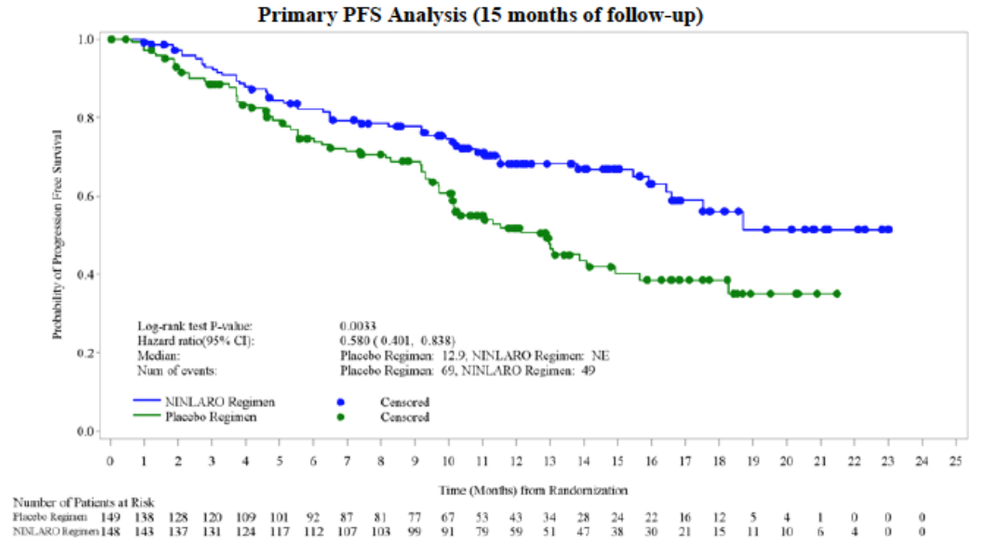
4.8.1.1 Progression-free survival in the subgroup of patients who received two or three prior therapies

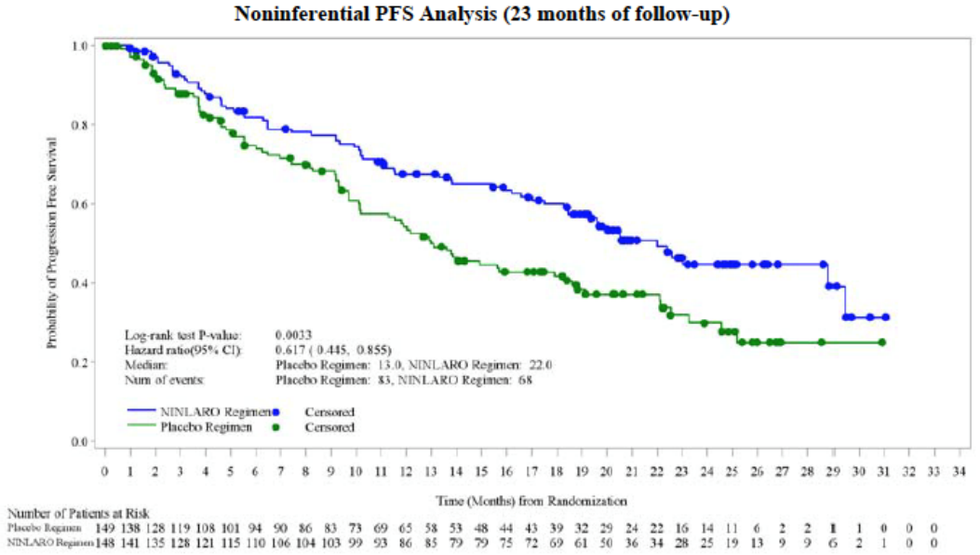
Median PFS in the IXA+LEN+DEX vs LEN+DEX groups for the first interim analysis (primary analysis of PFS) and second interim analysis (non-inferential analysis) were:

- ITT population: 20.6 vs 14.7 months (HR: 0.74), and 20.0 vs 15.9 months (HR: 0.82), respectively.
- 2 or 3 prior therapy subgroup: not estimable (NE) vs 12.9 months (HR: 0.58), and 22.0 vs 13.0 months (HR: 0.62), respectively, representing an approximate 9-month improvement in median PFS in the IXA+LEN+DEX group (Figure 17).

At both interim analyses, the median PFS for IXA+LEN+DEX were similar in both the 2 or 3 prior line subgroup and overall ITT population (NE versus 20.6 months and 22.0 versus 20.0 months, for IA1 and IA2 respectively). In contrast, it was numerically inferior for the LEN+DEX control arm for patients who had received 2 or 3 prior treatments versus the ITT population (12.9 versus 14.7 months and 13.0 versus 15.9 months, for IA1 and IA2 respectively).

Figure 17: Kaplan-Meier plots of PFS in the subgroup with 2 or 3 prior therapies





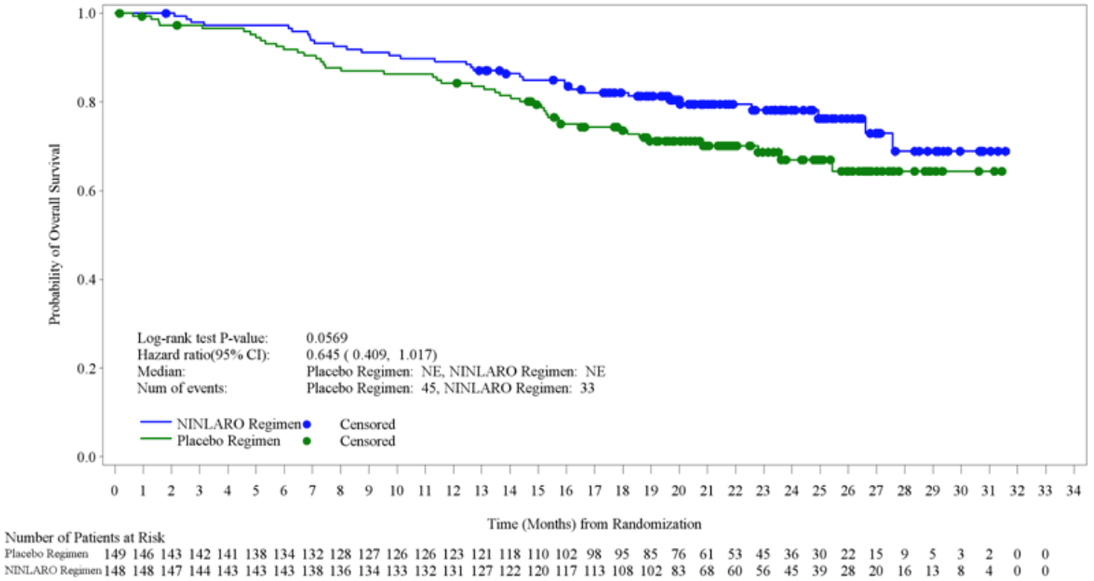
Abbreviations: CI = confidence interval; NE = not estimable; NINLARO regimen = ixazomib with lenalidomide and dexamethasone; Placebo regimen = placebo with lenalidomide and dexamethasone

Source: Takeda data on file UK/IXA/1612/0103 [131] TOURMALINE-MM1 CSR [42]

4.8.1.2 Overall survival in subgroups of patients who received two or three prior therapies

As expected, the OS data were not mature. In the subgroup with 2 or 3 prior therapies, the median OS was NE after either 15 or 23 months of follow-up in both arms, but a consistent trend toward OS benefit can be seen, with HRs of 0.618 (95% CI 0.350-1.090) and 0.645 (95% CI 0.409-1.017), respectively. As of the 23 months of follow-up, 33 of 148 patients (22%) in the IXA+LEN+DEX group had died, versus 45 of 149 patients (30%) in the LEN+DEX group who had received 2 or 3 prior therapies.

Figure 18: Kaplan-Meier plots of OS in the subgroup with 2 or 3 prior therapies (23-month analysis) [132]



4.8.1.3 Time to progression and response rates in the subgroup of patients who received two or three prior therapies

The PFS benefit with the IXA+LEN+DEX regimen was supported by improvements versus the LEN+DEX regimen in TTP and response rates (Table 42).

Table 42: Response to treatment and TTP in the ITT population and two or three prior line stratified subgroup (15- and 23-month analysis)

	ORR (%)		CR+VGPR (%)		CR (%)		Median TTP (months)		
	IRd	Rd	IRd	Rd	IRd	Rd	IRd	Rd	HR (p-value)
ITT									
IA1	78	72	48	39	12	7	21.4	15.7	0.712 (0.007)
IA2	79	73	51	44	15	10	22.4	17.6	0.792 (0.034)
2 or 3 prior therapies									
IA1	80	67	53	32	16	5	NE	13.0	0.550 (0.003)
IA2	80	66	54	36	18	7	28.8	14.1	0.584 (0.002)

Abbreviations: CR = complete response; HR = hazard ratio; IA = interim analysis; IRd = ixazomib with lenalidomide and dexamethasone; ITT = intent to treat; Rd = placebo with lenalidomide and dexamethasone; ORR = overall response rate; TTP, time to progression; VGPR = very good partial response
Source: TOURMALINE-MM1 CSR [42]

4.8.1.4 Discussion and conclusion

There is a pronounced efficacy benefit for IXA+LEN+DEX in the subgroup of patients treated with 2 or 3 prior therapies in the TOURMALINE-MM1 trial, as shown by a significant improvement in PFS, TTP and overall response rates versus LEN+DEX. This is compatible with the clonal evolution theory of MM that sees the emergence of

different clones in advanced MM, driven by different biology, which become refractory to certain type of therapies (Section 3.1.1). It is commonly accepted that a multidrug combination such as a triplet of drugs, with different mechanisms of action, is required for relapsed or refractory disease where there is extensive clonal evolution. A single drug or two-drug combination, such as LEN+DEX, may have insufficient strength to control all the aggressive clones in the bone marrow and therefore outcomes are particularly poor. This hypothesis is consistent with the numerically worse PFS seen for LEN+DEX treated patients in the 2 or 3 prior lines subgroup versus the ITT population, whereas PFS outcomes were not inferior for the IXA+LEN+DEX triplet when comparing these groups. Thus, the addition of IXA provided more sufficient disease control with a broader mechanism of action, which is of particular clinical importance for patients who have been treated with more lines of therapy and therefore have more advanced disease.

In conclusion, in the stratified subgroup of MM patients who had received 2 or 3 prior therapies, IXA+LEN+DEX showed a statistically significant improvement in the response rates, TTP, and median PFS compared to LEN+DEX. These improvements in efficacy were consistent across both the first and second interim analyses. In addition, the HRs for OS were 0.618 and 0.645, with a clear separation in the KM survival plot, indicating a positive trend towards an OS benefit with IXA+LEN+DEX. These results are clinically noteworthy given the current positioning of LEN+DEX in the UK pathway in patients who have received at least 2 prior therapies and compare favourably to the efficacy seen with other novel triplet regimens in this treatment setting.

4.8.2 PFS in various pre-specified subgroups according to baseline demographics and disease characteristics

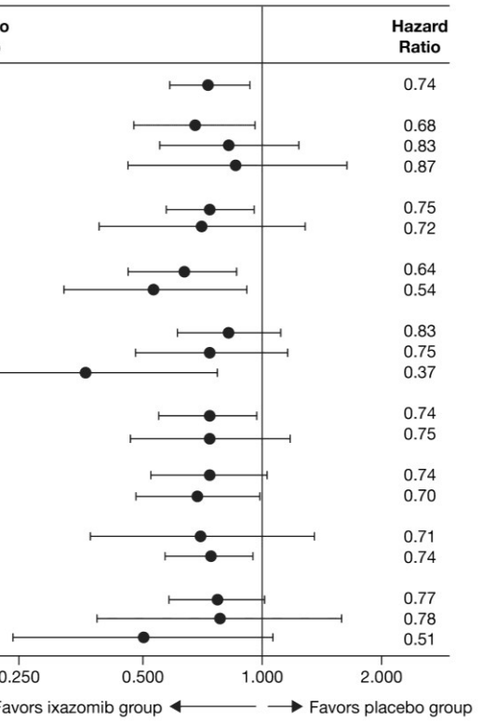
PFS was evaluated in a number of pre-specified subgroups defined according to baseline patient and disease characteristics. PFS at the first interim analysis is presented (i.e. the final analysis for PFS for statistical testing purposes); data from the second interim analysis is not presented as it was only conducted as a sensitivity analysis. The PFS benefit was consistent across key pre-specified patient subgroups (Figure 19), including those with poor prognosis such as patients with high-risk cytogenetic abnormalities, those with ISS stage III, those aged ≥75 years, relapsed and refractory disease and those who had received 2 or 3 prior therapies, and those with relapsed and refractory disease, with no statistically significant interactions observed between these subgroup indicators and treatment. [1]

Median PFS was 21.4 and 9.7 months in patients with high-risk cytogenetics in the IXA+LEN+DEX and LEN+DEX groups, respectively (HR 0.54 [95% CI, 0.32, 0.92], p=0.02); in patients carrying del(17p), median PFS was 21.4 and 9.7 months, respectively (HR 0.60 [95% CI, 0.29, 1.24]), and in patients with t(4;14) alone, median PFS was 18.5 and 12.0 months, respectively (HR 0.65 [95% CI, 0.25, 1.66]) [1] Therefore, these data suggest that IXA+LEN+DEX may improve or overcome the known traditional poor prognosis in patients with high-risk cytogenetic features [63] for whom LEN+DEX doublet alone is emerging as suboptimal treatment. [41]

Figure 19: Forest plots of PFS with IXA+LEN+DEX vs LEN+DEX in pre-specified patient subgroups (15-month analysis)

B

Variable	Subgroup	Number of Patients: Ixazomib group	Number of Patients: Placebo group	Median Progression-Free Survival (months): Ixazomib group	Median Progression-Free Survival (months): Placebo group	Hazard Ratio
All Patients	ALL	360	362	20.6	14.7	0.74
Age (years)	≤65	168	176	20.6	14.1	0.68
	>65-75	145	125	17.5	17.6	0.83
	>75	47	61	18.5	13.1	0.87
ISS Stage (Stratification Factor)	I or II	314	318	21.4	15.7	0.75
	III	46	44	18.4	10.1	0.72
Cytogenetic Risk	Standard-risk	199	216	20.6	15.6	0.64
	High-risk	75	62	21.4	9.7	0.54
Number of Prior Therapies	1	224	217	20.6	15.9	0.83
	2	97	111	17.5	14.1	0.75
	3	39	34	NE	10.2	0.37
Proteasome Inhibitor	Exposed	250	253	18.4	13.6	0.74
	Naïve	110	109	NE	15.7	0.75
Prior Immunomodulatory Drug Therapy	Exposed	193	204	NE	17.5	0.74
	Naïve	167	158	20.6	13.6	0.70
Refractory to Last Prior Therapy	Yes	59	55	NE	NE	0.71
	No	301	307	20.6	14.1	0.74
Relapsed or Refractory	Relapsed	276	280	18.7	15.6	0.77
	Refractory	42	40	NE	13.0	0.78
	Relapsed and Refractory	41	42	NE	13.1	0.51



Source: Moreau, 2016[1]

4.9 Meta-analysis

No meta-analyses were performed.

4.10 Indirect and mixed treatment comparisons

4.10.1 Search strategy

A Network meta-analysis (NMA) has been performed of the relative clinical effectiveness of ixazomib in combination with lenalidomide + dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy and are not refractory to lenalidomide or proteasome inhibitors. Of particular interest are the comparisons for the sub-groups of patients who have received one prior therapy, and those who have received at least 2 prior therapies, in line with the NICE scope for this STA. An NMA was necessary in order to provide a comparison of the relative clinical effectiveness of IXA+LEN+DEX vs. BORT+DEX in patients who have received one prior therapy, as this was considered a key comparator and there is no direct head to head evidence available vs. this comparator (see Table 1, section 1.3.3).

The systematic review and NMA was also designed to include studies that covered a range of comparators of potential interest to UK health technology assessment (HTA) i.e. according to the NICE scope for ixazomib, and also potential comparators for the submission to the Scottish Medicines Consortium (SMC). The NMA represents a decision focussed analysis as it focuses on those comparators and outcomes of direct interest for the NICE and SMC STA's.

The systematic search strategy for the NMA consisted of searching for both RCT and observational studies, and if both available in the base case NMA's for each study population and outcome both types of study were used in order to maximise the amount of evidence available, with scenario analysis using only RCT evidence if sufficient data was available from this source alone to form a network.

Where possible separate networks were formed for each outcome of interest for three RRMM populations: a) the one or more prior therapies population (whole ITT population for ixazomib + lenalidomide + dexamathesone in the TOURMALINE MM-1 trial, b) the one prior therapy population, and c) the two or more prior therapies population, with both b and c sub-groups of the TOURMALINE MM-1 trial (see section 4.11.3.3).

The systematic review search strategy for the NMA is presented in Appendix 2 as for the systematic review.

4.10.2 Study selection

4.10.2.1 Treatment comparators

The potential comparisons for ixazomib + lenalidomide + dexamethasone covered by the NMA are as follows:

- vs. lenalidomide + dexamethasone – this represents the reference treatment in the NMA
- vs. bortezomib + dexamethasone
- vs. bortezomib monotherapy
- vs. panobinostat + bortezomib + dexamethasone
- vs. carfilzomib + lenalidomide + dexamethasone
- vs. pomalidomide + dexamethasone
- vs. carfilzomib + dexamethasone
- vs. carfilzomib + dexamethasone.

However, the key comparisons for this submission are those for IXA+LEN+DEX vs. BORT+DEX in patients who have received one prior therapy (2nd line), and vs LEN+DEX in patients who have received two prior therapies (3rd line) (see Table 1, section 1.1.3). There is direct comparative trial evidence for the comparison with lenalidomide + dexamethasone from the TOURMALINE MM1 study, and so this head to head data is used for the key outcomes in the economic analysis (see section 5). In the absence of direct comparative evidence, the comparison with BORT+DEX the results from the NMA for BORT+DEX vs.LEN+DEX is utilised (see section 5.3).

4.10.2.2 Inclusion and exclusion selection

Key inclusion criteria for the NMA were as follows:

- Studies including adult patients (≥18 years) with RRMM who have received at least one prior therapy.
- RCTs and follow up studies/ analyses (e.g. for OS assessment). Observational studies to be included in the base case, and RCT evidence alone in a scenario analysis if there was sufficient data from this source to form a network.

- Results from full published journal articles represent the primary source, but other potential secondary level sources are clinical study reports (e.g. if needed for ixazomib), UK HTA reports (e.g. as available on NICE website), specific data provided by authors or other authorised bodies (e.g. NICE, investigators).

Key exclusion criteria for the NMA were as follows:

- Non-English language publications
- Abstracts with insufficient detail on the outcomes of interest for the NMA

4.10.2.3 Summary of the trials used to carry out the network meta-analysis

Table 43 presents the summary of the studies used to carry out the NMA, which were included in either the base case analyses, or scenario analyses for each network.

Table 43: Data sources of all identified RCTs and observational studies for ixazomib plus lenalidomide – dexamethasone and other treatments for the treatment of RRMM (Primary and Scenario Doses)

Study ID	Study type (RCT or Observational)	Primary data source	Location	Comparator 1	Comparator 2
Tourmaline-MM1*	**RCT**	***Data cut IA1 (30th October 2014)* Publication: Moreau et al., 2016** [1]	**North America and Canada**	**Ixazomib + LenDex**	**Placebo + LenDex**
Tourmaline-MM1	RCT	*Data cut IA2 (12th July 2015)* CSR ixazomib 2015 [114]	North America and Canada	Ixazomib + LenDex	Placebo + LenDex
Tourmaline-MM1	RCT	Hou et al., 2016 (*Data cut 12th July 2015*[117])	China	Ixazomib + LenDex	Placebo + LenDex
Matched-pairs of patients from 3 clinical trials: MMY-2045, APEX, and DOXIL-MMY-3001	Observational (retrospective analysis)	Dimopoulos et al., 2015 [133]	North America, Canada, and Europe (including the UK)	Bortezomib + Dex	Bortezomib
eVOBS	Observational	Dimopoulos et al., 2010 [134]	Belgium, France, Greece, Spain, Sweden, Turkey, and Brazil	Bortezomib + Dex	Bortezomib
Phase III	RCT	Montefusco et al., 2015 [135]	Italy	Bortezomib + Dex + cyclophosphamide	Len + Dex + cyclophosphamide
APEX	RCT	Richardson et al., 2005 [136]	North America, Canada, and Europe (including the UK)	Bortezomib	Dexamethasone
APEX	RCT	Richardson et al., 2007a[137]	North America, Canada, and Europe (including the UK)	Bortezomib	Dexamethasone
ENDEAVOR*	**RCT**	**Dimopoulos et al., 2016** [138]	**North and South America, Canada, Europe (including the UK), and the Asia-Pacific region**	**Carfilzomib + Dex**	**Bort + Dex**
ENDEAVOR	RCT	Moreau et al., 2015c [139]	North and South America, Canada, Europe (including the UK), and the Asia-Pacific region	Carfilzomib + Dex	Bort + Dex
ASPIRE	**RCT**	**Stewart et al., 2015a**[18]	**North America, Canada, and Europe (including the UK)**	**Carfilzomib + Len + Dex**	**Len + Dex**
ASPIRE	RCT	Dimopoulos et al., 2015b[140]	North America, Canada, and Europe (including the UK)	Carfilzomib + Len + Dex	Len + Dex
MM-010	RCT	Dimopoulos et al., 2007 [141]	Europe (including the UK), and Asia-Pacific region	Len + Dex	Placebo + Dex
MM-009	RCT	Weber et al., 2007 [142]	North America and Canada	Len + Dex	Placebo + Dex
–	Observational (retrospective analysis)	Zagouri et al., 2016 [143]	–	Len + intermediate dose Dex	Len + low dose Dex
Match-adjusted indirect analysis of patients from 3 clinical trials: PANOROMA-1, MM009/010, MM-003	Systematic review	Majer et al., 2016 [144]	–	Pano + Bort + Dex Pano + Bort + Dex	Len + Dex Pom + Dex

Study ID	Study type (RCT or Observational)	Primary data source	Location	Comparator 1	Comparator 2
PANORAMA-1*	**RCT**	**San-Miguel et al., 2014 [145]**	**North and South America, Canada, Europe (including the UK), and the Asia-Pacific region**	**Pano + Bort + Dex**	**Bort + Dex**
PANORAMA-1	RCT	Richardson et al., 2016 [146]	North and South America, Canada, Europe (including the UK), and the Asia-Pacific region	Pano + Bort + Dex	Bort + Dex
PANORAMA-1	RCT	San-Miguel et al., 2015c[147]	North and South America, Canada, Europe (including the UK), and the Asia-Pacific region	Pano + Bort + Dex	Bort + Dex
PANORAMA-1	RCT	SMC Detailed Advice Document, 2016 [148]	North and South America, Canada, Europe (including the UK), and the Asia-Pacific region	Pano + Bort + Dex	Bort + Dex
MM-002	RCT	Richardson et al., 2014 [149]	North America and Canada	Pom + Dex	Pom
MM-003*	**RCT**	**San-Miguel et al., 2013 [150]**	**North America, Canada, Europe (including the UK), and the Asia-Pacific region**	**Pom + Dex**	**High dose Dex**
MM-003	RCT	San-Miguel et al., 2015d[151]	North America, Canada, Europe (including the UK), and the Asia-Pacific region	Pom + Dex	High dose Dex

Abbreviations: CSR = clinical study report; LenDex = lenalidomide + dexamethasone; Bort = Bortezomib; Dex = dexamethasone; Len = lenalidomide; Cyclo = cyclophosphamide; Pano = panobinostat; Pom = pomolidomide

* Studies in **bold** font indicate the primary publication

4.10.3 Methods and outcomes of included studies

4.10.3.1 Choice of outcome measure

The following clinical and safety endpoints were intended to be included in the NMA:

- Progression free survival (PFS): defined using either the European Group for Blood and Marrow Transplantation (EBMT) or International Myeloma Working Group (IMWG) Uniform Response Criteria for disease progression. Measured as time from the date of randomisation to the date of progression or death.
- Overall survival (OS): defined as the time from the date of randomisation to the date of death.
- Overall response rate (ORR): defined using either the European Group for Blood and Marrow Transplantation (EBMT) or International Myeloma Working Group (IMWG) [152] criteria (i.e. complete + partial response, although precise definition may vary between studies).
- Best overall response rates (BoR): defined using either the EBMT or IMWG criteria (i.e. very good partial response or better, partial response, stable disease [minimal response], worse than minimal response [progressive disease]). For the NMA BoR was assessed as those patients who achieved a BoR of very good partial response or better.
- Best Response (BR): sub-categorised into complete/ near-complete response, complete response, near-complete response, complete response or better, stringent complete response, partial response, very good partial response, electrophoresis-negative partial response (EN-PR), <partial response, minimal response, ≥minimal response, no change, stable disease, and progressive disease.
- Treatment discontinuation due to AE's.

Following the systematic review, BR was dropped as an endpoint owing to lack of cohesion in how this endpoint was reported with no obvious merging strategy. The SR and NMA was informed by an earlier larger NMA in RRMM performed internally by Takeda for global purposes (hence, had a large number of comparators including those of no direct interest to UK HTA). Based on information from this it was concluded that a coherent NMA for HRQoL outcomes, and treatment duration/time to treatment discontinuation were not feasible and so these outcomes were not included as endpoints in our UK decision focussed NMA.

The key outcomes covered in the NMA that were utilised in the economic model for the comparison with bortezomib + dexamethasone were PFS and OS. The use of these data in the economic analysis is presented in section 5.3.3.3.

4.10.3.2 Study design and populations of interest

The base case networks were based on using RCT and observational study designs in order to maximise the amount of evidence available for the NMAs for each population of interest and outcome. In scenario analysis RCT's alone were used where there was sufficient data for networks to be formed. In some instances there were no observational studies in a network, in which case the base case consisted of RCTs only.

The overall patient population of interest were adult patients (≥18 years) with RRMM who have received at least one prior therapy (at least as a sub-group). In order to capture all the relevant survival and response data for the population of interest, according to the NICE final scope and decision problem specified in Table 1(section 1.3.3), the NMA was planned to include three separate networks based on patient populations:

- ≥1 prior therapy (1+ prior therapy [ITT population])
- 1 prior therapy.
- ≥2 prior therapies (2+ prior therapies)

Whilst the NICE scope specifies 1 prior therapy and ≥2 prior therapies as the populations of interest, the overall ≥1 prior therapy population is included to assess overall efficacy and safety vs. key comparators according to the full licensed indication for IXA+LEN+DEX . These networks also provide the most robust assessments as they are based on larger numbers of studies and larger networks for running the base case and several scenario analyses, compared to the 1 prior or at least two prior therapy sub-groups, which often had limited networks for each outcome of interest. Indeed for the comparison of IXA+LEN+DEX vs. BORT+DEX in 1 prior therapy, no networks could be formed (see section 4.10.6.2) and hence the 1+ prior therapy NMA data was utilised in the economic model as a proxy for the PFS and OS outcomes associated with the 1 prior therapy sub-group (see section 5.3.3.3).

The ixazomib regimen and the primary comparisons of interest for the NMA for the NICE submission and scheduled doses (based on rationale presented in Table 1 in section 1.3.3) are:

- Ixazomib 4mg + lenalidomide 25mg + dexamethasone 40mg
- Bortezomib 1.3mg/m^2 + dexamethasone 20mg
- Lenalidomide 25mg + dexamethasone 40mg

The reference treatment in the NMA is lenalidomide + dexamethasone, hence other treatments are compared to this for the purposes of the indirect comparisons. The SR and NMA contained studies with other doses specified than those above, in particular lenalidomide 25mg with dexamethasone 20mg. Where data was available for a combined patient population/outcome network comparator studies including those above with the specific doses specified were included separately in the base case network (labelled 'specific dose', studies). Where specific dose studies alone were insufficient to form a network and also as scenario analysis, studies with different doses or unclear doses were combined and included in the network (labelled 'combined dose').

The base case also used the first interim datacut from the TOURMALINE-MM1 study (October 2014), which represented the primary analysis for PFS, the primary endpoint in the study (see section 4), and reported in the main clinical publication of the TOURMALINE-MM1 study.[1] The base case NMA's use this datasource as well as the data from the primary publications of comparator studies included in a network. Hence, when there is more than one source available for the same trial in any analysis, necessitating inclusion of only one (to avoid double-counting of patients), the following occurs:

- Only one of the studies is placed into "Primary Publication Data Cut" sub-group – the main publication linked to the trial
- The most recent publication/latest data cut of any remaining publications are placed into "Secondary Publication Data Cut".
- "Unique" publications – those that solely represent a trial – are placed into both publication sub-groups defined above (maximising each network size).

The "Primary Publication Data Cut" has the most potential to reduce publication bias – published results from TOURMALINE MM-1 taken from the first data cut of 30 October 2014 are included within it (and only published sources are compared to each other – labelled 'primary publications'). The "Secondary Publication Data Cut" includes the unpublished TOURMALINE MM-1 second interim data cut of 12th July 2015 (see section 4). This

secondary publications source is used as a scenario analysis across the NMA's performed (labelled 'secondary publications').

In addition, where data exists, two versions of the "Secondary Publication Data Cut" exist based on inclusion and exclusion of published results from TOURMALINE MM-1 continuation study in China (Hou et al 2016 [117]). These data for IXA+LEN+DEX are used in scenario analyses across the NMA's where available for specific patient populations and outcomes. Further details of the methods and results of this study are provided in Appendix 4.

4.10.3.3 Apparent or potential differences in patient populations

The patient population of every trial included in the NMA lies within the definition of the target population (i.e. patients who had relapsed, refractory or relapsed and refractory multiple myeloma, and had received at least 1 prior treatment). However, some heterogeneity will be present based on previous treatment (patients may have received 1, 1+ or 2+ prior therapies), and disease severity (e.g. patients in the Chinese extension of the global ixazomib Tourmaline-MM-1 study[117] were more heavily pretreated and more refractory than those in the global study (Moreau).[1] See Table in Appendix 5 for details on patient and study design characteristics.

The identified RCT and observational studies utilised across the networks reported here for the comparisons with bortezomib + dexamethasone, and vs. lenalidomide + dexamethasone are summarised in Appendix 5 (study design, methods/endpoints, and patient characteristics).

4.10.4 Risk of bias

A complete quality assessment of each trial included is shown in Appendix 5.

4.10.5 Methods of analysis for the NMA

4.10.5.1 Data extraction and treatment effect measures

For NMA selected studies, data extraction was performed with a standard Data Extraction Template (DET) in Excel. Key data for the NMA from each eligible study were extracted by recording data from original publications and reports onto the DET. Extracted details included information on study design, selection criteria, study population and patient characteristics, interventions, outcome measures, and length of follow-up, and data on treatment effect/safety outcomes.

Of the treatment effect outcomes, PFS and OS were compared across studies using (log) hazard ratio (HR) and 95%CI data. There are several ways that a publication can present aggregate results, and that can be converted into (log) hazard ratios if not directly presented.[153-155] These include contingency table output, log rank test results, regression results (e.g. parameters from semi-parametric Cox or fully parametric Weibull regression) and median survival estimates. In addition, where aggregate data is lacking but Kaplan-Meier curves are presented for treatments in a trial then it was intended that they be digitilised and HR estimated from them using methods described in Guyot et al.[156] and Tierney et al.[156] However, no such digitilisation was necessary. These methods were to be employed if necessary in order to maximise the number of trials that could potentially contribute to the evidence network.

Odd ratios were used as the evaluation statistic for the binary variables ORR and discontinuations due to AE's, and also for BoR which was modelled as a binary variable: whether" very good partial response or better" was recorded in a study.

For imputing missing log hazard ratio statistics related to the PFS and OS analysis, recommended techniques were used. [153-155] In particular, where (as was common) hazard ratio and 95% confidence intervals were quoted, log hazard ratio (and its standard error) imputations required only the 95% confidence intervals. Similarly, when binary data was only presented as odds ratios with 95% confidence intervals the exact same methods were utilised to generate log odds ratios (and their standard errors). Conventional techniques for imputing standard errors utilising standard deviations, t-values, confidence intervals or *P* values reported in articles were adopted where appropriate.

4.10.5.2 Evidence synthesis method

A Bayesian analysis framework using Markov Chain Monte Carlo, MCMC methods, was implemented to conduct all network meta-analysis. The general algorithms and approach followed are all in accordance with the Evidence Synthesis Technical Support Documents produced by the NICE Decision Support Unit. [157-160] All programming code was written in the statistical package R v3.3.2. This code inputted the relevant Excel data extraction sheet, performed any necessary data transformations and conducted the Bayesian NMA utilising the R package R2Jags v0.5-7. This package itself utilised JAGS (v4.2.0 standalone software) to perform the appropriate Bayesian analysis. Frequency meta-analysis techniques were also programmed in R.

Convergence of the MCMC algorithms was assessed by Brooks Gelman & Rubin diagnostics and checking the "effective sample size" (a value greater than 400 imply Monte Carlo standard errors < 5% of parameter standard deviations – often cited as necessary). Analysis involved three MCMC chains, each with 50,000 "burn-in" followed by 150,000 further repetitions where every 1 in five was sampled (i.e. thin rate = 5). Thus, there were 90, 000 sampled MCMC repetitions per parameter for analysis (30,000 from each chain). Non- informative priors were used for all modelling (assigning priors for log hazard ratios and log odd ratios as normally distributed with mean of zero and variance of 1000).

Dispersed, randomly (standard normal) generated initial starting values were generated for each parameter in a chain. With unit variance, these achieve starting values more likely to correspond to reasonable values for the parameters (that are on the log scale implying fairly wide relative effects). This is in line with recommendations from leading Bayesians such as Gelman (1[161]) and Kruschke (2[162]) in order to prevent non-convergence problems. As an added safety check we increased the variance to four on a random selection of models and noted it made no difference to results (affecting nearly always the fourth decimal).

The NMA protocol specified that if possible both fixed and random effects models were to be run with fit statistics (Deviance Information Criterion, DIC) to choose between them. However random effect models require trials that repeat the same pairwise comparisons. This often did occur and when it did, it still involved far too few trials (nearly always two) to estimate the between study contrast variance within the random effects model. Fixed effect models were therefore the only alternative and were utilised throughout the analysis.

The specific approach proposed by Woods et al 2010 for [154] incorporating median survival (PFS and OS) data (if hazard ratios are not presented) was implemented to maximize the amount of trials that could contribute to OS and PFS evidence networks (utilizing equation 20 in this publication). Although not discussed in the Woods paper, their method for utilising arm level should take into consideration a "pseudo drop out rate" (unless patients do not drop out of studies or is negligible). The reason is that their method relies on entering the patient base the median

survival relates to (whatever is entered is halved to produce the number of patient events and modelled in a binomial distribution assuming constant hazard rate over time). However medium survival in the presence of patient drop out (commonly estimated using Kaplin-Meier techniques) implies an artificially over-precise estimate would be generated in such circumstances. Therefore, in the NMAs where this is an issue two "pseudo drop out rates" have been applied: one at 10% and another at 60%. The latter is thought too conservative but serves as a safety net – this pseudo rate should not include the often large contingent of patients classed as censored at the end of the study simply because they have not experienced the event.

Likewise, in order to maximize the number of trials that could contribute to the analysis of the remaining endpoints (all binary) "shared parameter" modelling was introduced where necessary. This meant that the model could handle both data presented as counts (bases and number of events) and data presented as log odd ratios. The latter are preferable if derived from logistic regressions adjusted for covariates.

The Bayesian approach adopted allows for rankings to be calculated for each regimen and are presented as a Rankogram and Surface Under the Cumulative Ranking Distribution, SUCRA, statistics. A Rankogram shows the proportion of instances a regimen achieved the best outcome measure (rank 1), second best etc. It plots the result for all regimens on the same figure. SUCRA values for a regimen range between 0 (certain to be the worst) and 1 (certain to be the best). It can be interpreted as the average proportion of regimens worse than it.

4.10.5.3 Heterogeneity assessment

Pair-wise meta-analysis

For direct pair-wise comparisons involving trials, frequentist chi-squared, I-squared and tau-squared statistics were calculated in order to detect the presence of heterogeneity and, respectively, assess its degree. I-squared provides an estimate of the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error. I-squared values were interpreted according to the Cochrane Handbook.[115] The Tau-squared statistic represents the between study variance in random-effects meta-analysis.

Network Meta-Analysis

Leverage plots were used to identify any specific trials that appeared as outliers (in terms of being either influential or poorly fitted). A leverage plot displays the leverage (a measure of influence) versus the signed, square root of the residual deviance (a measure of fit) for each data point. Points with a high leverage are influential, which means that they have a strong influence on the model parameters that generate their fitted values. Trials that are heterogeneous on key parameters are likely to be either influential or poorly fitted and hence will stand out on such a plot.

4.10.5.4 Consistency assessment

Inconsistency can occur when there is a discrepancy between a direct and indirect estimate of treatment effect (an inconsistency in the loop). When loops were independent of each other we utilized Butcher's method (single or extended loops) as recommended in NICE's Evidence Synthesis TSD 4 (http://www.nicedsu.org.uk/TSD4%20Inconsistency.final.08.05.12.pdf) [163] All loops that existed were independent (only ever involved one loop). Hence there was no need to employ planned node-splitting/inconsistency models on non-independent loops.

It was planned that if inconsistency was detected (it was not) then the trials involved would be investigated to establish if there was any obvious rationale for the discrepancy.

4.10.5.5 Scenario Analysis

Scenario analysis performed included:

- Including only RCT studies in the network
- Combining studies with different doses and including studies unclear on dosage.
- Choice of publication when more than one existed for a trial – "Primary" or "Secondary", and inclusion of Hou et al data. [117]

The sensitivity of the results to these scenario analyses was explored where possible for the patient populations and outcomes of interest. Other scenario analyses involving sensitivity to key average baseline disparities between trials formed from sub-group analysis and/or meta-regression was not pursued due to insufficient studies (and lack of presented data).

4.10.6 NMA results

In the following NMA's it should be noted the comparison of ixazomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone is only informed by the direct comparative evidence from the TOURMALINE MM-1 study, and there is no indirect evidence informing this comparison in any of the networks for each patient population/outcome. Given that lenalidomide + dexamethasone is the reference treatment the NMA only draws on this direct evidence for this comparison, and the results generated for each outcome are virtually the same as the results reported in section 4 of this submission based on the TOURMALINE MM-1 trial alone (see

Table 41 in section 4.8.1).

4.10.6.1 1+ prior therapies population

Networks for the base case analyses were created for each of the outcomes of interest for this patient population as presented below. The results for comparisons of IXA+LEN+DEX with BORT+DEX and LEN+DEX are presented for the 1+ prior therapies population which relates to the ITT patient population of the TOURMALINE MM-1 study.

Progression free survival (PFS)

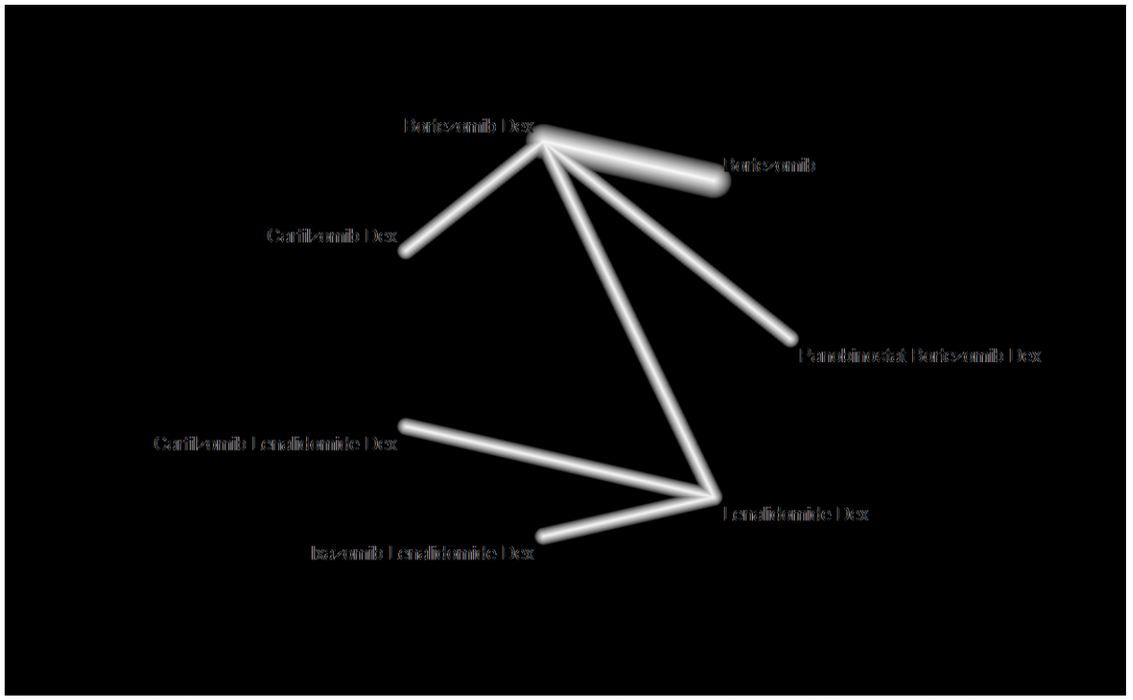
For PFS a base case network for the comparison of ixazomib + lenlalidomide + dexamethasone vs. bortezomib + dexamethasone could only be created based on combining specfic dose studies (studies considering the marketing authorisation dose of BORT: 1.3mg/m^2) with other non-dose specific studies (most often studies considering a 1.0mg/m^2 dose of BORT). A network based on the specific doses of direct interest for BORT+DEX was not possible due to the lack of data.

For this network, (see Figure 20 below) there were 8 studies,[1,18,133,133-135,138,143,145] of which 5 were RCTs [1,18,135,138,145] and 3 were observational studies, [68,133,143] with all studies directly contributing to a comparison of ixazomib + lenalidomide + dexamethasone vs. bortezomib + dexamethasone, and vs. lenalidomide + dexamethasone). See Table in Appendix 5 for study and patient characteristics of these trials.

The combining of studies with different doses is facilitated by the inclusion of the Montefusco et al. publication, [135] an abstract that reported results on bortezomib 1.3mg/m^2 + dex 20mg versus lenalidomide 15mg+dex 20mg. This study forms a bridge to an otherwise disconnected network that involved bortezomib+dex. However, the study did not present hazard ratio estimates but instead presented medium survival times for both arms. As explained in section 4.10.5.2, the technique described for handling this that utlilises medium survival times requires a patient "pseudo drop-out rate". A "pseudo" drop-out rate of 10% is assumed in the base case (with 35% explored in scenario analysis).

In summary, the base case consisted of RCT and observational studies, combined doses, and based on primary publications (see Figure 20).

Figure 20: Network for PFS in the 1+ prior therapies population – RCT and observational studies, combined doses, and primary publications



The results for the base case analysis using the network in Figure 20 above for the comparisons of interest are presented in Table 44 below. This shows that for PFS the IXA+LEN+DEX has better efficacy than LEN+DEX, and numerically better PFS efficacy than BORT+DEX based on the overall patient population. Scenario analyses based on RCTs only, secondary publications, adding Hou et al 2016, and using a pseudo drop-out rate of 60% have been performed, showing the results were not highly sensitive to alternative scenarios (Table 44).

Table 44: Hazard ratios from the NMA for PFS comparisons in the 1+ prior therapies population

PFS NMA – 1+ prior therapies population	Definition	Ixazomib+len+dex vs. len+dex Hazard Ratio (95% CrI)	Ixazomib+len+dex vs. bort+dex Hazard Ratio (95% CrI)
Base case PFS network	RCT and observational studies, combined doses, and primary publications (+ 10% pseudo drop out).*	0.74 (0.59, 0.94)	0.72 (0.41, 1.19)
Scenario analysis 1:	**RCT studies only**, combined doses, and primary publications	0.74 (0.58, 0.94)	0.72 (0.41, 1.18)
Scenario analysis 2:	RCT and observational studies, combined doses and **secondary publications**	0.82 (0.67, 1.01)	0.80 (0.46, 1.29)
Scenario analysis 3:	RCT and observational studies, combined doses and secondary publications **+ Hou et al. (2016)**	0.78 (0.65, 0.94)	0.76 (0.44, 1.22)
Scenario analysis 4:	RCT and observational studies, combined doses, and primary publications **(+ 60% pseudo drop out).**	0.74 (0.59, 0.94)	0.74 (0.38, 1.29)

*Based on method of Woods et al [154]or incorporating median PFS data if HRs are not present. See section – 4.10.5.2

Rankograms were produced for the whole network shown in Figure 20, and a SUCRA score estimated. The SUCRA score for PFS for IXA+LEN+DEX was 0.624, compared to 0.270 for LEN+DEX, and 0.255 for BORT+DEX, indicating a better outcome for IXA+LEN+DEX relative to these comparators.

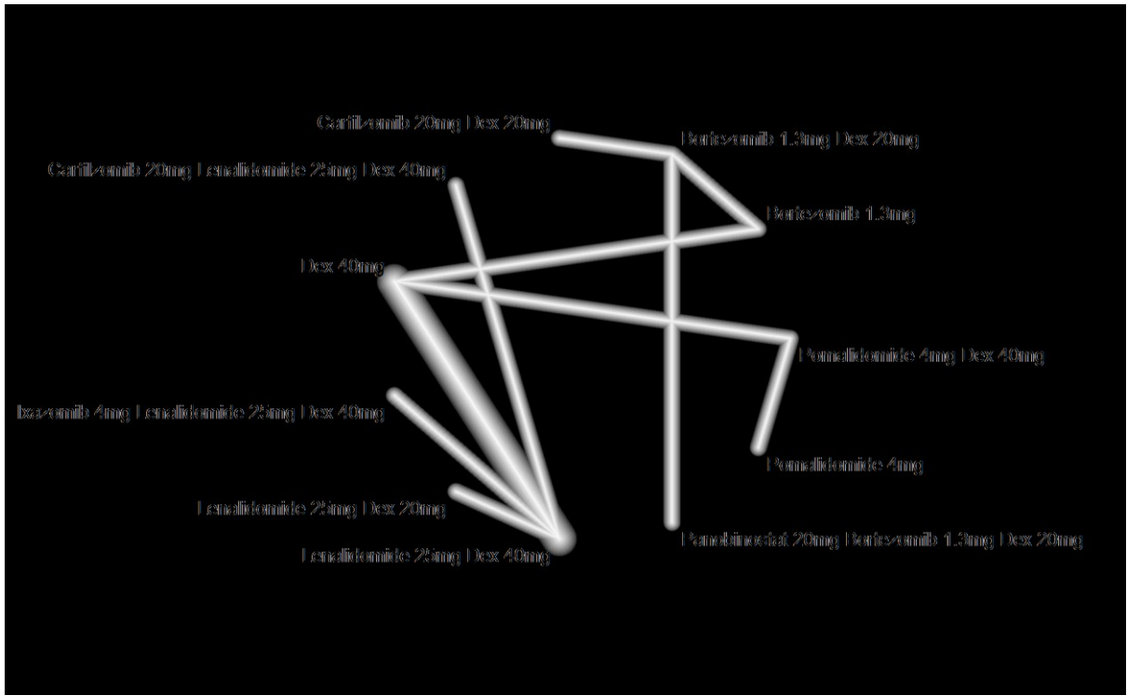
Leverage plots for the whole network indicated no outlier studies and hence heterogeneity does not appear to be an issue in the base case or scenario analyses.

Overall Survival (OS)

For OS the base case network including comparisons of ixazomib + lenalidomide + dexamethasone vs. bortezomib + dexamethasone, and vs. lenalidomide + dexamethasone were based on RCT and observational study designs, only specific doses of interest and primary publications, which is the preferred base case (see Figure 21).

For this network, there were 11 studies [1,18,133,136,138,141-143,145,149,150] of which 10 were RCTs [1,18,133,136,138,141,142,145,149,150] and 1 was an observational study, [143] with 8 studies [1,133,138,141-143,145] directly contributing to a comparison of ixazomib + lenalidomide + dexamethasone vs. bortezomib + dexamethasone, and vs. lenalidomide + dexamethasone). See Table in Appendix 5 for study and patient characteristics of these trials.

Figure 21: Network for OS in the 1+ prior therapies population – RCT and observational studies, specific doses, and primary publications.



The results for the base case analysis using the network in Figure 21 above for the comparisons of interest are presented in Table 45 below. This shows a HR of 0.90 vs lenalidomide + dexamethasone, but a significantly lower risk of death for the comparison with bortezomib + dexamethasone with a HR or 0.31 (Table 45). Scenario analyses based on RCTs only, combining doses, secondary publications show a similar pattern to the base case results (Table 45).

Table 45: Hazard rates from the NMA for OS comparisons in the 1+ prior therapies population

OS NMA – 1+ prior therapies population	Definition	Ixazomib+len+dex vs. len+dex Hazard Ratio (95% CrI)	Ixazomib+len+dex vs. bort + dex Hazard Ratio (95% CrI)
Base case OS network	RCT and observational studies, specific doses, and primary publications	0.90 (0.61, 1.31)	0.31 (0.13, 0.65)
Scenario analysis 1:	**RCT studies only**, specific doses, and primary publications	0.90 (0.61, 1.31)	N/A
Scenario analysis 2:	RCT and observational studies, **combined doses** and primary publications	0.87 (0.64, 1.18)	0.31 (0.15, 0.57)
Scenario analysis 3:	RCT and observational studies, specific doses and **secondary publications**	0.87 (0.64, 1.18)	0.41 (0.18, 0.79)

N/A = not available

Rankograms were produced for the whole network shown in Figure 21, and a SUCRA score estimated. The SUCRA score for OS for IXA+LEN+DEX was 0.846, compared to 0.747 for LEN+DEX, and 0.110 for BORT+DEX, indicating a better outcome for ixazomib + lenalidomide + dexamethasone relative to these comparators.

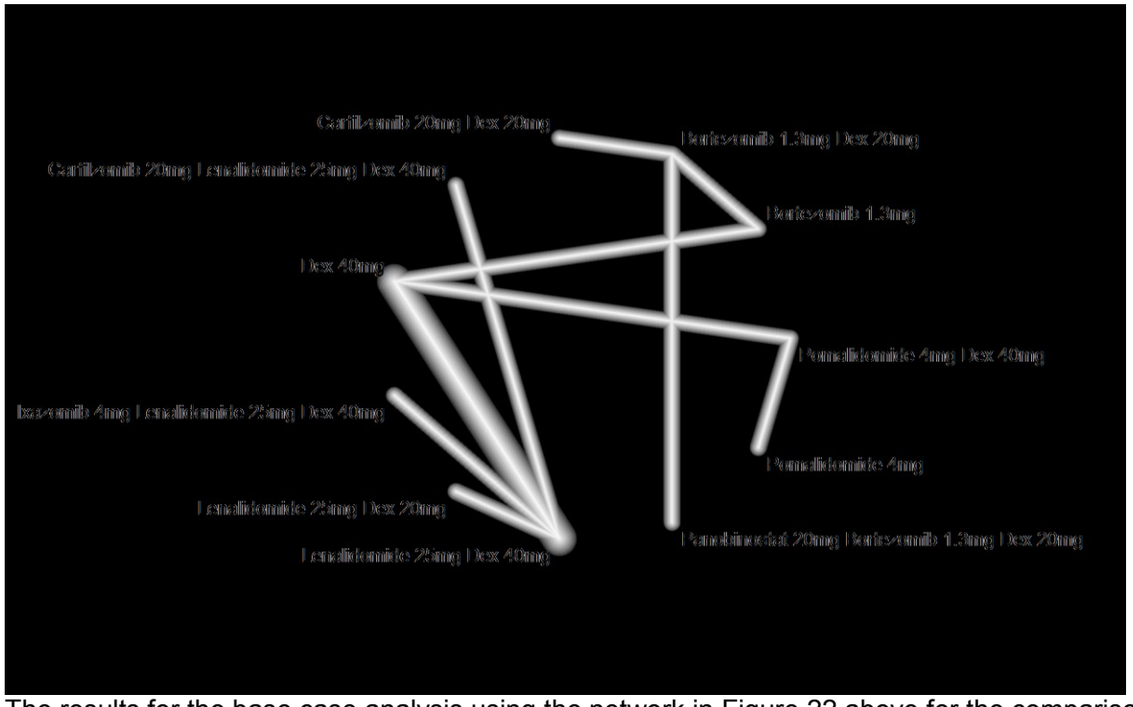
Leverage plots for the whole network indicated no outlier studies and hence heterogeneity does not appear to be an issue in the base case or scenario analyses.

Overall response rate (ORR)

For ORR the base case network including comparisons of IXA+LEN+DEX vs. BORT+DEX, and vs. LEN+DEX utilised RCT and observational study designs, specific doses, and primary publications (see Figure 22).

For this network were 12 studies [18,114,117,133,136,138,141,142,145,149,151], of which 10 were RCTs [18,117,136,138,141,142,145,149,151] and 2 were observational studies, [133,143] with x studies directly contributing to a comparison of ixazomib + lenalidomide + dexamethasone vs. bortezomib + dexamethasone, and vs. lenalidomide + dexamethasone) See Table in Appendix 5 for study and patient characteristics of these trials.

Figure 22: Network for ORR in the 1+ prior therapies population – RCT and observational studies, specific doses, and primary publications.



The results for the base case analysis using the network in Figure 22 above for the comparisons of interest are presented in Table 46 below. This shows a statistically higher ORR for IXA+LEN+DEX vs LEN+DEX, but a slightly lower ORR vs BORT+DEX, although the OR of 0.88 was not statistically significant (see Table 46). Scenario analyses demonstrated the ORR results were not highly sensitive to using RCTs only, combining different dose studies, using secondary publications (Table 46) for the comparison with LEN+DEX, although there was sensitivity to combining dose studies for the comparison with BORT+DEX (scenasrio 2, although there were wideCrI's with this comparison and still not statistically significant). The inclusion of Hou et al data for ixazomib improved the OR for ORR to some extent in favour of IXA+LEN+DEX vs. the comparators.

Table 46: Odds ratios from the NMA for ORR comparisons in the 1+ prior therapies population

ORR NMA – 1+ prior therapies population	Definition	Ixazomib+len+dex vs. len+dex Odds Ratio (95% CrI)	Ixazomib+len+dex vs. bort + dex Odds Ratio (95% CrI)
Base case ORR network	RCT and observational studies, specific doses, and primary publications	1.44 (1.03, 2.03)	0.88 (0.35, 1.85)
Scenario analysis 1:	**RCT studies only**, specific doses, and primary publications	1.44 (1.03, 2.03)	N/A
Scenario analysis 2:	RCT and observational studies, **combined doses** and primary publications	1.44 (1.03, 2.03)	1.71 (0.8, 3.21)
Scenario analysis 3	RCT and observational studies, specific doses and **secondary publications**	1.38 (0.96, 1.91)	0.83 (0.33, 1.74)
Scenario analysis 4:	RCT and observational studies, specific doses and **secondary publications + Hou et al.(2016)**	1.56 (1.13, 2.11)	0.94 (0.38, 1.94)

ORR=defined as complete + partial response

Rankograms were produced for the whole network shown in Figure 22, and a SUCRA score estimated. The SUCRA score for ORR for IXA+LEN+DEX was 0.487, compared to 0.269 for lenalidomide + dexamethasone, and 0.530 for bortezomib + dexamethasone, indicating a better outcome for IXA+LEN+DEX and BORT+DEX relative to LEN+DEX..

Leverage plots and frequency meta-analysis indicated hetereogeneity issues for the RCT and observational studies combined dose networks. The leverage plot shown in Figure 23 shows two points lying on or beyond the red parabola, indicating outliers. These represent two trials: [68,133] Dimopoulos et al., 2010 and Dimopoulos et al., 2015 - both observational and both compare BORT+DEX to BORT. Performing frequentist meta-analysis over the three trials (other trial is Bruno et al. 2006) that contrast these two treatments produces a high I-squared value of 79.6% and a p-value < 0.008 associated with the test of heterogeneity (Q statistic) – again indicating heterogeneity.

Further leverage plots establish that it is Dimopoulos et al., 2015 study that is the outlier – when it is removed, all points lie inside the red parabola (Figure 23); whilst this is not the case on removing Dimopoulos et al., 2010 [68,133](Figure 24).

Figure 23: Leverage versus Deviance Residual Plot: Overall Response Rate: 1+ Prior Therapies: RCT and Observational Studies,combined doses, primary publications

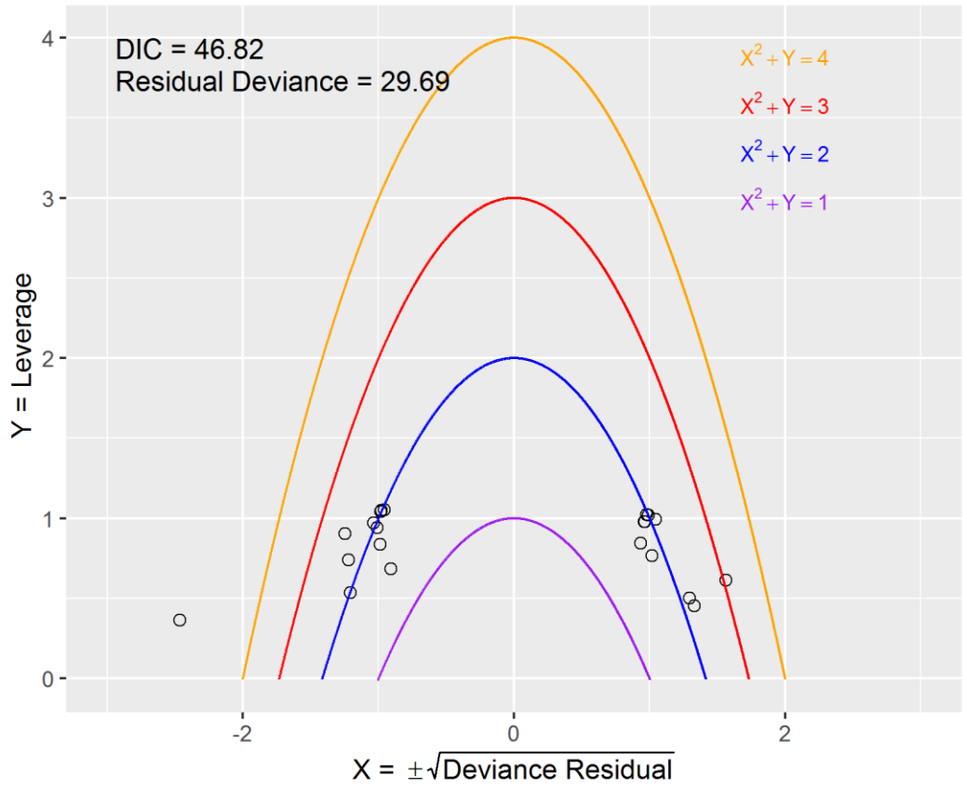


Figure 24: Leverage versus Deviance Residual Plot: Overall Response Rate: 1+ Prior Therapies: RCT and Observational Studies, oses combined, primary publications: Dimopoulos et al., 2015 study omitted

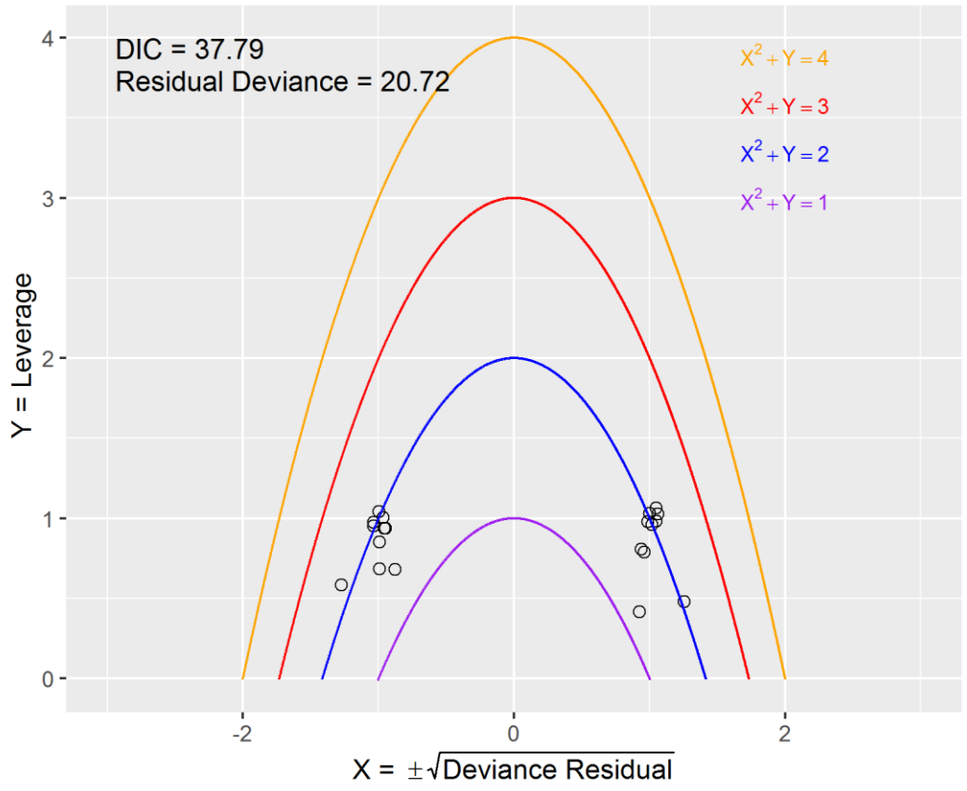
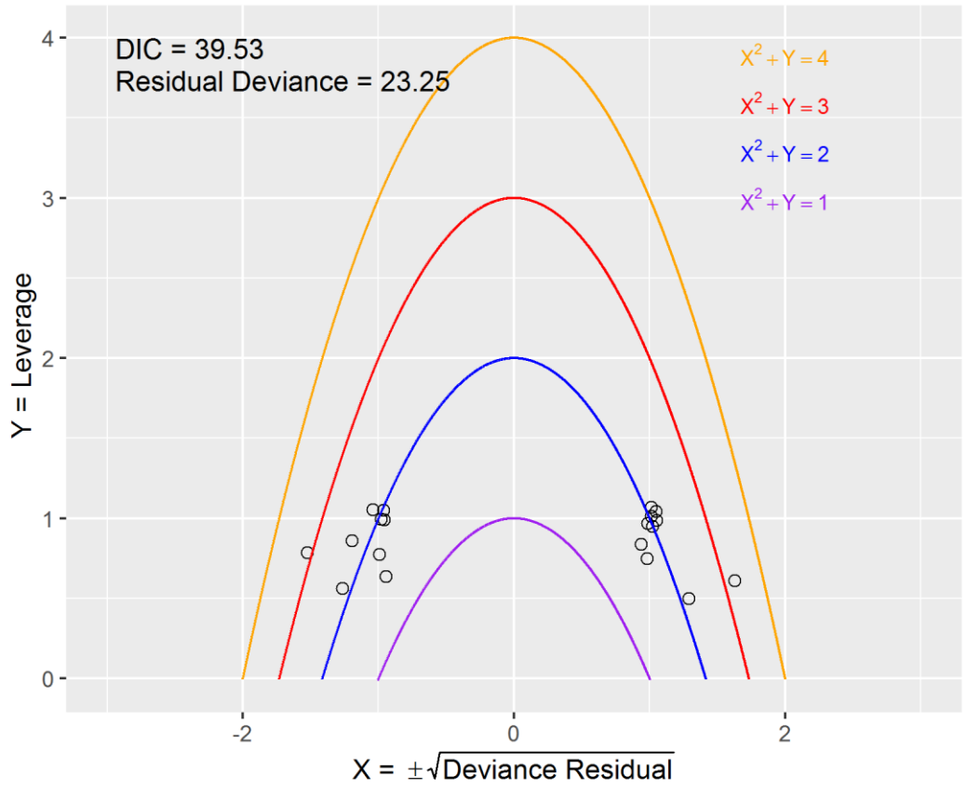


Figure 25: Leverage versus Deviance Residual Plot: Overall Response Rate: 1+ Prior Therapies: RCT and Observational Studies, combined doses, primary publications Dimopoulos et al., 2010 study omitted



Removing the Dimopoulos et al., 2015 study from the RCT and observational studies combined dose network (it was not possible to remove it from the specific dose base case network as a network could no longer be formed) resulted in a large shift in the odd's ratio comparison between IXA+LEN+DEX versus BORT+DEX. Specifically the OR shifted from 1.71 (0.8, 3.21 95% credible interval) to a "statistically significant" 2.67 (1.16, 5.27) for the primary pulications analysis group.

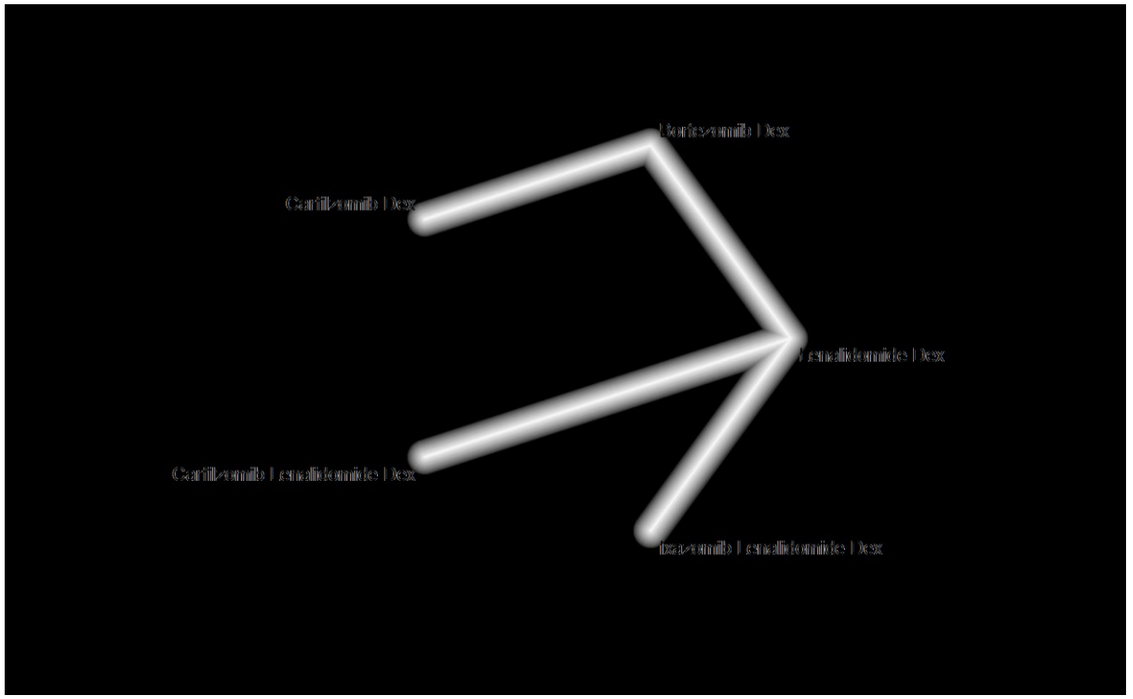
This was the only patient population and outcome for which heteroegeneity problems existed, based on leverage plot analysis.

Best overall response (BoR)

For BoR the base case network including comparisons of IXA+LEN+DEX vs. BORT+DEX, and vs. LEN+DEX were based on RCTs only as no observational studies were available, combined doses (as a network could not be formed using specific dose studies), and using primary publications (see Figure 26).

For this network there were 3 studies, [1,18,117] all of which were RCTs. and all directly contributing to a comparison of ixazomib + lenalidomide + dexamethasone vs. bortezomib + dexamethasone, and vs. lenalidomide + dexamethasone. See Table in Appendix 5 for study and patient characteristics of these trials.

Figure 26: Network for BoR in the 1+ prior therapies population – RCT studies, combined doses, and primary publications.



This shows a statistically better BoR for IXA+LEN+DEX vs LEN+DEX, and also vs BORT+DEX (see Table 47), with these results supported by scenario analysis that was possible based on using secondary publications and adding Hou et al 2016 [117](Table 47).

Table 47: Odds ratios from the NMA for BoR comparisons in the 1+ prior therapies population

BoR NMA – 1+ prior therapies population	Definition	Ixazomib+len+dex vs. len+dex Odds Ratio (95% CrI)	Ixazomib+len+dex vs. bort + dex Odds Ratio (95% CrI)
Base case BoR network	RCTs, combined doses, and primary publications	1.47 (1.08, 1.95)	3.82 (1.32, 8.93)
Scenario analysis 1:	RCTs, combined doses, and **secondary publications**	1.37 (1.01, 1.81)	3.56 (1.23, 8.35) /A
Scenario analysis 2:	RCTs, combined doses, and secondary publications **+ Hou et al**	1.43 (1.07, 1.88)	3.71 (1.29, 8.60)

BoR= defined as patients who achieved a best overall response of very good partial response or better

Rankograms were produced for the whole network shown in Figure 26, and a SUCRA score estimated. The SUCRA score for BoR for IXA+LEN+DEX was 0.647, compared to 0.320 for LEN+DEX, and 0.009 for BORT+DEX, indicating a better outcome for IXA+LEN+DEX relative to these comparators.

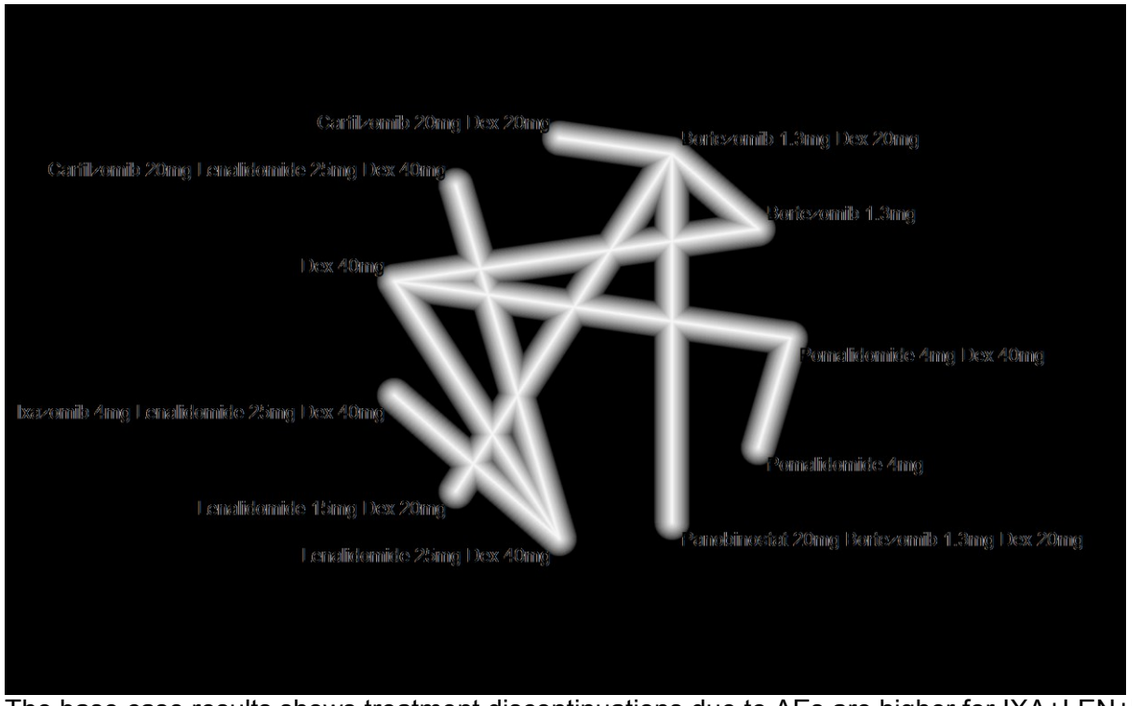
Leverage plots for the whole network indicated no outlier studies and hence heterogeneity does not appear to be an issue in the base case or scenario analyses

Treatment discontinuation due to AE's

The results for this outcome in each clinical study related to the "safety population" and hence analysis could not be separated for different patient populations based on number of prior therapies. The base case however consisted of the preferred use of RCT and observational studies, the specific doses of interest, and primary publications (Figure 27).

For this network, there were 10 studies, [1,18,117,135,136,138,142,145,149,150] of which all were RCTs, with 7 studies directly contributing to a comparison of ixazomib + lenalidomide + dexamethasone vs. bortezomib + dexamethasone, and vs. lenalidomide + dexamethasone (See Table Appendix 5 for study and patient characteristics of these trials.).

Figure 27: Network for Treatment discontinuation due to AEs in the 1+ prior therapies population – RCT and observational studies, specific doses, and primary publications.



The base case results shows treatment discontinuations due to AEs are higher for IXA+LEN+DEX vs LEN+DEX, although not statistically different, with the same finding for the comparison with bortezomib + dexamethasone. This finding is supported by each of the scenario analyses performed (Table 48).

Table 48: Odds ratios from the NMA for treatment discontinuations due to AEs comparisons in the 1+ prior therapies population

Discontinuation due to AE's NMA – 1+ prior therapies population	Definition	Ixazomib+len+dex vs. len+dex Odds Ratio (95% CrI)	Ixazomib+len+dex vs. bort + dex Odds Ratio (95% CrI)
Base case AE discontinuation network	RCT and observational studies, specific doses, and primary publications	1.25 (0.77, 1.92)	2.58 (0.81, 6.32)
Scenario analysis 1:	**RCT studies only**, **combined doses,** and primary publications	1.25 (0.77, 1.92)	1.84 (0.56, 4.62)
Scenario analysis 2:	RCT and observational studies, **combined doses** and primary publications	1.25 (0.77, 1.93)	2.07 (0.86, 4.29)
Scenario analysis 3	RCT and observational studies, specific doses and **secondary publications**	1.28 (0.83, 1.89)	2.64 (0.85, 6.35)
Scenario analysis 4:	RCT and observational studies, specific doses and **secondary publications + Hou et al 2016**	1.16 (0.77, 1.67)	2.38 (0.78, 5.68)

Rankograms were produced for the whole network shown in Figure 27, and a SUCRA score estimated. The SUCRA score for treatment discontinuation due to AEs for IXA+LEN+DEX was 0.271, compared to 0.140 for LEN+DEX, and 0.689 for BORT+DEX, indicating a better outcome for IXA+LEN+DEX relative to BORT+DEX, although a better outcome for LEN+DEX.

Leverage plots for the whole network indicated no outlier studies and hence heterogeneity does not appear to be an issue in the base case or scenario analyses

4.10.6.2 1 prior therapy population

There were insufficient studies and data available to enable networks to be created for comparing ixazomib + lenalidomide + dexamethasone vs the key comparator of bortezomib + dexamethasone in the one prior therapy patient population for any of the outcomes of interest (PFS, OS, ORR, BoR). Whilst there was data available for IXA+LEN+DEX for each outcome for this patient population (which has been utilised in the economic analysis for PFS and OS, small networks could only be formed for PFS and ORR. Neither of these networks involved BORT+DEX . No study provided data involving BORT+DEX for PFS, whilst for ORR there was one such study (Moreau et al.,2015), however it could not connect to the IXA+LEN+DEX network.

4.10.6.3 2+ prior therapies population

Networks for the base case analyses were created for each of the outcomes of interest for this patient population as presented below. The relevant comparator for this patient population to support a 3rd line positioning of ixazomib is LEN+DEX. However, all the network plots for 2+ prior therapies clearly show that the only source of information informing the IXA+LEN+DEX vs. LEN+DEX comparison comes from direct evidence from the TOURMALINE-MM1 trial. There is no indirect link between these regimens on the network. Therefore, the NMA results should

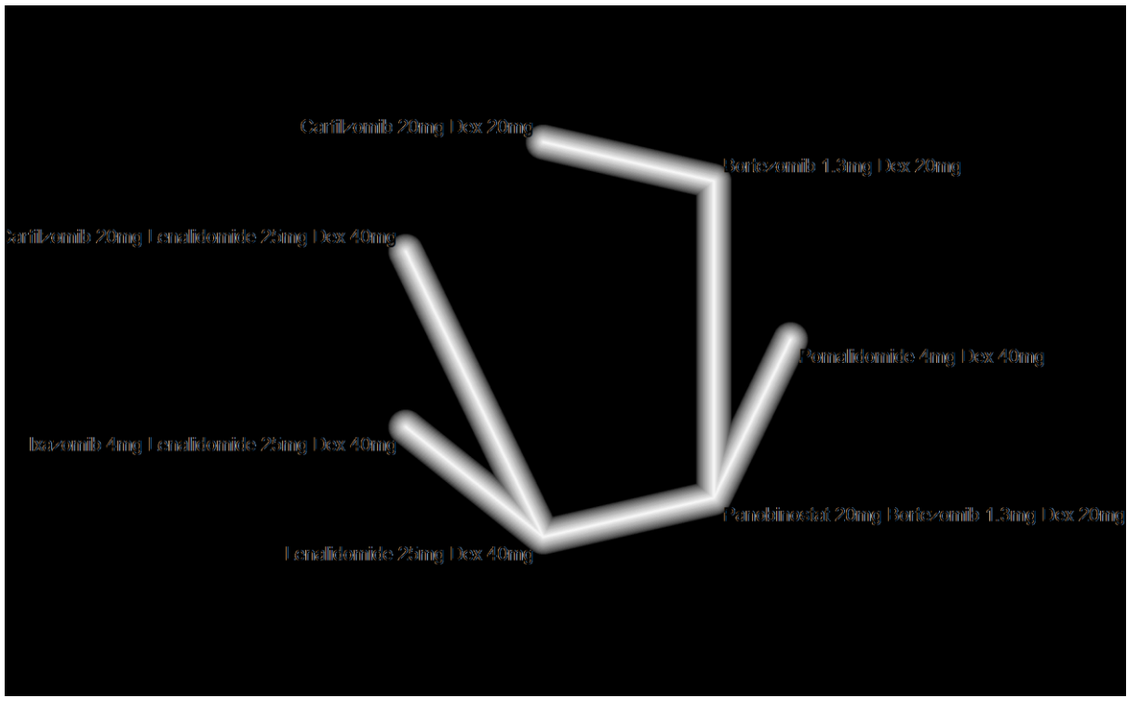
correspond to the direct trial evidence. Any deviation is an accumulation of small imputation, rounding, and monte carlo sampling errors. Validity checks have confirmed this to be the case. Nonetheless, the results are reported below for completeness.

Progression free survival (PFS)

For PFS the base case network including comparisons of IXA+LEN+DEX vs. LEN+DEX was based on including RCT studies only (no observational studies were identified for this patient population), although studies with specific doses and primary publication studies could be used to form a network in the base case (Figure 28).

For this network, there were 6 analyses, [1,139,140,144,145] of which 4 were RCTs [1,139,140,145] and 1 was a systematic review with 2 analyses (a and b), [144] with 3 analyses [1,140,144][analysis a]) directly contributing to a comparison of ixazomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone). See Table in Appendix 5 for study and patient characteristics of these trials.

Figure 28: Network for PFS in the 2+ prior therapies population – RCT only, dose specific, primary publications



The results for the base case analysis using the network in Figure 28 above for the comparison of interest is presented in Table 49 below. This shows that for PFS IXA+LEN+DEX has better efficacy then LEN+DEX (HR of 0.59), in the 2+ prior therapies patient population, and this was supported by the one scenario analysis that was possible using secondary publications (Table 49).

Table 49: Hazard rates from the NMA for PFS comparisons in the 2+ prior therapies population

PFS NMA – 2+ prior therapies population	Definition	Ixazomib+len+dex vs. Len + dex* Hazard Ratio (95% CrI)
Base case PFS network	RCT studies, specific doses, and primary publications	0.59 (0.40, 0.84)
Scenario analysis 1:	RCT studies, specific doses, and **secondary publications**	0.63 (0.44, 0.86)

*This comparison in the NMA draws on only direct evidence in for ixazomib + lenalidomide+ dexamethasone vs lenalidomide + dexamethasone from the TOURMALINE MM-1 trial, hence the results are very similar to the trial based results reported in table 38 in the clijnical section.

Rankograms were produced for the whole network shown in Figure 28, and a SUCRA score estimated. The SUCRA score for PFS for IXA+LEN+DEX was 0.946, compared to 0.421 for LEN+DEX, indicating a better outcome for IXA+LEN+DEX relative to this comparator.

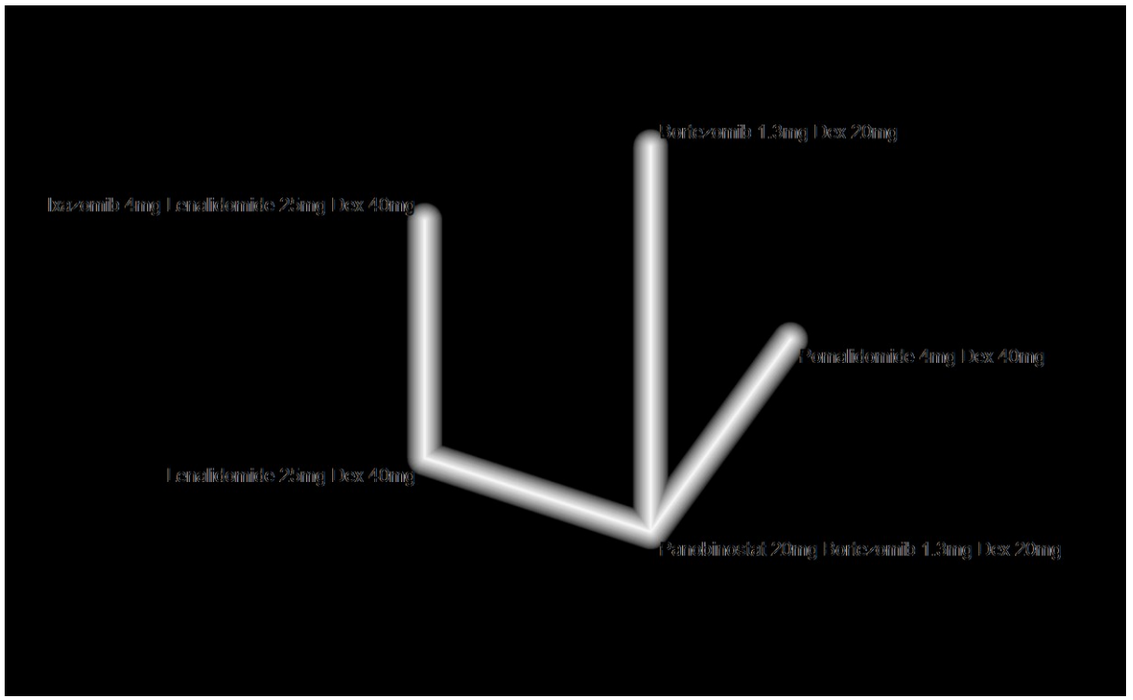
Leverage plots for the whole network indicated no outlier studies (indeed there are no loops in Figure 28 above and no two trials for the same treatment constrast in it) and hence heterogeneity does not appear to be an issue in the base case or scenario analyses

OS

For OS a base case network including comparison of IXA+LEN+DEX vs. LEN+DEX was based on including RCT studies only (no observational studies were identified for this outcome and patient population), although studies with specific doses of interest and primary publication studies could be used to form a network in the base case).

For this network, there were 4 analyses, of which 2 were RCTs [1,147] and 1 was a systematic review with 2 analyses (a and b) from RCTs [144](Majer 2016). Two analyses directly contributed to a comparison of ixazomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone). See Table in Appendix 5 for study and patient characteristics of these trials.Figure 29

Figure 29: Network for OS in the 2+ prior therapies population: RCT only, dose specific: primary publications Data



The main result for the comparison with LEN+DEX was a numerically favourable HR for IXA+LEN+DEX. The scenario analyses conducted found the results were not sensitive to assuming a pseudo drop out rate of 10% (or 35%), and use of secondary publications (Table 50).

Table 50: Hazard rates from the NMA for OS comparisons in the 2+ prior therapies population

OS NMA – 2+ prior therapies population	Definition	Ixazomib+len+dex vs. Len + dex** Hazard Ratio (95% CrI)
Base case OS network	RCT studies, specific specific doses, and primary publications	0.64 (0.35, 1.09)
Scenario analysis 1:	RCT studies, specific doses, and primary publications (**assuming 10% drop-out**)*	0.64 (0.35, 1.09)
Scenario analysis 2:	RCT studies, specific doses and **secondary publications**	0.66 (0.41, 1.20)

*Based on method of Woods et al[154] for incorporating median OS data if HRs are not present. See section – 4.10.5.2
**This comparison in the NMA draws on only direct evidence in for ixazomib + lenalidomide+ dexamethasone vs lenalidomide + dexamethasone from the TOURMALINE MM-1 trial, hence the results are very similar to the trial based results reported in table 38 in the clijnical section.

Rankograms were produced for the whole network shown in Figure 29, and a SUCRA score estimated. The SUCRA score for OS for IXA+LEN+DEX was 0.892, compared to 0.334 for LEN+DEX, indicating a better outcome for IXA+LEN+DEX relative to this comparator.

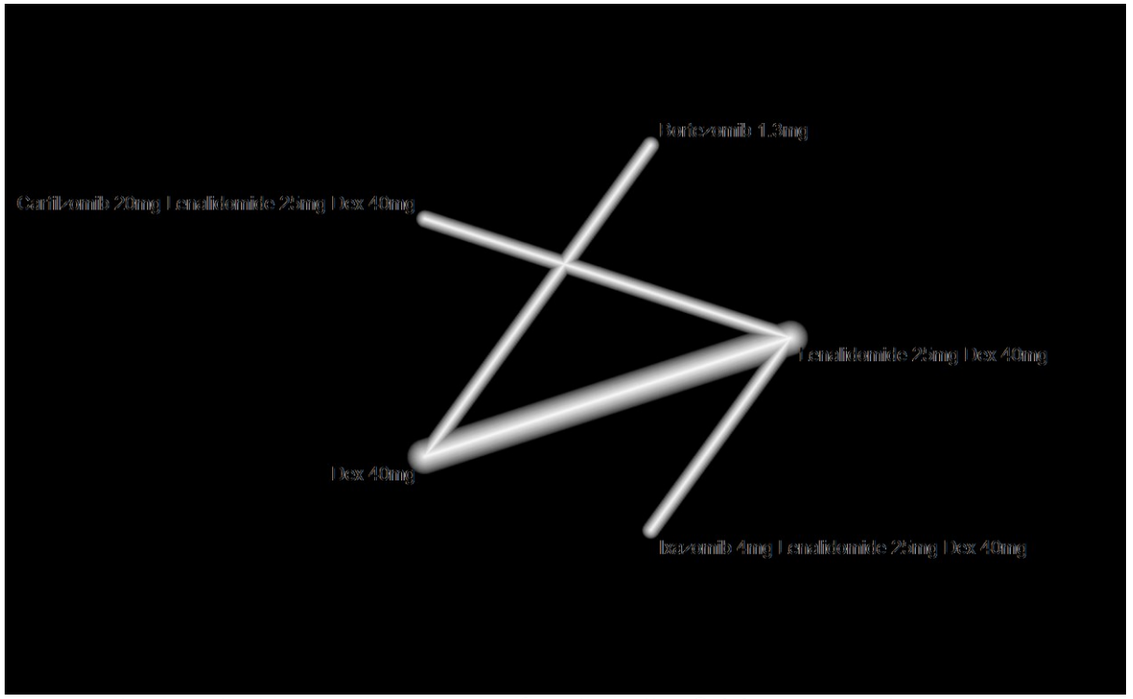
Leverage plots for the whole network indicated no outlier studies (indeed there are no loops in Figure 29 above and no two trials for the same treatment constrast in it) and hence heterogeneity does not appear to be an issue in the base case or scenario analyses

ORR

For ORR a base case network including comparisons of IXA+LEN+DEX vs. LEN+DEX could be created based on including RCT studies only (no observational studies were identified for this outcome and patient population), although studies with specific doses of interest and primary publication studies could be used to form a network in the base case (Figure 30).

For this network were 5 studies,[1,9,136,141,142] of which all were RCTs, with 4 studies ,[1,9,141,142] directly contributing to a comparison of ixazomib + lenalidomide + dexamethasone vs. lenalidomide + dexamethasone) See Table in Appendix 5 for study and patient characteristics of these trials.

Figure 30: Network for ORR in the 2+ prior therapies population: RCT only, dose specific, and primary publications



The results show that ixazomib had a significantly better ORR compared to lenalidomide + dexamethasone in the 2+ prior therapies patient population, with an OR of 2.1, supported by the scenario analysis using secondary publication data (Table 51).

Table 51: Odds ratios from the NMA for ORR comparisons in the 2+ prior therapies population

ORR NMA – 2+ prior therapies population	Definition	Ixazomib+len+dex vs. len + dex* Odds Ratio (95% CrI)
Base case ORR network	RCT studies, specific doses, and primary publications	2.1 (1.19, 3.46)
Scenario analysis 1	RCT and observational studies, specific doses and **secondary publications**	2.16 (1.23, 3.56)

*This comparison in the NMA draws on only direct evidence in for ixazomib + lenalidomide+ dexamethasone vs lenalidomide + dexamethasone from the TOURMALINE MM-1 trial, hence the results are very similar to the trial based results reported in table 38 in the clijnical section.

Rankograms were produced for the whole network shown in Figure 30, and a SUCRA score estimated. The SUCRA score for OS for IXA+LEN+DEX was 0.677, compared to 0.310 for LEN+DEX, indicating a better outcome for IXA+LEN+DEX relative to this comparator.

Leverage plots for the whole network indicated no outlier studies and hence heterogeneity does not appear to be an issue in the base case or scenario analyses

BoR

There were insufficient studies to enable a network to be created for BoR in the 2+ prior therapies patient population.

4.10.6.4 Conclusion

The NMA has primarily been performed in order to enable a comparison of the relative effectiveness and safety of ixazomib 4mg + lenalidomide 25mg + dexamethasone 40mg with bortezomib 1.3mg/m^2 + dexamethasone 20mg, the key comparator for patients who have received one prior therapy (2nd line positioning – see table 1). Other licensed RRMM drugs that are potential comparators to ixazomib in a broader UK and Ireland HTA context have been included in the systematic search and networks, so the network diagrams are presented here with these included. Unfortunately, there was not sufficient evidence in order to create networks for the key outcomes using data specifically for one prior therapy. Hence, results are presented for the comparison with BORT+DEX using evidence networks for the whole ≥1 prior therapy population, on the grounds this is a larger evidence network and hence more robust, and an assumption that this is sufficiently representative of the results for a one prior therapy sub-group. It is these data that is used as a proxy in the economic analysis reported in section 5 to enable a comparison of the cost-effectiveness of IXA+LEN+DEX vs BORT+DEX

The key results for this comparison based on the 1+ prior therapy analysis shows the numerical efficacy benefits of the ixazomib regimen in PFS, and statistically significant benefits in OS and BoR. For ORR there was a numerical benefit for LEN+DEX , although not significant and in a scenario analysis was favourable for IXA+LEN+DEX, so there is some sensitivity to different studies included there. In terms of treatment discontinuations due to AEs the odds ratio was greater than one for IXA+LEN+DEX vs BORT+DEX, hence indicating higher discontinuations for the former, but the difference was not statistically significant with wide credible intervals. In general the CrI's were wider for the ORR, BoR and discontinuatins due to AEs networks, indicating a potential higher level of uncertainty in these results. Heterogeneity was only an issue in one network (ORR in 1+ prior therapies). Removing the

Dimopoulos et al., 2015 [133] study from the RCT and observational studies combined dose network (it was not possible to remove it from the specific dose base case network as a network could no longer be formed) in this network resulted in a large shift in the odd's ratio comparison between IXA+LEN+DEX versus BORT+DEX. Specifically the OR shifted from 1.71 (0.8, 3.21 95% credible interval) to a statistically significant 2.67 (1.16, 5.27) for the primary pulications analysis group.

The key comparator for the 2+ prior therapy sub-group (used to support a 3rd line positioning for ixazomib) is lenalidomide 25mg + dexamethasone 40mg. Networks could be created for PFS, OS and ORR for the 2+ sub-group, however, as the only evidence informing the networks for the ixazomib regimen vs. lenalidomide + dexamethasone comparison was the TOURMALINE MM-1 trial, (no indirect evidence infomed the network for this comparison) the results closely depicted the direct trial results reported in section 4, with PFS and ORR showing a statistically signifiant benefit for ixazomib, and for OS a numerical benefit. The results from the 1+ therapies analyses supported these findings for this comparison, and also demonstrated a statistically significant benefit for ixazomib regimen vs. lenalidomide + dexamethasone for the BoR outcome.

The results were largely consistent across several scenario analyses that were feasible across networks. The base case made use of all available data and so included observational studies as well as RCTs. Scenario analyses just including RCTs did not appear to have a large impact on the results. Also there were relatively small differences in results according to whether primary publications were used or later datacut secondary evidence (including the unpublished 2nd datacut form ixazomib). The results tended to improve when the data from the extension study to TOURMALINE MM1 in China were included (for PFS and ORR).

There were several limitations in the NMA, for example to support the positioning of ixazomib regimen in a 2nd line use instead of BORT+DEX (lack of specific 1 prior therapy evidence for the comparators to form a network). Other limits include only fixed effects modelling was possible, and for PFS it was not possible to use specific dose studies only to create networks in the 1+ prior therapies population. The evidence base was larger for the 1+ population than for the sub-groups of interest so can be considered more robust, althoigh ideally more evidence would be useful for the 1 and 2+ prior therapy populations. The NMA also did not particularly contribute any further evidence for a comparison with LEN+DEX in the 2+ prior therapies sub-group, hence the results mirrored those from the clinical trial. Finally, there is insufficient evidence to enable NMA's to be performed for the outcomes of HRQoL and for time to treatment discontinuation for the patient populations of interest.

4.11 Non-randomised and non-controlled evidence

The SLR identified 3 observational studies, and one systematic literature review with 2 analyses (Pano + Bort + Dex versus either Len + Dex or Pom + Dex) (Section 4.1.4). The NMA included both RCTs and observational studies (Section 4.10.6). There is no non-randomised evidence identified from the SR for ixazomib in the relevant patient population.

4.12 Adverse reactions

4.12.1 TOURMALINE-MM1 pivotal Phase III clinical study of IXA in relapsed/refractory multiple myeloma: safety and tolerability

4.12.1.1 Safety population and treatment exposure

Safety data were evaluated at both the first and second interim analyses (median follow-up of ~15 months and ~23 months, respectively). A consistent safety profile was demonstrated following the longer duration of exposure. At the 23-month analysis, the safety population included 361 patients in the IXA+LEN+DEX group and 359 in the LEN+DEX group (see Figure 11). Patients had received a median of 17 (range 1-34) and 15 (range 1-34) treatment cycles in the IXA+LEN+DEX and LEN+DEX groups, respectively (48% and 43% had received ≥18 cycles; 20% and 19% had received ≥25 cycles). Study treatment had been discontinued in 62% and 63% of the patients in the IXA+LEN+DEX and LEN+DEX groups, respectively (Table 52; the primary reasons for treatment discontinuation were disease progression in 34% and 40%, and adverse events (AEs) in 17% and 14%, respectively.

Table 52: Reasons for treatment discontinuation (median follow-up of ~23 months)

Reason for treatment discontinuation, n (%)	IRd (N=360)[a]	Rd (N=362)
Any	222 (62)	229 (63)
Progressive disease	124 (34)	146 (40)
Adverse event	60 (17)	50 (14)
Common adverse events resulting in treatment discontinuation[b]		
Diarrhoea	6 (2)	1 (<1)
Peripheral neuropathy NEC	7 (2)	2 (<1)
Fatigue	4 (1)	2 (<1)
Thrombocytopenia	4 (1)	4 (1)
Cardiac failure	1 (<1)	3 (<1)
Neutropenia	3 (<1)	3 (<1)
Decreased platelet count	1 (<1)	3 (<1)
Withdrawal by patient	7 (2)	11 (3)
Protocol violation	0	1 (<1)
Lost to follow-up	1 (<1)	0
Other	30 (9)	21 (6)

Abbreviations: IRd = ixazomib+lenalidomide+dexamethasone; Rd = placebo+lenalidomide+dexamethasone; NEC, not elsewhere classified
[a] Two patients did not receive the allocated intervention (see Figure 11).
[b] Reported for at least 3 patients.
Source: Moreau, 2016 [1]

The median relative dose intensity for lenalidomide and dexamethasone was similar in the two study groups; the median relative dose intensity for ixazomib was 97.4% and for placebo was 98.8% (Table 53).

Table 53: Relative dose intensity of study drugs (median follow-up of ~23 months)

Median relative dose intensity, %	IRd (N=361)	Rd (N=359)
Ixazomib	97.4	Not applicable
Placebo	Not applicable	98.8
Lenalidomide	93.8	96.6
Dexamethasone	92.2	94.9

Abbreviations: IRd = ixazomib+lenalidomide+dexamethasone; Rd = placebo+lenalidomide+dexamethasone

Relative dose intensity determined as the % of the total amount of dose taken divided by the total amount of planned dose over treated cycles.

Source: Moreau, 2016 [1]

4.12.1.2 Adverse events in the Safety population

The safety profiles at the 23-month analysis are summarised in Table 54 [1] rates of serious adverse events (SAEs), discontinuations due to AEs, and on-study deaths were similar in the IXA+LEN+DEX and LEN+DEX groups.

Table 54: Overall safety profile at the 23-month analysis (Safety population)

Median follow-up	IRd 23.3 months (N=361)[a]	Rd 22.9 months (N=359)[a]
Adverse events, n (%)		
Any AE	355 (98)	357 (99)
Any grade ≥3 AE	267 (74)	247 (69)
Any serious AE	168 (47)	177 (49)
AE resulting in dose reduction of any drug	203 (56)	181 (50)
AE resulting in discontinuation of any drug[b]	91 (25)	73 (20)
AE resulting in discontinuation of regimen[c]	60 (17)	50 (14)
On-study death	15 (4)	23 (6)

Abbreviations: AE = adverse event; IRd = ixazomib+lenalidomide+dexamethasone; Rd = placebo+lenalidomide+dexamethasone
Adverse events were graded per National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.
[a] Two of the 360 patients randomised to the ixazomib group did not receive any study treatment, and at the time of the first interim analysis 2 of the 362 patients randomised to the placebo group accidentally received limited dosing of ixazomib and were therefore conservatively included in the ixazomib group for analyses of exposure and safety. A third patient was similarly included in the ixazomib group for analyses of exposure and safety at the second interim analysis.
[b] Discontinuation of 1 or more of the 3 agents in the study drug regimen.
[c] Discontinuation of the full study drug regimen including discontinuation for disease progression.
Source: Moreau, 2016 [1]

The most common haematologic and non-haematologic AEs in the overall safety population are summarised in Table 55 [1] Thrombocytopenia, an overlapping AE seen with ixazomib and lenalidomide-dexamethasone [164-167] was reported for 31% and 16% of patients in the IXA+LEN+DEX and LEN+DEX groups (including grade 3/4 in 12%/7%

and 5%/4%, respectively), with transient and cyclical decreases in platelet count observed. The need for platelet transfusions was similar between groups (8% vs. 6%), as were the rates of serious AEs (2% in each group) and discontinuations (1% in each group) due to thrombocytopenia.

Overlapping non-haematologic AEs seen with ixazomib and with lenalidomide-dexamethasone include gastrointestinal events and rash. [164-167] Gastrointestinal events were more common in the IXA+LEN+DEX group but were primarily seen within the first 3 months and were low-grade and manageable with supportive therapy; in the IXA+LEN+DEX and LEN+DEX groups, 22% and 19% of patients received anti-diarrhoeal agents, and 21% and 13% of patients used anti-emetics. Medical management of diarrhoea included the use of anti-diarrhoeals (primarily loperamide) and dose modification of lenalidomide or ixazomib as needed. The incidence of rash (standardised MedDRA query) was 36% versus 23% in the IXA+LEN+DEX versus LEN+DEX group, respectively, with the difference between groups primarily driven by grade 1 and grade 2 events. The rash events occurred primarily in the first 3 months and were frequently self-limiting, with 21% and 12% of patients in the IXA+LEN+DEX and LEN+DEX groups, respectively, reporting events that resolved without intervention. Medical management of rash included symptomatic management with antihistamines (primarily cetirizine) or topical glucocorticoids and dose modification as required.

Peripheral neuropathy (PN) is a known side-effect of the first-in-class PI bortezomib. [168] The incidence of PN was 27% (15% grade 1, 10% grade 2) and 22% (14% grade 1, 6% grade 2) in the IXA+LEN+DEX and LEN+DEX groups, respectively; 2% of patients in each arm had grade 3 events, and no grade 4, grade 5, or serious AEs of PN were reported. The incidence of PN with pain was 4% and 3% in the IXA+LEN+DEX and LEN+DEX groups, respectively.

There were no differences between the IXA+LEN+DEX and LEN+DEX groups with respect to heart failure (4% in each group), arrhythmias (16% vs. 15%), hypertension (6% vs. 5%), and myocardial infarction (1% vs. 2%). At current follow-up there was no difference in the rate of new primary malignancy (5% vs. 4%).

Table 55: Common Adverse Events and other Adverse Events of clinical importance (Safety Population, 23-month analysis)

	IRd (N=361)			Rd (N=359)		
	Any-grade	**Grade 3**	**Grade 4**	**Any-grade**	**Grade 3**	**Grade 4**
Common[a] haematologic AEs of any cause, n (%)						
Neutropenia[b]	118 (33)	64 (18)	17 (5)	111 (31)	63 (18)	22 (6)
Thrombocytopenia[b]	112 (31)	43 (12)	26 (7)	57 (16)	19 (5)	13 (4)
Anaemia	103 (29)	34 (9)	0	98 (27)	48 (13)	0
Common[a] non-haematologic AEs of any cause, n (%)						
Diarrhoea	164 (45)	23 (6)	0	139 (39)	9 (3)	0
Rash SMQ[c]	131 (36)	18 (5)	0	82 (23)	6 (2)	0
Rash HLT[c]	72 (20)	9 (2)	0	45 (13)	6 (2)	0
Constipation	126 (35)	1 (<1)	0	94 (26)	1 (<1)	0
Fatigue	106 (29)	13 (4)	0	102 (28)	10 (3)	0
Nausea	104 (29)	6 (2)	0	79 (22)	0	0
Peripheral oedema	101 (28)	8 (2)	0	73 (20)	4 (1)	0
Peripheral neuropathy[d]	97 (27)	9 (2)	0	78 (22)	6 (2)	0
Back pain	87 (24)	3 (<1)	0	62 (17)	9 (3)	0
Vomiting	84 (23)	4 (1)	0	42 (12)	2 (<1)	0
Upper respiratory tract infection	83 (23)	2 (<1)	0	70 (19)	3 (<1)	0
Nasopharyngitis	81 (22)	0	0	73 (20)	0	0
Insomnia	73 (20)	7 (2)	0	98 (27)	11 (3)	0
Muscle spasms	66 (18)	0	0	95 (26)	2 (<1)	0
Other AEs of clinical interest, n (%)						
Arrhythmias[b,e]	56 (16)	17 (5)	3 (<1)	53 (15)	10 (3)	1 (<1)
Thromboembolism [b,e]	29 (8)	9 (2)	2 (<1)	38 (11)	11 (3)	1 (<1)
Liver impairment [b]	26 (7)	7 (2)	0	21 (6)	4 (1)	0
Hypertension (any)	22 (6)	11 (3)	0	18 (5)	4 (1)	0
Hypertension crisis	1 (<1)	0	0	0	0	0

	IRd (N=361)			Rd (N=359)		
	Any-grade	**Grade 3**	**Grade 4**	**Any-grade**	**Grade 3**	**Grade 4**
Hypotension [b,e]	22 (6)	4 (1)	0	21 (6)	1 (<1)	0
Heart failure [b,e]	16 (4)	7 (2)	2 (<1)	14 (4)	4 (1)	2 (<1)
Acute renal failure [b]	31 (9)	7 (2)	2 (<1)	41 (11)	12 (3)	4 (1)
Myocardial infarction [b,e]	5 (1)	0	3 (<1)	8 (2)	2 (<1)	2 (<1)
Encephalopathy [b]	2 (<1)	2 (<1)	0	4 (1)	0	0
Interstitial lung disease	4 (1)	1 (<1)	1 (<1)	7 (2)	2 (<1)	0
Events of special interest, n (%)[f]						
New primary malignancy [b]	17 (5)			14 (4)		

Abbreviations: AE = adverse event; IRd = ixazomib+lenalidomide+dexamethasone; Rd = placebo+lenalidomide+dexamethasone

AEs were graded per National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. Two of the 360 patients randomised to the ixazomib group did not receive any study treatment, and 2 of the 362 patients randomised to the placebo group accidentally received limited dosing of ixazomib and were therefore conservatively included in the ixazomib group for analyses of exposure and safety.

[a] Reported in ≥20% of patients in either group.

[b] Data based upon standardised MedDRA query, incorporating pooled preferred terms, or multiple preferred terms. Thrombocytopenia incorporates preferred terms of thrombocytopenia and platelet count decreased. Neutropenia incorporates preferred terms of neutropenia and neutrophil count decreased. Peripheral neuropathy represents the high-level term peripheral neuropathies NEC, excluding neuritis

[c] Data for 'Rash SMQ' based on a standardised MedDRA query (SMQ) pooling 27 preferred terms; data for 'Rash HLT' taken from the high-level term (HLT) of Rashes, eruptions and exanthems NEC, per the data on rash reported in the United States prescribing information.

[d] Data based on the higher-level term, preferred terms included peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy.

[e] Additionally, 2 grade 5 arrhythmias reported in the ixazomib group and 3 grade 5 arrhythmias in the placebo group; 1 grade 5 thromboembolism reported in each group; 1 grade 5 hypotension reported in the ixazomib group; 1 grade 5 heart failure reported in the ixazomib group and 3 grade 5 heart failure in the placebo group; 1 grade 5 myocardial infarction reported in the ixazomib group and 2 grade 5 myocardial infarction in the placebo group

[f] Includes AE data and data from study follow-up period.

Source: Moreau, 2016 [1] (ref)

4.12.1.3 Adverse events: subgroups by prior line of therapy

The safety data in the subgroups of patients who received 1 prior therapy and 2 or 3 prior therapies are consistent with the safety data from the overall Safety population (Table 56). Despite having received more prior therapy, patients in the subgroup who received 2 or 3 prior therapies did not experience more AEs than patients with 1 prior therapy (Table 56).

Table 56: Safety profile at the 23-month analysis in the subgroups by prior line of therapy

	1 prior therapy†		2-3 prior lines†		Safety population	
AEs, n (%)	**IRd N=149**	**Rd**	**IRd**	**Rd**	**IRd**	**Rd**
Any AE	208 (98)	209 (99)	147 (99)	148 (100)	355 (98)	357 (99)
Any grade ≥3 AE	153 (72)	134 (64)	114 (77)	113 (76)	267 (74)	247 (69)
Any serious AE	99 (47)	94 (45)	69 (46)	83 (56)	168 (47)	177 (49)
AE resulting in dose reduction of any drug	158 (75)	149 (71)	113 (76)	101 (68)	203 (56)	181 (50)
AE resulting in discontinuation of any drug[a]	53 (25)	35 (17)	38 (26)	38 (26)	91 (25)	73 (20)
AE resulting in discontinuation of regimen[b]	36 (17)	20 (9)	24 (16)	30 (20)	60 (17)	50 (14)
On-study death	10 (5)	10 (5)	5 (3)	13 (9)	15 (4)	23 (6)

Abbreviations: AE = adverse event; IRd = ixazomib+lenalidomide+dexamethasone; Rd = placebo+lenalidomide+dexamethasone
Adverse events were graded per National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.
[a] Discontinuation of 1 or more of the 3 agents in the study drug regimen.
[b] Discontinuation of the full study drug regimen including discontinuation for disease progression.
Source: Moreau, 2016[1] (ref); † Takeda data on file UK/IXA/1612/0103 [131]

4.12.1.4 Discussion and conclusion

Overall, the addition of IXA to LEN+DEX was associated with limited additional toxicity. [1] Rates of serious AEs, discontinuations due to AEs, and on-study deaths were similar, and the only grade ≥3 AE for which there was a ≥5% difference between the IXA+LEN+DEX and LEN+DEX groups was thrombocytopenia, a known side effect of bortezomib and carfilzomib [43,44] and for which there were no apparent clinical sequelae. There was no cardiac, renal, or respiratory safety signals associated with ixazomib. Addition of IXA to LEN+DEX resulted in an increased rate of PN (27% vs. 22%), with 2% grade 3 events (compared with 6% with subcutaneous bortezomib [1] and 3% with carfilzomib [18] in other clinical trials).

Duration of therapy with IXA+LEN+DEX was notable, with almost half of patients having received at least 18 cycles at the 23-month analysis. Treatment compliance appeared high and similar between groups, consistent with the observed tolerability, suggesting that the all-oral IXA+LEN+DEX regimen was as simple and convenient for patients to take as the LEN+DEX regimen.

The safety data was consistent across the subgroups by prior line of therapy and the overall safety population; despite having received more prior therapy, patients in the subgroup who received 2 or 3 prior therapies did not experience more AEs than patients with 1 prior therapy.

Overall, the favourable tolerability profile of IXA+LEN+DEX is important in RRMM patients who are typically older and less fit, and has implications for reducing patient burden and NHS resource use. Taken together with its efficacy and convenient oral dosing schedule, the favourable tolerability profile of ixazomib represents a therapeutic innovation and offers a significant benefit for patients with RRMM.

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 Principal findings

IXA+LEN+DEX vs LEN-DEX

- **The TOURMALINE-MM1 Phase III RCT has shown that the addition of IXA to LEN+DEX significantly improves outcomes including progression-free survival (PFS) and response rates, with limited additional toxicity with this all-oral regimen** [1]

Efficacy of IXA+LEN+DEX vs LEN+DEX in the ITT population and the subgroup of patients who received 2 or 3 prior lines of therapy [1]

- A statistically significant PFS improvement was demonstrated with oral IXA+LEN+DEX versus LEN+DEX in patients with RRMM, showing a clinically meaningful ~6 month improvement in median PFS: ITT population: median, 20.6 vs. 14.7 months, hazard ratio (HR) 0.74, p=0.012; median follow-up 14.7 months
- The treatment effect with IXA+LEN+DEX on PFS was beneficial across key subgroups:
    - In the stratified subgroup of patients who had received 2 or 3 prior therapies, median PFS was not estimable (NE) vs 12.9 months (HR 0.58), and 22.0 vs 13.0 months (HR 0.62), respectively, at the first and second interim analyses. This represents an approximate 9-month improvement in median PFS for the IXA+LEN+DEX group.
    - PFS benefit was also observed consistently across other key pre-specified subgroups, including in poor-prognosis subgroups such as elderly patients, patients with advanced disease stage, and patients with high-risk cytogenetic abnormalities (for whom LEN+DEX is emerging as suboptimal treatment ([41]).
- With median follow-up of 23 months, overall survival (OS) was not yet mature; follow-up is ongoing. The third and final OS analyses are due in Q2 2017 and Q3 2019, respectively:
    - Although immature, a trend for an OS benefit is apparent in the ITT population in favour of IXA+LEN+DEX at the 2nd IA (HR 0.87, 95% CI 0.64, 1.18)
    - In the subgroup treated with 2 or 3 prior therapies, the median OS was NE after either 15 or 23 months of follow-up in both arms, but a consistent trend toward an OS benefit can be seen with IXA+LEN+DEX, with HRs of 0.618 (95% CI 0.350-1.090) and 0.645 (95% CI 0.409-1.017), respectively
- Overall response rates (ORRs) in the ITT population were 78.3% in the IXA+LEN+DEX group and 71.5% in the LEN+DEX group (p=0.04). Responses were rapid and durable and deepening responses were noted with increasing treatment duration; median time to response was 1.1 vs. 1.9 months, and median duration of response was 20.5 vs. 15.0 months for the IXA+LEN+DEX regimen vs the LEN+DEX regimen, respectively.
    - ORRs were 80.4% vs 67.1% in patients who had received 2 or 3 prior lines of therapy.
- Median time to response in the ITT population was 1.1 vs. 1.9 months, and median duration of response was 20.5 vs. 15.0 months, respectively.

- Reflecting the findings for the primary endpoint of PFS, time to progression (TTP) was also significantly longer for IXA+LEN+DEX vs. LEN+DEX: ITT population: median 21.4 vs 15.7 months, HR 0.71, p=0.007.
    - In patients who had received 2 or 3 prior lines of therapy, the median TTP was NE vs 12.9 months at the first interim analysis and was 28.8 vs 14.1 months at the second interim analysis
- There was no adverse impact on patient-reported quality of life (EORTC-QLQ-C30 and MY-20 questionnaires) with the addition of IXA to LEN+DEX in this double-blind study.

Safety of IXA+LEN+DEX vs LEN+DEX (TOURMALINE-MM1 study) [1]

- IXA+LEN+DEX had a manageable tolerability profile, and the frequencies of serious adverse events (47% vs. 49%), discontinuations due to adverse events (17% vs 14%) and on-study deaths (4% vs. 6%) were similar in both the IXA+LEN+DEX and LEN+DEX groups.
    - 74% and 69% of patients experienced grade ≥3 adverse events. The only grade ≥3 adverse event for which there was a ≥5% difference between the IXA+LEN+DEX and LEN+DEX groups was thrombocytopenia, a known side effect proteasome inhibitors [43,44] for which there were no apparent clinical sequelae. Addition of IXA to LEN+DEX resulted in a slightly increased rate of peripheral neuropathy (27% vs. 22%), with 2% grade 3 events (compared with 6% with subcutaneous bortezomib [45] and 3% with carfilzomib. [18]
- Duration of therapy with the IXA+LEN+DEX regimen was notable, with almost half of patients having received at least 18 cycles at the 23-month analysis.
- The addition of Ixazomib to LEN+DEX had no impact on the median relative dose intensity of lenalidomide or dexamethasone.
- Treatment compliance appeared high and similar between groups, consistent with the observed tolerability, suggesting that the all-oral IXA+LEN+DEX triplet regimen was as simple and convenient for patients to take as the LEN+DEX doublet regimen.
- The safety data was consistent across the subgroups by prior line of therapy and the overall safety population; despite having received more prior therapy, patients in the subgroup who received 2 or 3 prior therapies did not experience more AEs
- Overall, the favourable tolerability profile of IXA+LEN+DEX is important in RRMM patients who are typically older and less fit, and has implications for reducing patient burden and NHS resource use.

Network meta-analysis (for a comparison with BORT+DEX in the absence of comparative evidence)

The results from the NMA show the relatve efficacy benefits of IXA+LEN+DEX vs BORT+DEX, the main comparator for a positioning of one prior line of therapy:

- For PFS, a hazard ratio of 0.72 (95%CrI: 0.41, 1.19) was estimated, showing a numerical benefit for IXA+LEN+DEX
- For OS, there was a significant benefit estimated for IXA+LEN+DEX with a HR of 0.31 (95%CrI:0.13, 0.65)
- For ORR and odds ratio of 0.88 (95%CrI: 0.35, 1.88) was estimated, showing a numerical benefit for LEN+DEX , although not significant and in a scenario analysis was favourable for IXA+LEN+DEX.
- For BoR there was a significant benefit for IXA+LEN+DEX vswith an OR of 3.82 (95%CrI: 1.32, 8.93)
- Treatment discontinuations due to AEs (safety measure) showed a difference vs BORT+DEX, which was numerically worse for for IXA+LEN+DEX but which was not statistically significant (OR= 2.58, 95%CrI: 0.81, 6.32).

There are some limitations to the NMA to support the relative clinical effectiveness of IXA+LEN+DEX vs BORT+DEX in RRMM patients who have received one prior therapy, in particular there is not specific comparator data published or available with which to form a network for this comparison, hence 1+ prior therapy evidence had to be used as a proxy. However, the advantage of this data is that is relatively robust as is based on a larger dataset and can be considered generalisable for a specific 1 prior treatment RRMM patient population.

Other limits of NMA was that only fixed effects modelling was possible for each of the networks, and there were limited studies with the approved doses for the comparator so for some outcomes (such as PFS) dose specific studies had to be combined with studies with other doses or where not specified. In general there were no heterogeneity issues in the networks, with the exception of the ORR network. In the base case evidence networks were based on all evidence, both RCT and observational, and used specific approved doses and evidence from study primary publications, but in general scenario analysis demonstrated low sensitivity in the HRs and ORs to using only RCT evidence, combining all dose studies, or using later datacuts/evidence (with the exception of the ORR analysis).

Although there is head to head data for IXA+LEN+DEX vs. LEN+DEX, this comparison is included in the NMA but for each patient population and outcome is only really informed by TOURMALINE MM-1 study so results not differ from NMA vs, evidence from trial reported in section 4.

Conclusions

- IXA is the first and only oral proteasome inhibitor; it is indicated in combination with LEN+DEX for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
- The all-oral combination of IXA+LEN+DEX provides a much needed treatment option that is effective in RRMM patients, with the added advantage of having a convenient administration schedule and good tolerability that should enable patients to stay on therapy.
- Relative PFS, OS and other efficacy outcomes were favourable for IXA+LEN+DEX from direct trial evidence, and also favourable vs. BORT +DEX from a NMA
- The NMA showed no significant difference in discontinuations due to AEs vs BORT+DEX in RRMM patients supporting the favourable tolerability profile of IXA

4.13.2 Applicability, strengths and limitations of the clinical evidence base for IXA+LEN+DEX

4.13.2.1 Applicability of the TOURMALINE-MM1 study to UK clinical practice

The demographics in the TOURMALINE-MM1 study are similar to the demographics of patients with MM in England. As reported by Cancer Research UK (CRUK), 57% of those diagnosed with MM in 2013 were male [169] which is the same percentage (57%) of males in the MM1 study [1] . In the MM1 study 85% of patients were of White Caucasian [1] which should reflect the demographics in England. The study was conducted in 147 centres in 26 countries across different continents. [1] The majority of patients (483 patients [67%]) were enrolled from the 91 sites in Europe, including 21 patients from nine centres in the UK. [42]

Although the average age in the study (median 66 years) may be slightly younger than that in the UK, this is common in cancer clinical trials as younger patients are more willing and able to travel to the treatment centre; in addition, MM patients are being diagnosed at an earlier age. [3] At a recent (October 2016) NICE Appraisal Committee meeting for the carfilzomib appraisal, the committee concluded that the patient characteristics in the

carfilzomib trials (median age 64 and 65) could be generalised to UK clinical practice. We would expect a similar conclusion to be reached by NICE in respect of ixazomib.

The study population included patients with poor prognostic features (who are not usually included in Phase III trials) such as primary refractory disease, free light chain (FLC)-only disease, and severe renal impairment as well as a robust representation of patients with high-risk cytogenetics, given the high rate of available cytogenetic data. Therefore, the patient population in the MM1 study consisted of a diverse and difficult to treat population, as would be expected in clinical practice.

4.13.2.2 Strengths of the TOURMALINE-MM1 study

The MM1 study is a robustly designed large, multi-centre, double-blind, RCT evaluating a comprehensive range of outcomes to assess the efficacy and safety of IXA+LEN+DEX compared to LEN+DEX. [1] The MM1 study has the benefit of being a double-blind RCT, in contrast to the majority of other trials in MM which are open label.

The MM1 study also analysed outcomes in pre-specified subgroups according to baseline demographics and disease characteristics, including by prior line of therapy. Therefore, in addition to the ITT population, clinical and economic evidence is presented based on these subgroups, in accordance with the NICE scope.

Response and disease progression assessments were based on central laboratory results and International Myeloma Working Group 2011 criteria, [67] as evaluated by the independent review committee blinded to both patient assignment and investigator assessment [1] Cytogenetic abnormalities were assessed by a central laboratory, therefore using high-quality and consistent methods.

Health-related quality of life was assessed using validated cancer-specific instruments (i.e the EORTC-QLQ-C30 with its multiple myeloma-specific module EORTC QLQ-MY20), which were obtained every 2 cycles until disease progression. [1] Patients were blinded to treatment assignment, which is particularly noteworthy given the tendency to overestimate quality of life benefits in open-label studies.[130] This is a particular strength of the MM1 trial and one that differentiates it from other trials of new agents for RRMM, most of which have an open label design.

4.13.2.3 Limitations of the TOURMALINE-MM1 study

Data on overall survival are not yet mature for statistical analysis, and follow-up is on-going. More mature OS data will be provided by the third interim analysis expected in Q2 2017, and later in the final analysis in Q3 2019. However, this is a common limitation which applies to most trials of new MM drugs, and indeed oncology drugs in general.

In addition, data from the second interim analysis (data cut off July 2015) showed a reduced difference in effect between arms in the overall ITT population for PFS compared to the primary analysis, with a HR for PFS of 0.82 (0.67, 1.00), p=0.054. [42] During the European regulatory submission, the significance of this second, non-inferential PFS analysis was discussed by the CHMP with an independent scientific advisory group (SAG), which included independent multiple myeloma experts. The SAG unanimously agreed that the data submitted on the basis of the primary ITT analysis of PFS in TOURMALINE MM-1 (HR 0.72, p=0.012) and its favourable toxicity profile, clearly established a positive benefit-risk balance for the ITT population. The SAG concluded that the fact that a subsequent, exploratory interim analysis showed some uncertainty about the level of statistical significance was not enough to change the conclusion on the clear benefit in PFS at the pre-planned and final PFS analysis (for full details, refer to section 2.2.4).

4.13.3 End-of-life criteria

At the time of this NICE submission, there is a trend for overall survival (OS) benefit for IXA+LEN+DEX versus LEN+DEX, however an insufficient number of events have taken place in the TOURMALINE MM-1 trial for the benefit to be statistically significant. The TOURMALINE MM-1 study remains double-blind with additional OS analyses due during summer 2017 and Q3 2019. Therefore, the currently available data for the ixazomib regimen does not meet all of the NICE end-of-life criteria as further follow up is warranted to determine the final benefit

Table 59 below presents the data available relating to the end of life criteria.

4.14 Ongoing studies

Ixazomib is being investigated in five Phase III clinical trials in MM and primary systemic AL amyloidosis (Table 57). These clinical trials are all referred to by the programme name of TOURMALINE. TOURMALINE-MM1 is the only clinical trial in the population of interest for this submission i.e in patients with RRMM. The third interim analysis and final OS analyses are due in Q2 2017 and Q3 2019, respectively, and estimated study completion date is December 2020.

Table 57: TOURMALINE Phase III trials of ixazomib in MM and primary systemic AL amyloidosis

Study name	Study number	NCT number	Design	Intervention and comparator	Population and size	Status
TOURMALINE-MM1	C16010	NCT01564537	Randomised, multicentre, double-blind, placebo-controlled	Ixazomib + Rd versus placebo + Rd until progression	722 RRMM patients randomised	Active, not recruiting Data from 1st and 2nd IA available
TOURMALINE-MM2	C16014	NCT01850524	Randomised, multicentre, double-blind, placebo-controlled	Ixazomib + Rd versus placebo + Rd until progression	701 (est.) transplant-ineligible NDMM patients	Ongoing, but not recruiting participants Est. primary completion date: June 2018
TOURMALINE-MM3	C16019	NCT02181413	Randomised, multicentre, double-blind, placebo-controlled	Ixazomib versus placebo as maintenance post-ASCT	652 (est.) NDMM patients post-ASCT	Ongoing, but not recruiting participants Est. primary completion date: Feb 2018

Study name	Study number	NCT number	Design	Intervention and comparator	Population and size	Status
TOURMALINE-MM4	C16021	NCT02312258	Randomised, multicentre, double-blind, placebo-controlled	Ixazomib versus placebo as maintenance post-initial therapy	761 (est.) transplant-ineligible NDMM patients	Recruiting Est. primary completion date: Dec 2018
TOURMALINE-AL1	C16011	NCT01659658	Randomised, multicentre, open-label, controlled	Ixazomib + dex versus physicians' choice of dex ± melphalan or cyclophosphamide or thalidomide or lenalidomide	248 (est.) patients with relapsed or refractory AL	Recruiting Est. primary completion date: Mar 2017

Abbreviations: AL = primary systemic amyloidosis; ASCT = autologous stem cell transplantation; dex, = dexamethasone; est = estimated; IA = interim analysis; NDMM = newly diagnosed multiple myeloma; Rd = lenalidomide + dexamethasone; RRMM = relapsed and/or refractory multiple myeloma.
Source: ClinicalTrials.gov

5. Cost effectiveness

5.1 Published cost-effectiveness studies

5.1.1 Identification of studies

An extensive systematic literature review (SLR) of cost-effectiveness and cost and resource use studies was conducted between August and December 2015. This has been updated using the same search terms and strategy to provide the evidence base for this submission. Updated searches were carried out from March 2016 through April 2016 and again from September 2016 to October 2016 to ensure that the latest available evidence is presented in this submission. The details of the search strategy are provided in Appendix 10.

The SLR was performed to identify and summarise the relevant economic and cost and resource use evidence for adult patients with RRMM receiving medical therapy. Studies considering a newly diagnosed MM population or treatment of RRMM using bisphosphonates, non-medical therapies, stem cell or bone marrow transplantation, surgery for bone metastasis were excluded. Studies reporting cost effectiveness or cost analysis were not filtered by study design. Reviews (including SLRs) were excluded at the screening stage, the reference lists associated with SLRs were screened to ensure all available evidence is included. Only conference proceedings or abstracts presented within the last year were included, as any high-quality studies should have been reported as journal articles within this time. Any abstracts older that this were excluded at the screening stage. Only conferences with freely available abstracts were included.

Primary screening of abstracts and secondary screening of full-texts were conducted by two independent reviewers. Data extraction from the included full-text of articles was also performed independently by two reviewers to ensure that everything was captured.

5.1.2 Description of identified studies

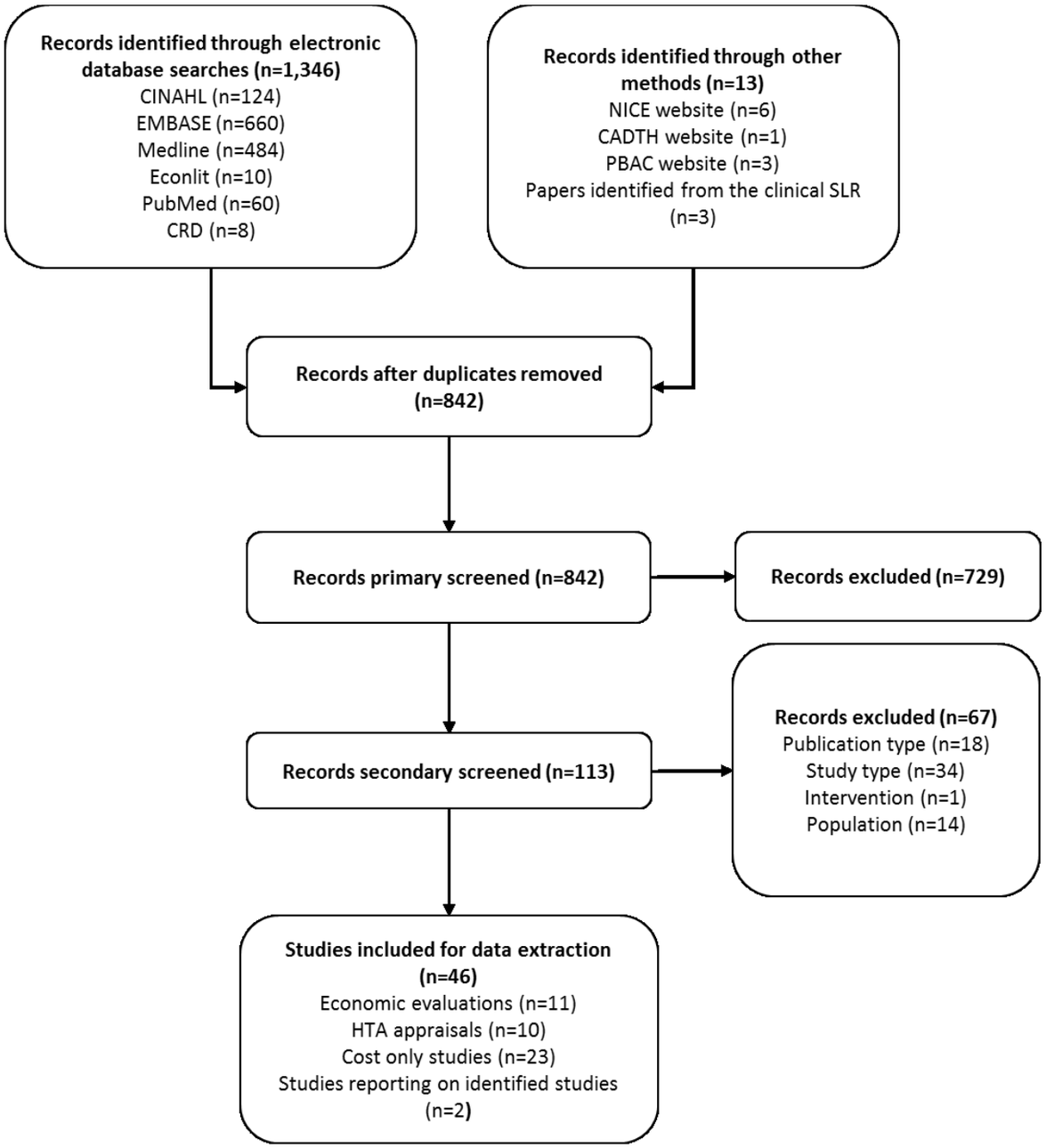
For the purpose of reporting the results of the SLRs, the results of the original SLR and the following two updates have been pooled. In total, 1,356 studies were identified; systematic database searched identified 1,346 records and 10 HTAs. Three additional abstracts were identified for data extraction from the clinical SLR conducted alongside the economic SLR (see Section 4.1). Primary screening of titles and abstracts against the pre-specified inclusion and exclusion criteria (as presented in Appendix 10) was performed for 842 records after removing 517 duplicates. Of these, 113 were included for full text screening. 67 papers were excluded following secondary screening, the most common reasons for exclusion at this stage were study type (n=34), publication type (n=18) and population (n=14).

After screening, only 46 papers were included for data extraction:

- Ten HTA documents including two NICE single technology appraisals (STAs) in development, four completed NICE STAs, one CADTH Economic Guidance Report and three PBAC public summary documents.
- Nine economic evaluations reported in 11 publications
- 20 budget impact or cost studies reported in 23 publications
- Two publications identified in updated SLRs reporting on identified studies (these studies were excluded at this stage as no additional information was provided)

The flow diagram of the economic and cost and resource use SLR is presented in Figure 31.

Figure 31: PRISMA diagram for economic and cost SLR [170]



Key: CADTH, Canadian Agency for Drugs and Technologies in Health; CINAHL, Cumulative Index to Nursing and Allied Health Literature; CRD, Centre for Reviews and Dissemination; HTA, health technology assessment; n, number; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; PRISMA, preferred reporting items for systematic reviews and meta-analyses

This section discusses the studies identified as HTA appraisals and economic evaluations (n=21), section discusses the studies identified as cost only studies (n=29).

Table 58 provides a summary of each HTA submission identified and

Table 59 details the response from evidence review groups (ERGs) or evidence guidance panels (EGPs) along with suggestions as to how this submission addresses previous critiques.

Two HTA appraisals in development were identified with expected publication in January 2017 and April 2017, for LEN post BORT and CARF for the treatment of RRMM, respectively. Of the remaining HTA submissions, four considered a Markov structure, three did not report on the model structure and one considered a DES constructed in Microsoft Excel. Considering the feedback from the ERGs and EGPs, it was interpreted that a Markov model structure was the most appropriate in this disease area – the DES structure was heavily criticised as lacing transparency.

The time horizons considered varied between 10- and 30-years; feedback from the identified submissions suggested that HTAs for RRMM were most commonly critiqued about unnecessarily long time horizons. For example, the CADTH submission requested the analysis at a 5-year time horizon.

Other comments identified across the submissions were the lack of transparency associated with extrapolation of clinical data, the heterogeneity of clinical datasets and methods used to adjust the clinical data and the source of utility estimates.

Table 58: Summary of HTA appraisals identified in the economic SLR

	Summary	Interventions	Time horizon	Efficacy source	Utility source	Model structure	Primary results
NICE submission in development (ID934) MM (treated) – CARF	Originally considered as two separate appraisals, now combined	CARF+DEX BORT+DEX CARF+LEN+DEX LEN+DEX (2L and 3L)	In development				
Partial update to TA171 (ID667) MM – LEN (post BORT)	Cost-utility analysis comparing the cost per QALY in patients for whom THAL is contraindicated and whose disease has progressed after at least one prior treatment with BORT.	LEN	In development				
NICE submission TA380, PANO for treating MM after at least 2 previous treatments (2016)	Cost-utility analysis comparing the cost per QALY in patients with MM who have received at least 1 prior therapy with: - BORT+DEX (in RRMM patients after 1 prior therapy) - LEN+DEX (in RRMM patients after 2 or more prior therapies including an immunomodulatory drug and BORT)	PANO+BORT+DEX LEN+DEX	25 years	PANORAMA-1, MM-009 and MM-010. Conducted a naïve comparison, an unadjusted Cox regression and an MAIC. Used the unadjusted Cox regression.	Patients in the PANORAMA-1 trial completed an EORTC QLQ-C30 questionnaire, which was mapped to obtain the corresponding EQ-5D utility value. No utility data were available for LEN+DEX so 2 scenarios were explored. In the first, the utility value for LEN+DEX was assumed to be the same as that for BORT+DEX. In the second scenario, it was assumed to be the same as the utility value associated with the progression-free no treatment health state. The first scenario was considered for the base-case analysis.	Area under the curve approach with three primary outcomes: pre-progression, post-progression and death	ICER £11,527 LYG: 2.40 vs. 2.19

	Summary	Interventions	Time horizon	Efficacy source	Utility source	Model structure	Primary results
NICE submission TA338, POM for RRMM previously treated with LEN and BORT (2015)	Cost-utility analysis comparing the cost per QALY in patients with RRMM previously treated with both LEN and BORT.	POM+LD-DEX BORT+DEX BEN+THAL+DEX CYC+THAL+DEX	25 years	MM-003 and Gooding et al.	The EQ-5D UK tariff was applied to the data obtained from the EQ-5D in the MM-003 trial. Multivariate analysis was then conducted in order to determine the most significant predictors of HRQL over all time points. Explanatory variables included in the analysis were determined to be potential influencers of HRQL in consultation with UK clinicians. All variables identified by stepwise selection method were included in the utility calculation	Area under the curve approach with four primary outcomes: pre-progression on treatment, pre-progression off-treatment, post-progression and death	POM+LD-DEX vs. BORT+DEX: £50,366 POM+LD-DEX vs. CYC+THAL+DEX: £77,915 POM+LD-DEX vs. BEN+THAL+DEX: £72,250
PBAC public summary document (40), POM (2014)	Cost-utility analysis comparing the cost per QALY over a 10-year time horizon for POM+LD-DEX vs. HD-DEX using a Markov structure.	POM+LD-DEX HD-DEX	10 years	MM-003	Utilities obtained from the MM-003 trial	Area under the curve approach	NR
CADTH final economic guidance report, POM for RRMM	Cost-utility analysis comparing the cost per QALY over a 10-year time horizon for POM+LD-DEX vs. HD-DEX using a Markov model	POM+LD-DEX HD-DEX	10 years	NR	NR	NR	The Submitter estimated that the ICER was $58,008/LYG or $84,476/QALY gained The EGP's best estimate for the ICER: POM+LD-DEX vs. HD-DEX: between

	Summary	Interventions	Time horizon	Efficacy source	Utility source	Model structure	Primary results
							$132,217/QALY and $173,430/QALY
NICE submission TA171, LEN for the treatment of MM in people who have received at least one prior therapy (2009)	Cost-utility analysis comparing the cost per QALY for the following subgroups: - One prior therapy only LEN+DEX vs. BORT - One prior therapy only and have pre-existing peripheral neuropathy LEN+DEX vs. DEX - At least two prior therapies LEN+DEX vs. DEX - Prior treatment with THAL (1 prior therapy only) LEN+DEX vs. DEX - Prior treatment with THAL (2 or more therapies) LEN+DEX vs. DEX	LEN+DEX BORT DEX	30 years	MM-009, MM-010 and APEX trials. Treatment crossover in MM-009 and MM-010 is adjusted for using data from the UK Medical Research Council trials. The model did not explicitly model the effectiveness of LEN (e.g. using a hazard ratio). The effectiveness of LEN was instead captured using the proportion of patients achieving a response to therapy and a treatment term included in the regression equation used to calculate time to progression.	Van Agthoven et al. (2004)	DES in Microsoft Excel	One prior therapy only and have pre-existing peripheral neuropathy LEN+DEX vs. DEX: £46,856 - At least two prior therapies LEN+DEX vs. DEX: £24,584 - Prior treatment with THAL (1 prior therapy only) LEN+DEX vs. DEX: £38,861 - Prior treatment with THAL (2 or more therapies) LEN+DEX vs. DEX: £22,589
PBAC public summary	Cost-utility of LEN in patients with RRMM for whom THAL	LEN	NR	NR	NR	NR	NR

	Summary	Interventions	Time horizon	Efficacy source	Utility source	Model structure	Primary results
document (39), LEN (2008)	therapy has failed or in whom there is severe intolerance/ toxicity to THAL.						
PBAC public summary document (38), BORT (2007)	NR	BORT	NR	NR	NR	NR	NR
NICE submission TA129, BORT monotherapy for RRMM (2007)	Cost-effectiveness analysis comparing the cost per life year saved in a cohort of patients with RRMM at first relapse	BORT HD-DEX	15 years	APEX and data from the Mayo observational study to predict OS for patients treated with HD-DEX (the APEX trial was terminated prematurely and so many patients in the HD-DEX arm crossed over to BORT and so long term trial outcomes for OS from APEX would have been biased).	The model did not capture HRQL	Markov model	ICER: £30,750 per life year gained

Key: BEN, bendamustine; BORT, bortezomib; CARF, carfilzomib; CYC, cyclophosphamide; DES, discrete event simulation; DEX, dexamethasone; HD-DEX, high-dose dexamethasone; HRQL, health related quality of life; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; ID, in development; LD-DEX, low-dose dexamethasone; LEN, lenalidomide; LYG, life year gained; NICE, National Institute for Health and Care Excellence; NR, not reported; OS, overall survival; POM, pomalidomide; QALY, quality adjusted life year; RRMM, relapsed and/or refractory multiple myeloma; TA, technology appraisal; THAL, thalidomide

Table 59: Response to HTA appraisals identified in the economic SLR

	Feedback from the ERG	How this submission addresses issues raised
NICE submission in development (ID934), CARF+LEN+DEX and CARF+DEX for RRMM	Ongoing	
Partial update to TA171 (ID667), LEN for treatment MM after 1 prior treatment with BORT (expected publication date: January 2017)	The ERG initially commented that: - The methods for modelling subsequent lines of therapy did not accurately reflect clinical practice due to lack of clinical data. - The data extrapolation process led to underestimation of PFS for LEN+DEX and overestimation of LEN+DEX OS. Using mean of covariates to adjust OS and PFS estimates may have skewed this further. Following a revised analysis, the ERG commented that: - The estimated clinical effectiveness of LEN compared with BORT is still a main source of concern. The process to estimate the HRs is methodologically weak and is potentially biased. Issues are still present with data extrapolation process – highlighted by the fact the OS curves cross the PFS and TTF curves after 10 years. - There are still issues with modelling subsequent lines of therapy. Further, the utility associated with post-progression is used for patients on 3L and 4L treatments.	In this submission, subsequent lines of therapy are modelled assuming a “basket” of subsequent therapies, where the proportion of patients receiving each subsequent therapy is multiplied by the average cost of therapy. The distribution of patients across subsequent therapies was obtained from the TOURMALINE-MM1 trial data, where IXA+LEN+DEX and LEN+DEX data were pooled as no significant differences were found between the trial arms. OS and PFS data have been covariate adjusted and parametric curves fit to the data following the guidance in the NICE DSU guidelines. Extensive scenario analysis considers the impact of different parametric curve fits and the impact of uncertainty on model results. The model ensures that PFS and TOT are always less that the OS estimates. In the base case, TOT is allowed to exceed PFS.
NICE submission TA380, PANO for treating MM after at least 2 previous treatments (2016)	The ERG commented that: - HRs had been obtained for PFS and OS using unadjusted Cox regression and matching adjusted indirect comparison (MAIC) NMA methods. The ERG comments that due to non-proportional hazards the MAIC was thought to provide more valid results - Clinical experts had advised the ERG that the cost of lymphopenia should be 0	This submission uses results from an NMA conducted using unadjusted Cox regression methods. As the proportional hazards assumption is demonstrated to be invalidated for IXA+LEN+DEX vs. LEN+DEX – trial data informs this comparison directly. It is assumed that proportional hazards hold for all other comparators compared with LEN+DEX.

	Feedback from the ERG	How this submission addresses issues raised
	Following a revised analysis, the ERG commented that: - The company only matched two baseline characteristics in the MAIC - Subsequent therapy was assumed to be equivalent across comparators. When the subsequent therapy was removed, the costs were removed but not the clinical effectiveness – the ERG was concerned that OS gain was likely to be driven by differences in the subsequent treatments given after disease progression - The company did not include a scenario where no survival difference was incorporated from cycle 55 onwards, which was shown by the data	
NICE submission TA338, POM for RRMM previously treated with LEN and BORT (2015)	The ERG commented that: - Clinical data came from heterogeneous populations and therefore resulted in questionable comparability - Cost savings associated with dose interruptions were only modelled for POM+LD-DEX - There was an error in the model that resulted in the under estimation of the impact of adverse events on HRQL	Clinical data have been adjusted for covariates to try and account for bias arising between heterogenous populations. However, the comparison of IXA+LEN+DEX with LEN+DEX uses data directly from an RCT and so in theory selection bias is reduced increasing the certainty of this comparison. Dose intensity is considered for IXA+LEN+DEX and LEN+DEX. No data were available for BORT+DEX and so in the base case dose intensity is assumed to be 100%. A scenario analysis considers the impact of setting this equal to the lowest dose intensity shown across the IXA+LEN+DEX and LEN+DEX arms. The economic model submitted as part of this submission has undergone both external and internal quality checks.
PBAC public summary document (40), POM (2014)	The PBAC recommended the listing of POM for the treatment of MM under the Section 100 Highly Specialised Drugs Program (HSDP). The PBAC noted that the submission agreed to the PBAC's previous recommendations regarding the restriction. The PBAC noted that the resubmission had redefined the inputs to the economic model as specified by the Committee in July 2014. This included changing the	This submission considers a lifetime horizon, defined as the point where >99.99% of patients in both arms have died (18.7 years). This is considered sufficiently long enough to capture the outcomes associated with this patient population. In the base case, utilities are obtained directly from the TOURMALINE-MM1 trial data.

	Feedback from the ERG	How this submission addresses issues raised
	time horizon to 5 years, using weighted goodness of fit extrapolation method, using the trial based utilities (instead of utilities derived from Agthoven et al. (2004)) and including cost offsets for anti-thrombotic prophylaxis.	
CADTH final economic guidance report, POM for MM	The Economic Guidance Panel commented that: - There was limited information on the methods used to adjust for crossover on the estimates of OS. - The comparator was not considered the most relevant. - The submitter assumed a statistically and clinically significant reduction in utility after transitioning to the progressed state which was not shown by the MM-003 data - A 5-year time horizon was considered more appropriate	This submission uses data from IA1, as such the OS data are immature and so it was not seen as appropriate to attempt to adjust for treatment crossover. However, this would be considered in future analyses using more mature data sets. The comparators considered in this submission are BORT+DEX (1 prior therapy) and LEN+DEX (2+ prior therapies). These are considered the most relevant comparators in current UK practice, see Section 5.2.2. In the base case, utilities are obtained directly from the TOURMALINE-MM1 trial data. This includes the pre-progression and post-progression health state.
NICE submission TA171, LEN for the treatment of MM in people who have received at least one prior therapy (2009)	The ERG commented that: - The model structure was too complex - BORT+DEX should have been included in the model, as specified in the scope. It was recognised that relevant clinical evidence was not identifiable for other comparators excluded in the analysis but stated in the NICE scope - The model did not include the BORT response-rebate scheme - There were issues in crossover bias within trials and the methods used to correct for this - There was high uncertainty in the OS data reflected by high uncertainty in the ICER due to the large degree of extrapolation for OS - The methods used for the MTC were considered inappropriate	This submission considers an area under the curve approach which is common for modelling cancer therapies. Section 5.2.2 explains the choice of comparators in this submission. Both the LEN and BORT response-rebate schemes are included in the base case. This submission uses data from IA1, as such the OS data are immature and so it was not seen as appropriate to attempt to adjust for treatment crossover. However, this would be considered in future analyses using more mature data sets. Given the immaturity of the OS data from the TOURMALINE-MM1 trial, there is high uncertainty from the extrapolated OS which has a large impact on results. Later data cuts from the TOURMALINE-MM1 trial will address this issue and provide a more robust estimate of cost-effectiveness.

	Feedback from the ERG	How this submission addresses issues raised
	- the medical management costs were different to the BORT submission which resulted in a more favourable outcome for LEN+DEX - No utility decrements were included for adverse events	The NMA used unadjusted Cox regression methods to obtain hazard ratios relative to LEN+DEX. This was assumed appropriate for all comparators (where the proportional hazards assumption was assumed to hold), except for the comparison with IXA+LEN+DEX where data directly from the trial was used. Utility decrements are included for adverse events
PBAC public summary document (39), LEN (2008)	The PBAC recommended the listing of LEN for the treatment of patients with RRMM for whom THAL therapy has failed or in whom there is severe intolerance/ toxicity to THAL. Listing was recommended on a cost minimisation basis with BORT with the equi-effective doses to be based on 6 cycles of BORT, in line with the submission's approach.	
PBAC public summary document (38), BORT (2007)	The PBAC recommended the listing of BORT on the pharmaceutical benefits scheme for the treatment of MM for patients who meet certain criteria on the basis of acceptable cost-effectiveness when compared to a mixture of salvage treatments and where the extent of substitution from mini-allogeneic transplants is zero.	
NICE submission TA129, BORT monotherapy for RRMM (2007)	The ERG commented that: - HD-DEX was not an appropriate comparator in a UK setting - A fixed cycle length was more suitable than the variable cycle length used - The 15-year time horizon was considered too long given patient prognosis - The use of Mayo patient level data to capture long term OS was highlighted as a limitation due to differences in treatment regimens and patient characteristics with the APEX trial - Disease progression was not captured - HRQL was not captured	Section 5.2.2 explains the choice of comparators in this submission. This submission considers a lifetime horizon, defined as the point where >99.99% of patients in both arms have died (25 years and 18.7 years for the 1 prior line and 2+ prior lines subgroups). This is considered sufficiently long enough to capture the outcomes associated with this patient population. Clinical data from the TOURMALINE-MM1 RCT have been adjusted for covariates to try and account for bias arising from differences in individual characteristics between the IXA+LEN+DEX and LEN+DEX treatment arms.

	Feedback from the ERG	How this submission addresses issues raised
	- No half cycle correction was included	Progression is captured within the model and subsequent therapies applied based on the TOURMALINE-MM1 trial data. In the base case, utilities are obtained directly from the TOURMALINE-MM1 trial data. This includes the pre-progression and post-progression health state. A half-cycle correction is applied

Key: 2L, second line; 3L, third line; 4L, fourth line; BEN, bendamustine; BORT, bortezomib; CADTH, Canadian Agency for Drugs and Technologies in Health; CARF, carfilzomib; DEX, dexamethasone; ERG, evidence review group; HD-DEX, high-dose dexamethasone; HR, hazard ratio; HRQL, health related quality of life; ICER, incremental cost effectiveness ratio; ID, in development; LEN, lenalidomide; MAIC, matched adjusted indirect comparison; MM, multiple myeloma; MTC, mixed treatment comparison; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; PANO, panobinostat; PBAC, Pharmaceutical Benefits Advisory Committee; PFS, progression free survival; POM, pomalidomide; QALY, quality adjusted life year; RRMM, relapsed and/or refractory multiple myeloma; TA, technology appraisal; THAL, thalidomide; ToT, time on treatment; TTF, time to treatment failure; UK, United Kingdom

Nine economic evaluations were identified in the SLR, reported in 11 publications (Table 60). Seven studies conducted a cost-utility analysis, reported in eight publications, with the cost per QALY as the primary outcome measure.[171] Two studies, reported in three publications, considered a cost-effectiveness analysis with the cost per life year gained as the primary outcome measure.[172]

Four of the cost-utility analyses appeared to use the DES model submitted as part of the LEN appraisal to NICE (TA171), one publishing the original model from a UK perspective and the other three studies adapting the model from a Greek, Swedish and Norwegian perspective.[173-176] Two Markov models were identified, discussed in three publications, considering a US and Swedish perspective.[177-179] Four papers (discussing three models) did not report the model structure and all reported results from a US perspective. [171,172,180,181]

All studies reporting the source of utility values used in the economic analysis used the data presented in van Agthoven et al. (2004).[182] This study obtained MM utility values through the Dutch-Belgian Haematology Oncology Cooperative Study Group; the paper found that the utility for progressive disease (0.64) was the same as for patients not responding to treatment and that the utility for responding patients (0.81) was the same independent of level of response. Jakubowiak et al. (2016) adjusted these baseline utility values using the relative difference in mapped utilities between difference cycles, using mapped utilities from the ASPIRE trial.

Of the five studies reporting on HRQL, only Brown et al. (2013) discussed utility decrements associated with adverse events.

Table 60: Economic evaluations identified in the economic SLR

Author, year	Title	Perspective	Population	Intervention and comparators	Time horizon	Utility source	Model structure and primary outcome	Primary results
Maiese et al. (2016)[172]	Cost per median overall month of survival in multiple myeloma patients with ≥3 lines of therapy or were double refractory	US	Patients with multiple myeloma (MM) with ≥ 3 prior lines of therapy (LOTs) including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), or who are double refractory (DR) to a PI and an IMiD	DARA CARF POM+DEX	NR	NR	Cost-effectiveness analysis The primary outcome was the cost per median overall month of survival. This was broken down for drug, pre- and post-medication, administration, monitoring and auxiliary and adverse events.	Total average cost per median overall month of survival: DARA, CARF, CARF in double refractory population and POM+DEX: $4,261, $4,883, $4,213 and $5,160, respectively.
Borg et al. (2016)[175]	Cost effectiveness of POM in patients with RRMM in Sweden	Swedish societal perspective	Patients refractory to both BORT and LEN, alone or in combination, and refractory to the last treatment.	POM+LD-DEX HD-DEX	Lifetime		DES model The primary outcome was the incremental cost per QALY	The incremental cost-effectiveness ratio (ICER) is SEK 798 613 (E84 869) per QALY gained (including societal costs)

Author, year	Title	Perspective	Population	Intervention and comparators	Time horizon	Utility source	Model structure and primary outcome	Primary results
Jakubowiak et al. (2016)[177]	Cost-effectiveness of adding CARF to LEN+DEX in RMM from a US perspective	US	RRMM who have received 1-3 prior therapies	CARF+LEN+DEX LEN+DEX	30 years	Van Agthoven et al. (2004) and adjusted using the relative difference in mapped utilities between difference cycles, using mapped utilities from the ASPIRE trial.	Cost utility analysis. Partitioned survival model: progression-free (includes on-treatment and off-treatment), post-progression (includes subsequent lines and BSC) and death. The primary outcome was the incremental cost per QALY	Incremental progression free life years: 1.20 Incremental life years: 1.99 Incremental QALYs: 1.67 Incremental costs: $179,393 ICER: $107,520

Author, year	Title	Perspective	Population	Intervention and comparators	Time horizon	Utility source	Model structure and primary outcome	Primary results
Lakdawalla et al. (2015) [171]	Quality-adjusted cost of care: a meaningful way to measure growth in innovation cost versus the value of health gains	US	RRMM	New second-line treatments for RRMM and older therapies used for the treatment of RRMM	N/A	NR	Cost-utility analysis. The primary outcomes were the annual cost of pharmaceuticals required to treat MM and the cost of associated health gains.	Between 2004 and 2009 the average annual cost of pharmaceuticals to treat MM increased by $72,937. Health gains valued $140,800. The quality-adjusted cost of care for patients with MM fell by $67,863
Brown et al. (2013)[173]	LEN for MM: cost-effectiveness in patients with one prior therapy in England and Wales	UK NHS & PSS	RRMM	LEN+DEX vs. DEX	30 years	Van Agthoven et al. (2004)	DES model designed in Microsoft Excel. Publication of LEN appraisal submitted to NICE (TA171). The primary outcome was cost per QALY gained.	The incremental cost per QALY gained: LEN+DEX vs. DEX was £30,153 per QALY

Author, year	Title	Perspective	Population	Intervention and comparators	Time horizon	Utility source	Model structure and primary outcome	Primary results
Fragoulakis et al. (2013)[174]	Economic evaluation of therapies for patients suffering from RRMM in Greece	Greek payer	RRMM	LEN+DEX vs. BORT	NR	Van Agthoven et al. (2004)	DES model. Local adaptation of LEN appraisal submitted to NICE (TA171). The primary outcome was cost per QALY gained.	The incremental cost per QALY gained: LEN+DEX vs. DEX was €38,268 (95% UI €27,001–€58,065).
Hornberger et al. (2010)[178] and Ishak et al. (2011) [179]	The cost-effectiveness of BORT in RRMM: Swedish perspective	Swedish healthcare perspective	RRMM	BORT, DEX and LEN+DEX	10 years (considered lifetime)	Van Agthoven et al. (2004)	Markov model The primary outcome was cost per QALY gained.	The incremental cost per QALY gained: BORT vs DEX was SEK 902,874 (€95 073) (95% CI: €514 791; €962 416). BORT was dominant with respect to LEN+DEX

Author, year	Title	Perspective	Population	Intervention and comparators	Time horizon	Utility source	Model structure and primary outcome	Primary results
Möller et al. (2011)[176]	Cost-effectiveness of novel RRMM therapies in Norway: LEN+DEX vs. BORT	Norwegian healthcare perspective	RRMM	BORT LEN+DEX	NR	Van Agthoven et al. (2004)	DES model developed using ARENA simulation software. This appeared to be a local adaptation of the LEN appraisal submitted to NICE (although not explicitly stated in the publication). The primary outcome was cost per QALY gaines.	The incremental cost per QALY gained Len/Dex vs BORT was NOK 247,978

Author, year	Title	Perspective	Population	Intervention and comparators	Time horizon	Utility source	Model structure and primary outcome	Primary results
Mehta et al. (2004) [180]and Cecchi et al. (2005)[181]	Cost effectiveness of BORT in the treatment of advanced MM	US third-party payer or government health care payer	RRMM	1-all BORT patients from the pivotal trial versus BSC 2- BORT patients who had been previously treated with THAL versus BSD 3- BORT patients who had not received THAL versus THAL patients.	Duration of survival in BORT arm (end of study)	NR	Decision-analysis model to compare bortezomib therapy versus BSC. The primary outcome was cost per life year gained	Incremental cost per life year gained in subgroup 1: $45,356, 2: $49,797 and 3: $21,483

Key: BORT, bortezomib; BSC, best supportive care; CYC, cyclophosphamide; DES, discrete event simulation; DEX, dexamethasone; LEN, lenalidomide; MM, multiple myeloma; MP, melphalan and prednisolone; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NR, not reported; PANO, panobinostat; PSS, Personal Social Services; QALY, quality adjusted life year; RRMM, relapsed and/or refractory multiple myeloma; TA, technology appraisal; THAL, thalidomide; UK, United Kingdom; US, United States

5.2 De novo analysis

5.2.1 Patient population

As there was no existing model for the evaluation of the cost-effectiveness of IXA+LEN+DEX in RRMM a de novo model as developed for HTA in the UK with appropriate comparators included. IXA+LEN+DEX has marketing authorisation in the UK for adult patients with MM who have received at least one prior therapy. The economic evaluation considers the role of IXA+LEN+DEX for this population, represented by patients included in the TOURMALINE-MM1 (TMM1) study. [1] This population is consistent with the NICE final scope for this technology appraisal.[113]

This population reflects the licensed indication discussed and is similar to patients included in the TMM1 trial (discussed in Section 4.13). All patients in TMM1 had received at least one prior therapy and patients were either relapsed or refractory (or both) to previous treatments, with the definition of refractory disease defined as "disease progression on treatment or progression within 60 days after the last dose of a given therapy".[183]

Due to statistically significant differences in clinical outcomes, two subgroups were considered within the economic model using the data from TMM1:

- Patients who had received 1 prior line (n = 425)
- Patients who had received 2+ prior lines (n = 297)

These patients make up the ITT population within the TMM1 trial (n=722). Baseline characteristics for the ITT population, 1 prior lines and 2+ prior lines subgroups are shown in Table 61. The TMM1 study reflects the expected positioning of IXA+LEN+DEX in clinical practice, and therefore the patient characteristics associated with these data are appropriate to use when predicting outcomes relevant to clinical practice. Patient characteristics from the TMM1 clinical trial are used in the covariate analysis in the model.

Table 61: Baseline patient characteristics

	ITT	1 prior lines	2+ prior lines
Number of participants	722	425	297
Age (years)*	65.67 (0.35)	65.44 (0.44)	66.01(0.57)
<= 65	344 (47.65%)	204 (48.00%)	140 (47.14%)
> 65 and <= 75	270 (37.40%)	163 (38.35%)	107 (36.03%)
> 75	108 (14.96%)	58 (13.65%)	50 (16.84%)
Male			
Male	409 (56.65%)	242 (56.94%)	167 (56.23%)
Female	313 (43.35%)	183 (43.06%)	130 (43.77%)
Race			
White	611 (84.63%)	366 (86.12%)	245 (82.49%)
Asian	64 (8.86%)	30 (7.06%)	34 (11.45%)
Unknown	22 (3.05%)	16 (3.76%)	6 (2.02%)
Other	12 (1.66%%	5 (1.18%)	7 (2.36%)
Black/African American	13 (1.80%)	8 (1.88%)	5 (1.68%)
Lines of prior therapy			
1 prior line	425 (58.86%)	425 (100.00%)	0 (0.00%)
2+ prior lines	297 (41.14%)	0 (0.00%)	297 (100.00%)
ISS stage at screening†			
ISS stage I or II	632 (87.53%)	373 (87.76%)	259 (87.21%)
ISS stage III	90 (12.47%)	52 (12.24%)	38 (12.79%)
Weight (kg)*	76.24 (0.59)	76.70 (0.78)	75.58(0.91)
High risk cytogenetics (del(17), t(4:14), t(14:16))	137 (18.98%)	79 (18.59%)	58 (19.53%)
Light chain myeloma	153 (21.19%)	90 (21.18%)	63 (21.21%)
Relapsed and refractory	83 (11.50%)	3 (0.71%)	80 (26.94%)
Primary refractory	46 (6.37%)	25 (5.88%)	21 (7.07%)
Proteasome inhibitor	503 (69.67%)	276 (64.94%)	227 (76.43%)
Immunomodulation agent	397 (54.99%)	195 (45.88%)	202 (68.01%)
ECOG score = 2	42 (5.82%)	17 (4.00%)	25 (8.42%)
ASCT undertaken	411 (56.93%)	244 (57.41%)	167 (56.23%)
History of bone lesions	503 (69.67%)	286 (67.29%)	217 (73.06%)
Renal dysfunction	92 (12.74%)	51 (12.00%)	41 (13.80%)

Key: ASCT, autologous stem cell transplant; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; ITT, intention to treat; kg, kilogram
*: Denoted as mean (SE)
†: Stage I: Serum beta2-microglobulin <3.5 mg/L and albumin ≥3.5 g/dL; Stage II: Neither Stage I or III, meaning that either: beta2-microglobulin level ≥3.5 and <5.5 mg/L (with any albumin level), OR albumin <3.5 g/dL with beta2-microglobulin <3.5 mg/L; Stage III: Serum beta2-microglobulin ≥5.5 mg/L. Normal serum beta2-microglobulin: <3.0 mg/L; normal albumin: 3.5–5.0 g/dL.
ISS: International Staging System

5.2.2 Comparators

The model compares IXA+LEN+DEX with BORT+DEX for the assessment of the cost-effectiveness of IXA+LEN+DEX for a 2nd line positioning and with LEN+DEX for assessment of the cost-effectiveness of IXA+LEN+DEX for a 3rd line positioning (using data fpr a 2-3 prior therapies population). See Section 1.1.3 for a discussion of this positioning. It is noted that the original scope requests comparisons to be made:

- For patients who have had at least 1 prior therapy; IXA+LEN+DEX compared with BORT monotherapy, BORT+DEX, BORT retreatment, BORT+DEX retreatment and LEN+DEX (subject to the NICE appraisal TA171)

- For patients who have had at least 2 prior therapies; IXA+LEN+DEX compared with LEN+DEX and PANO+BORT+DEX

However, the recent carfilzomib ACD clearly specifies the relevant treatment pathway, with 2nd line consisting of patients having received one prior therapy, and 3rd line based on having received two prior therapies. Like carfilzomib the positioning of ixazomib in combination with lenalidomide and dexamethasone is that it will mainly be used as a 3rd line agent, but with potential use as a second line agent also, and so the relevant comparators are lenalidomide + dexamethasone in 3rd line, and bortezomib + dexamethasone in 2nd line.

Section 3.3 presents the current MM treatment pathway in England along with the proposed positioning of the IXA+LEN+DEX regimen. Although BORT monotherapy is reimbursed by NICE, in practice BORT is usually given in combination with DEX (as agreed in the scope). In the latest MM IMS therapy tracker market research (from Oct 2016, based on 37 specialists and 347 patient records across all lines of therapy), BORT has a 68% market share at 2nd line and so this is by far the dominant therapy (Table 62). BORT+DEX is therefore the appropriate comparator for the IXA+LEN+DEX regimen at 2nd line. However, according to expert clinical opinion, some of the other comparators in the NICE scope are unlikely to be displaced by the IXA+LEN+DEX regimen in clinical practice for the following reasons:

- BORT retreatment (with or without DEX): this treatment option is not recommended by NICE and is no longer available on the CDF

- LEN+DEX (subject to ongoing NICE appraisal [part review of Technology appraisal 171]): this treatment option is not currently recommended by NICE, is not available on the CDF and recently received a negative draft opinion from NICE at the appraisal consultation stage (ACD published on 11th November 2016). [25]

For patients who have received two prior treatments, LEN+DEX is recommended by NICE. The latest MM IMS therapy tracker market research shows that LEN is dominant in 3rd line with a 69% market share (Table 62). Therefore, this submission considers a comparison of IXA+LEN+DEX with LEN+DEX in the two-prior therapies population only (to reflect a 3rd line positioning). Although specific data for the 1 prior therapy population can be obtained from the TMM1 clinical trial data, this is not the case for the 2 prior therapies population. In the TMM1 trial, randomization was stratified according to three important cofounding variables:

- The number of prior therapies (1 vs. 2 or 3)
- Previous exposure to proteasome inhibitors (not exposed vs. exposed)
- ISS disease stage (I or II vs. III, with higher stages indicating more advanced disease).

This stratification is important to control for these confounding variables, thereby ensuring balanced subgroups and robust interpretation of outcomes. Post hoc analysis of the 2 prior therapies only subgroup would not benefit from prior stratification, meaning likely imbalances in important clinical, patient and disease-related factors across the IXA+LEN+DEX and LEN+DEX arms, confounding the interpretation of the results. Therefore, it is statistically more robust and increases confidence in the health economic results to use the combined 2 or 3 prior therapies stratified subgroup as a proxy for the 2-prior therapies population. In total, there were 281 patients (136 for IXA+LEN+DEX and 145 for LEN+DEX) in the 2 or 3 prior therapies sub-group. This consisted of:

- 208 patients who had received 2 prior therapies

- 73 who had received 3 prior therapies

The 3 prior therapies patients therefore only accounted for 26% of the patients within the combined stratified sub-group. Hence, any efficacy benefits seen in the combined 2 or 3 prior therapies subgroup have been driven primarily by the 2 prior therapies patients. Therefore, the patient level data from the 2+ prior lines population is used in this submission to proxy the outcomes for the 2-prior line population. Throughout this submission this comparison is associated with the “2+ prior lines population” to reflect the data available. However, results are presented for the expected 3rd line positioning.

In January 2016, PANO+BORT+DEX received a positive recommendation by NICE within its marketing authorisation, that is, for 'adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent'. As THAL (immunomodulatory agent) and BORT are typically used first and second line in England and Wales, this places the PANO+BORT+DEX regimen at 3rd line onwards. However, the predominant use of the PANO+BORT+DEX regimen in England and Wales is at 4th line, after LEN+DEX; this was confirmed by the clinical experts during the CARF and POM NICE Appraisal Committee meetings in October 2016. The PANO+BORT+DEX regimen was shown to have a low market share in the MM IMS market research tracker data at both 3rd and 4th line (currently 7% and 19% respectively; Table 62). Therefore, PANO+BORT+DEX is not considered a relevant comparator at 3rd line for patients eligible for LEN+DEX. This was supported by the NICE Committee in response to the CARF NICE submission.[3]

Based on the above rationale, the proposed positioning of the IXA+LEN+DEX regimen is as either a 2nd or 3rd line treatment option. Given where LEN is currently used, and based on clinician feedback, we would expect the predominant use of the IXA+LEN+DEX regimen to be in the 3rd line setting. Based on the current treatment pathway, the relevant comparator for the IXA+LEN+DEX regimen in patients who have received 1 prior therapy is BORT+DEX, while for patients who have received 2 prior therapies it is LEN+DEX.

Table 62: IMS MM therapy tracker market share data of therapies by line of treatment

Line of treatment	Market share by line of therapy (>5% market share only)
2nd line (1 prior therapy)	68% BORT 26% LEN 19% THAL
3rd line (2 prior therapies)	69% LEN 12% BORT 7% PANO
4th line (3+ prior therapies)	39% POM 25% LEN 25% BORT 19% PANO
Key: BORT, bortezomib; LEN, lenalidomide; MM, multiple myeloma; PANO, panobinostat; POM, pomalidomide; THAL, thalidomide	

5.2.3 Model structure

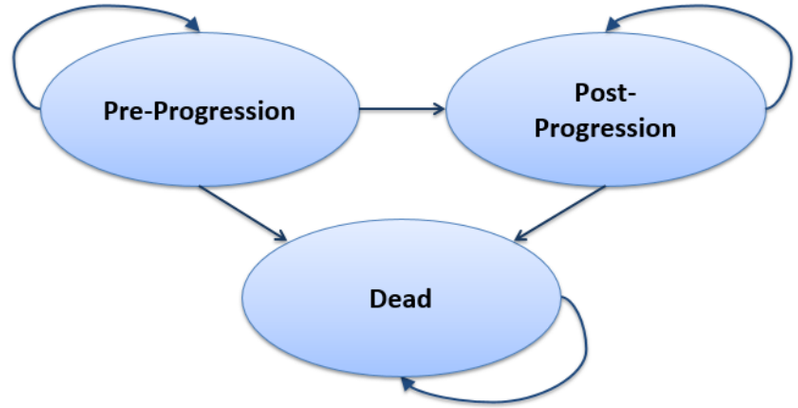
A de-novo cost-utility model has been developed to conform with the NICE Guide to the Methods of Technology Appraisal and the NICE reference case criteria. This model was developed in Microsoft Excel 2010 as a partitioned-survival model (PSM). Similar area under the curve approaches have been previously used in MM HTA submissions.

A PSM considers estimates for each clinical endpoint separately (i.e. OS, PFS and ToT are modelled independently) and, as such, maintains consistency between the endpoints used in the cost-effectiveness analysis and the published clinical data. This approach also enables external data sources to be incorporated into the model for each of the clinical endpoints, such as supporting real world evidence (RWE) or results from network meta-analyses (NMAs).

The three model health states comprise of pre-progression, post-progression and death; which are commonly used in cancer indications. Disease progression was defined as the time from the date of randomisation to the date of first documentation of disease progression based on central laboratory results and International Myeloma Working Group (IMWG) criteria as evaluated by an Independent Review Committee (IRC), or death due to any cause, whichever occurred first.

The model structure is depicted in Figure 32.

Figure 32: Three state partitioned-survival model structure



The model health states were designed to capture the factors most important to MM patients at this stage of disease, including: whether or not the patient is responding to treatment or maintaining a stable disease (pre-progression) and whether a patient is in post-progression which impacts the quality of life and costs of managing the disease and survival.

Although the TMM1 trial protocol [184]states that patients are treated until progression or until a TRAE, whichever occurs first, the observed Kaplan-Meier data shows that some patients in TMM1 were treated beyond progression. Therefore, to accurately reflect treatment costs, ToT was modelled independently. This means in the base case, ToT may surpass PFS. The literature and clinician feedback indicate that treatment with LEN+DEX should not exceed progression in an EU setting. Yong et al. (2016)[93] collect real world data from retrospective patient charts across Belgium, France, Germany, Italy, Spain, Switzerland and the UK and find that treatment with LEN is stopped at or prior to progression. The authors present the reasons for ending LEN treatment before progression, these include: remission, planned, progression, poor condition, patient refusal, toxicity, death and other reasons. Therefore, it was considered that the TMM1 trial data for ToT does not accurately reflect the ToT expected in the UK for treatment with LEN+DEX. To explore the impact of this on results a scenario analysis was performed capping ToT by PFS, so treatment cannot exceed past the point of progression (see Section 5.8).

Furthermore, ToT data from the TMM1 trial is immature with a large proportion of patients still on treatment at end of follow-up; 42.18 % and 34.75% of patients remain on treatment with IXA+LEN+DEX and LEN+DEX after 24 treatment cycles, in the ITT population. A presentation given at the American Society of Haematology (ASH) conference in 2012 presents RWE on the use of LEN+DEX in a UK setting; the authors found that after 24 treatment cycles only 17.59% of patients remained on treatment. It was further confirmed by UK clinicians (see Section 5.3.5.2) that the ToT for LEN+DEX observed in the TMM1 clinical trial surpassed what would be expected in UK clinical practice, and so by inference there is also uncertainty that the duration of IXA+LEN+DEX is also above that which would be expected in clinical practice. The immaturity of the ToT data for IXA+LEN+DEX, means there is high uncertainty associated with extrapolation. To explore the uncertainty associated with ToT scenario analyses consider:

- The impact on results of a 25% reduction in estimated ToT associated with IXA+LEN+DEX (see Section 5.8)
- The impact on results of using the observed duration on treatment from the TMM1 clinical trial (see Section 5.8)

To maintain consistency with OS, PFS and ORR estimates, in the base case the trial data for ToT were used and extrapolation performed in the standard way by the fitting of parametric functions to the data. The base case analysis considered a lifetime perspective based on 99% of patients predicted to have died within the LEN+DEX arm; this equated to 25.0 years and 18.7 years in the 1 prior and 2+ prior therapies populations, respectively. Scenario analyses considered the impact of a 15- and 20-year time horizon in both populations. The model used a weekly cycle, with half-cycle correction applied, which was considered sufficient to capture the rapid progression of RRMM. Table **63** summarises the key features of this de novo analysis.

Table 63: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (99% patients deceased; 25.0 years and 18.7 years in the 1 prior and 2 prior lines populations, respectively) The maximum time horizon in the model is 25 years	25-years is sufficiently long enough to be considered a lifetime horizon for patients who have received at least 1 prior therapy based on the majority of patients being over the age of 65 at baseline.
Were health effects measured in QALYs; if not, what was used?	QALYs	NICE reference case[185]
Discount of 3.5% for utilities and costs	3.5% for utilities and costs	NICE reference case
Perspective (NHS/PSS)	NHS and PSS	NICE reference case
Key: NICE, National Institute for Health and Care Excellence; PSS, personal social services; QALYs, quality-adjusted life years		

5.2.4 Intervention technology and comparators

The doses of the intervention and comparator treatments were implemented in the model as per their marketing authorisation. The TMM1 clinical trial considered treatment with IXA+LEN+DEX and LEN+DEX as per their marketing authorisation. The NMA, described in section 4.9, was used to obtain comparative efficacy estimates for BORT+DEX. In the base case, the network which included only studies adhering to the dosing marketing authorisation for BORT+DEX was considered. A scenario analysis considered the impact of combining doses for BORT+DEX in the NMA network.

5.3 Clinical parameters and variables

5.3.1 Primary clinical data source

The evidence used within the economic model is in line with evidence presented in Section 4.13 to inform comparative effectiveness.

Key model inputs related to IXA+LEN+DEX were obtained from the TMM1 trial. The primary analysis interim data cut (IA1), recording outcomes up to October 2014 (15 months follow-up), was used to model clinical endpoints associated with IXA+LEN+DEX for both the 1 prior therapy (2nd line) and two prior therapies (3rd line) analyses. The primary endpoint in the TMM1 study was PFS. Secondary endpoints were OS and ORR. Comparative efficacy for BORT+DEX in the one prior line population was based on data from the NMA, see Section 4.10. The NMA was conducted to obtain hazard ratios for OS, PFS and ORR for BORT+DEX relative to LEN+DEX. These hazard ratios were then applied to the LEN+DEX 1 prior lines subgroup data from the TMM1 trial to obtain a relative estimate for each of the clinical endpoints.

For the 3rd line positioning analysis, the IA1 data cut was directly used to model relative efficacy between IXA+LEN+DEX and LEN+DEX using the sub-group data for the 2+ prior therapies population.

It was noted that whilst IA1 represents the primary analysis data cut for the PFS endpoint from the TMM1 trial and was the most mature data available at the time of model construction, there is a later unpublished interim data cut available with more mature OS and ToT data (see Section 4.1). Although this datcut considers a longer follow up period, data are still immature as median OS is not yet reached in either arm. At the decision problem meeting with NICE for this submission, it was agreed the primary data cut IA1 was appropriate for the base case of the economic analysis. Therefore, a scenario analysis has been performed which considersw the impact on results using the IA2 data cut. TMM1 trial follow-up is ongoing with a further interim analysis planned for Q2 2017 (IA3), and final OS analysis planned for Q3 2019.

5.3.2 Covariate adjustment

Previous NICE submissions for the treatment of RRMM have been criticised for making comparisons between heterogenous populations, for example the ERG commented in the NICE submission for POM+LD-DEX (TA338) [97]that the clinical data came from heterogenous populations and therefore resulted in questionable comparability. Although, the comparison of IXA+LEN+DEX with LEN+DEX uses data from an RCT, various imbalances have the potential to exist between the two treatment arms. This is particularly relevant when investigating the subgroups 1 prior line and 2+ prior lines, which yield smaller sample sizes relative to the ITT population for the TMM1 trial.

Log-rank tests were used to detect evidence of significant differences in clinical endpoints between the two treatment arms in the 1 prior and 2+ prior ltherapies subgroups based on observed data for PFS, OS and ToT. These tests indicated that in addition to treatment, there were several patient risk factors that appeared to be associated with differences in clinical endpoints. Therefore, in the base case, covariate adjustment accounts for potential imbalances between the two treatment arms in the 1 prior and 2+ prior therapies subgroups. This is implemented within the economic model using the mean of covariates method. The data for covariate adjustment were obtained from the TMM1 trial, see Section 5.2. Variables from the IA1 sub-grouped data were assessed for collinearity and significance in a multivariable Cox regression model using backwards stepwise regression techniques. The covariates included in the economic model are presented in Table 64. A scenario analysis considers the impact on results of using unadjusted estimates.

Table 64: Base case analysis covariate data

	1 prior line covariates	2+ prior lines covariates
PFS	ECOG performance score = 2 ISS = Stage III Primary refractory = Yes	Light chain myeloma = Yes
OS	ECOG performance score = 2 ISS = Stage III	Age > 65 years
ToT	ISS = Stage III	Renal dysfunction = Yes Light chain myeloma = Yes
Key: ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; OS, overall survival; PFS, progression free survival; ToT, time on treatment		

5.3.3 Survival analysis

5.3.3.1 Overview of extrapolation

In line with the NICE Decision Support Unit (DSU)[186] guidance the applicability of a single parametric model or a Cox proportional hazards model was determined using visual inspection of the KM curves, the log cumulative hazard plots (LCHPs) and the Q-Q curves. LCHPs were assessed to determine the suitability of using a single parametric model for the two treatment arms in terms of the underlying hazard and in assessing the suitability of projecting using exponential, Weibull and Gompertz curves. Q-Q plots were assessed to determine the suitability of the use of accelerated failure time (AFT) models. [186]

Six parametric distributions (exponential, log-normal, log-logistic, Gompertz, generalised gamma and Weibull) were examined for each clinical outcome (OS, PFS and ToT), in line with the NICE DSU guidance. [186] The fit of each parametric model to the covariate adjusted survival data was explored using visual inspection, LCHPs, Schoenfeld residual plots, Q-Q plots, Akaike information criterion (AIC) and Bayesian information criterion (BIC) goodness of fit statistics and clinical plausibility. AIC and BIC provide an estimated relative fit of the alternative parametric models to the observed trial data. All curves were fitted using statistical software package R.

5.3.3.2 2+ prior therapies population: IXA+LEN+DEX vs. LEN+DEX

Efficacy estimates for OS, PFS and ToT associated with IXA+LEN+DEX and LEN+DEX were obtained from the pivotal ixazomib clinical study TMM1 described in Section 4. The data for the 2+ prior therapies population from the TMM1 clinical trial was used to proxy the outcomes associated with a 3rd line positioning of IXA+LEN+DEX in the MM treatment pathway, see Section 5.2.2.

Progression free survival (PFS)

Appendix 11 presents the Kaplan-Meier curves, the LCHPs, the Schoenfeld residual plots, the QQ plots and AIC and BIC estimates for the covariate adjusted PFS associated with LEN+DEX for the 2+ prior therapies population. These methods suggest that the generalised gamma provides the most appropriate choice of model; the data satisfy the AFT assumption required when fitting a generalised gamma curve, these curves have relatively low AIC/BIC and provide a good fit to the observed data (Figure 33).

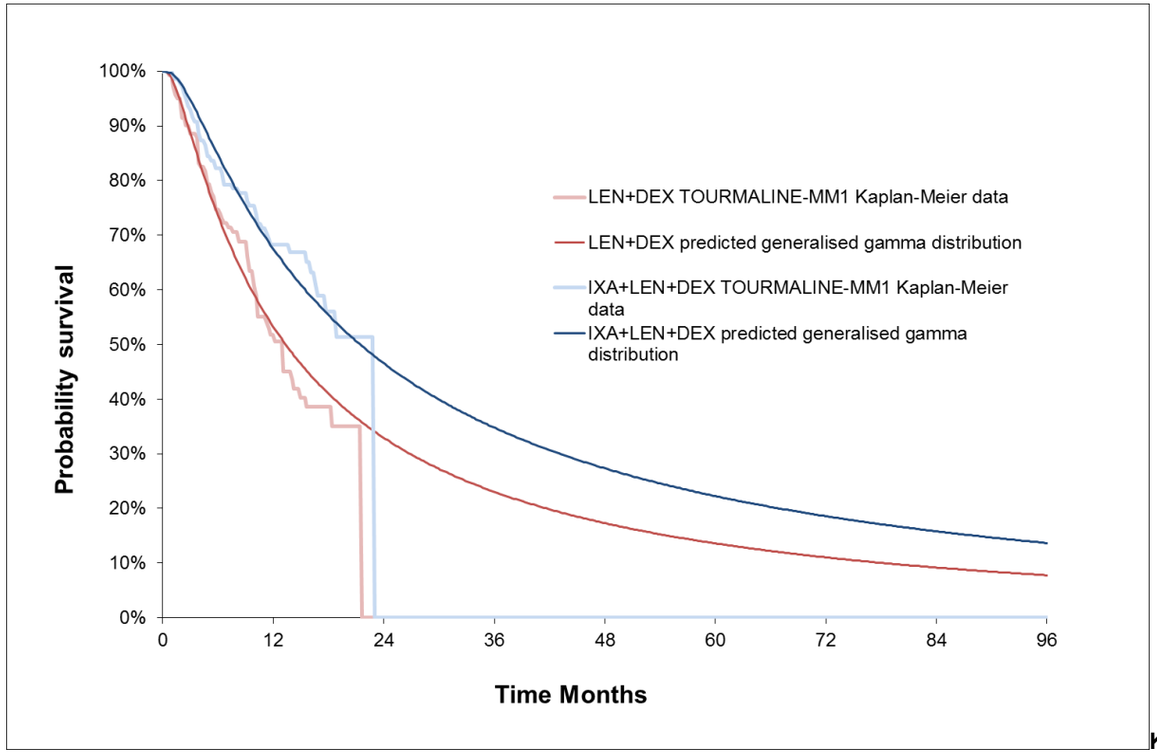
Appendix 11 depicts the comparison of fitted covariate-adjusted parametric curves to the underlying data for LEN+DEX. Interpreting the AIC/BIC the log-logistic and lognormal curves also provide a good fit to the observed data; however, these curves result in clinically implausible estimates (after 6 years >10% of patients have not progressed which is not considered clinically plausible given the relapsing nature of the disease) and so are considered inappropriate for extrapolation.

The applicability of using unstratified models for the comparison of IXA+LEN+DEX with LEN+DEX for PFS was determined using the LCHP plots, the QQ plots and visual inspection. The LCHP and the QQ curves support the assumption of proportional hazards and AFT functionality, respectively, and as such a treatment effect was estimated for IXA+LEN+DEX compared with LEN+DEX [treatment effect: 0.62 relative to LEN+DEX, 95% CI: 0.44 - 0.87] and applied to the LEN+DEX fitted generalised gamma covariate-adjusted PFS curve. Treatment with IXA+LEN+DEX is shown to result in a significant improvement in PFS compared with LEN+DEX for the 2+ prior therapies subgroup.

Comparisons of the modelled IXA+LEN+DEX curves with the original IXA+LEN+DEX PFS data (Figure 33) indicate a reasonably good visual fit and validate this method of modelling IXA+LEN+DEX PFS estimates. These curves were presented to clinicians, who validated the estimates over time as being clinically plausible for the given population, see Section 5.3.5.

Within the model the potential for the PFS curve to cross the OS curve was curtailed by applying the minimum of PFS and OS if PFS was greater than OS at a given time point. This was apparent in only early model cycles and was adjusted to attain clinical validity. The impact on model results of selecting different parametric curves for PFS was tested in scenario analyses, see Sections 5.8.13 and 5.8.2.3 for the 1 prior and 2 prior therapies populations, respectively.

Figure 33: Comparison of fitted covariate adjusted PFS curves (generalised gamma) with unadjusted KM curves for IXA+LEN+DEX and LEN+DEX in the 2+ prior lines subgroup



Key: DEX, dexamethasone; IXA, ixazomib; KM, Kaplan-Meier; LEN, lenalidomide; PFS, progression free survival

Overall survival (OS)

Appendix 11 presents the Kaplan-Meier curves, the LCHPs, the Schoenfeld residual plots, the QQ plots and AIC and BIC estimates for OS associated with LEN+DEX for the 2+ prior therapy population.

The LCHP and QQ curves support the assumption of proportional hazards and AFT functionality, respectively, and so a single parametric model was fit to the LEN+DEX data. The AIC/BIC statistics suggest that the Weibull provides the most appropriate choice of model; the data satisfy the proportional hazards assumption required when fitting a Weibull curve, these curves have relatively low AIC/BIC and provide a good fit to the observed data (Figure 34). Interpreting the AIC/BIC the log-logistic and lognormal curves also provide a good fit to the observed data; however, these curves result in clinically implausible estimates (>10% of patients are still alive after 25 years which is not considered clinically plausible in an RRMM population based on the fact the majority of patients are over 65-years at baseline) and so are considered inappropriate for extrapolation.

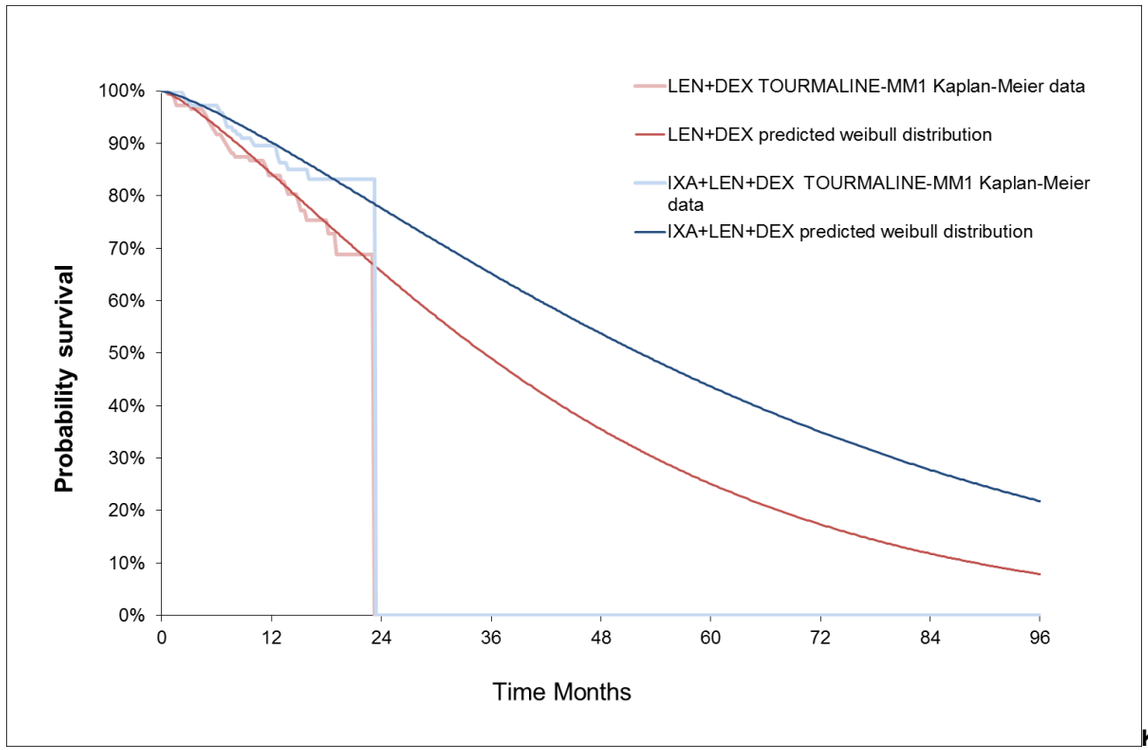
The applicability of using unstratified models for the comparison of IXA+LEN+DEX with LEN+DEX for OS was determined using the LCHP plots, QQ curves and visual inspection. The QQ curves support the AFT assumption for the 2+ prior therapies subgroup and therefore a treatment effect was estimated for IXA+LEN+DEX compared with LEN+DEX [treatment effect: 0.67, 95% CI: 0.43 - 1.05] and applied to the covariate-adjusted Weibull OS curve for the 2+ prior therapies subgroups.

The treatment effect for the 2+ prior therapiessubgroup does not show a significant improvement in OS; the 95% confidence interval spans across one. This is likely caused by the immature OS data in the IA1 data cut; median survival has not yet been reached in the IA1 dataset and so more uncertainty is encompassed in extrapolation techniques. It can be anticipated that more mature OS data from later data cuts (IA3 data cut is planned for Q2 2017) could reduce the clinical uncertainty associated with OS estimates and, in doing so, increase the robustness of the model results.

Comparisons of the modelled IXA+LEN+DEX curves with the original IXA+LEN+DEX OS data (Figure 34) indicate a good fit and validate this method of modelling IXA+LEN+DEX OS estimates. The model time horizon extends to the point at which 99% of patients have died in the LEN+DEX arm: 18.7-years in the 2+ prior therapies population. At 10 years, 13.06% of patients are expected to still be alive on the IXA+LEN+DEX arm, 3.19% at 15 years and 0.67% at 20-years. These curves and estimates were presented to clinicians, who validated the estimates over time as being clinically plausible for the given population (see Section 5.3.5).

The impact on model results of selecting different parametric curves for OS was tested in scenario analyses, see Sections 5.8.13 and 5.8.2.3 for the 1 prior and 2 prior therapies populations, respectively.

Figure 34: Comparison of fitted OS curves (Weibull) with unadjusted KM curves for IXA+LEN+DEX and LEN+DEX in the 2+ prior lines subgroup



Key: DEX, dexamethasone; IXA, ixazomib; KM, Kaplan-Meier; LEN, lenalidomide; PFS, progression free survival

Time on treatment (ToT)

ToT was used to determine duration of time on treatment, allowing for potential treatment discontinuation due to progression or unacceptable toxicity to be included in the analysis. Appendix 11 presents the Kaplan-Meier curves, the LCHPs, the Schoenfeld residual plots, the QQ plots and AIC and BIC estimates for ToT associated with LEN+DEX for the 2+ prior lines population.

The LCHP and the QQ curves for the 2+ prior therapies population support the assumption of proportional hazards and AFT functionality, respectively, and so a single parametric model was fit to the LEN+DEX ToT data. The AIC/BIC statistics suggest that the exponential provides the most appropriate choice of model; the data satisfy the proportional hazards assumption required when fitting an exponential curve, these curves have relatively low AIC/BIC scores and provide a good fit to the observed data (Figure 35). Appendix 11 depicts the comparison of fitted covariate-adjusted parametric curves to the underlying data for LEN+DEX. The Weibull curve also provides a reasonable fit to the ToT data and is considered in a scenario analysis (see Sections 5.8.13 and 5.8.2.3 for the 1 prior and 2 prior therapies populations, respectively).

The applicability of using unstratified models for the comparison of IXA+LEN+DEX with LEN+DEX for ToT was determined using the LCHP plots, the QQ curves and visual inspection. The LCHP and the QQ curves for the 2+ prior therapies subgroup support the assumption of proportional hazards and AFT functionality, and as such a hazard ratio was estimated for IXA+LEN+DEX compared with LEN+DEX [HR: 1.36, 95% CI: 0.97 - 1.90] and applied to the LEN+DEX fitted exponential ToT curve for the 2+ prior therapies subgroup. The 95% confidence interval spans over 1 which shows a non-significant difference in ToT in the 2+ prior therapies population.

Comparisons of the modelled IXA+LEN+DEX curves with the original IXA+LEN+DEX ToT data (Figure 35) indicate a good fit and validate this method of modelling IXA+LEN+DEX ToT estimates.

The literature and clinician feedback indicate that treatment with LEN+DEX should not exceed progression in an EU setting. Yong et al. (2016) [93] collect real world data from retrospective patient charts across Belgium, France, Germany, Italy, Spain, Switzerland and the UK and find that treatment with LEN is stopped at or prior to progression. The estimated curves were presented to clinicians, who commented that the fitted ToT curves over-estimated the time patients are expected to be on treatment in current UK practice.Furthermore, clinican feedback and RWE (see Section 5.2.3) found that the ToT for LEN+DEX observed in the TMM1 clinical trial surpassed what would be expected in UK clinical practice, and so by inference there is also uncertainty that the duration of IXA+LEN+DEX is also above that which would be expected in clinical practice. The immaturity of the ToT data means that there is uncertainty associated with a high degree of extrapolation beyond the trial and the extent to which the extrapolated estimates will reflect clinical practice.

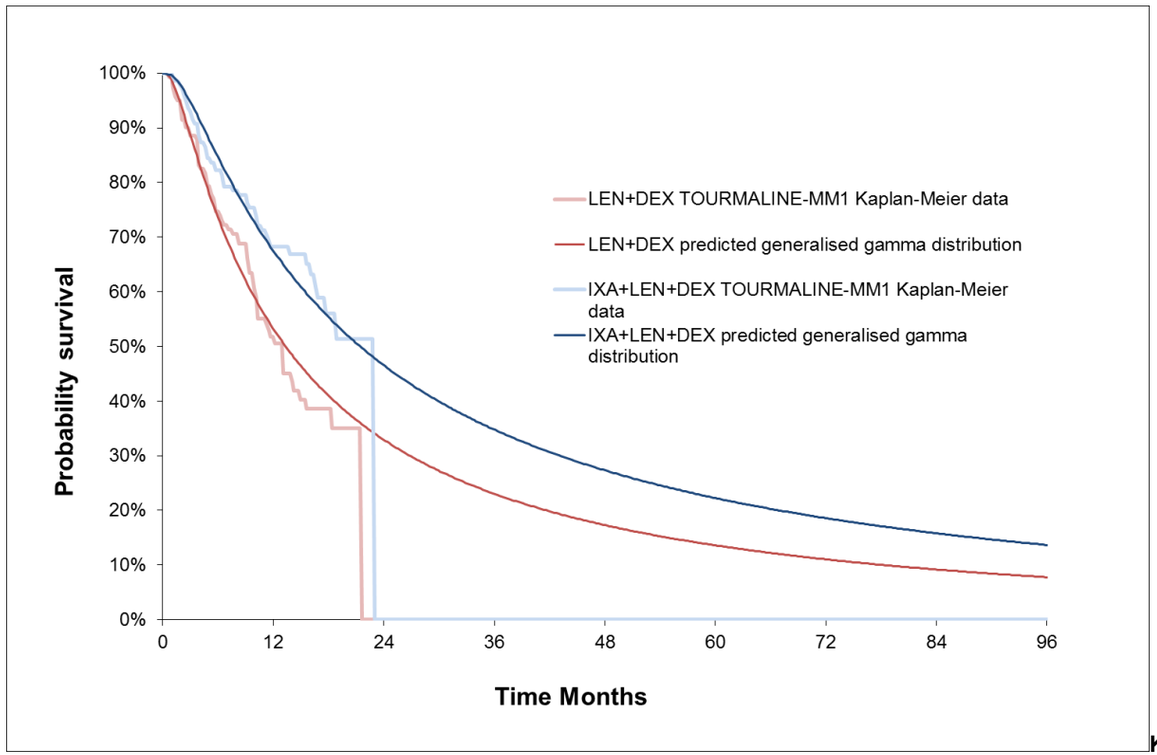
To maintain consistency with the OS and PFS estimates, the trial data with extrapolation based on parametric function fitting to the observed data were used to estimate ToT for both LEN+DEX and IXA+LEN+DEX in the base case. This submission also considered:

- A scenario capping ToT at progression for both the LEN+DEX and IXA+LEN+DEX arms, on the grounds that both treatment regimens are intended to be treat to progression.

- Scenarios assuming a 25% reduction in ToT associated with IXA+LEN+DEX, and a scenario based on the actual observed duration of treatment in the TMM1 trial without extrapolation to explore the sensitivity to assumptions regaridng a lower potential duration of treatment in clinical practice on the ICER.

The potential for the ToT curve to cross the OS curve was curtailed by applying the minimum of ToT and OS if ToT was greater than OS at a given time point. This was apparent in only early model cycles and adjusted to attain clinical validity. The impact on model results of selecting different parametric curves for ToT was tested in scenario analyses, see Sections 5.8.13 and 5.8.2.3 for the 1 prior and 2 prior therapies populations, respectively.

Figure 35: Comparison of fitted adjusted ToT curves (generalised gamma) with unadjusted KM curves for IXA+LEN+DEX and LEN+DEX in the 2+ prior lines subgroup



Key: DEX, dexamethasone; IXA, ixazomib; KM, Kaplan-Meier; LEN, lenalidomide; PFS, progression free survival

5.3.3.3 1 prior therapy population: IXA+LEN+DEX vs. BORT+DEX

Overview

Efficacy estimates for OS, PFS and ToT associated with IXA+LEN+DEX were obtained from the TMM1 clinical trial described in Section 4.

Relative efficacy estimates for OS, PFS and ORR associated with BORT+DEX were obtained from the NMA described in Section 4.10 No data were available allowing for a network of evidence to be constructed for a 1 prior therapy population and so the results from the NMA for BORT+DEX are from an ITT population (1+ prior therapies patient population) and were used as a proxy for the 1 prior line population in this submission (see section 4.10.6.1).

In the base case, the hazard ratios estimated for OS and ORR relative to LEN+DEX were obtained from all identified studies (RCTs and observational studies) based on including only studies with the dose specific to the marketing authorisation. A scenario analysis considers the impact of combining all doses observed in the literature, or where dose not specified in the study.

In the base case, the hazard ratio estimated for PFS relative to LEN+DEX was obtained from all identified studies (RCTs and real world evidence) by pooling all observed doses. Due to lack of data no network could be formed considering the dose specific to the BORT+DEX marketing authorisation (1.3mg/m^2).

The hazard ratios used in the base case analysis and in the scenario analyses are presented in Table 44. The treatment effects calculated from the NMA were applied relative to the LEN+DEX arm from the TMM1 clinical trial. Therefore, although LEN+DEX was not considered a relevant comparator in the 1 prior therapiespopulation in this submission, the data were analysed to allow for the BORT+DEX comparison.

Table 65: NMA results used in the 1 prior therapies (IXA+LEN+DEX vs. BORT+DEX) comparison

	Definition	BORT+DEX vs. LEN+DEX Hazard Ratio (95% CrI)
Base case PFS network	ITT population (1+ prior therapies). RCT and observational studies, combined doses, and primary publications	1.06 (0.61, 1.85)
Scenario analysis PFS:	ITT population (1+ prior therapies). **RCT studies only**, combined doses, and primary publications	1.06 (0.60, 1.84)

Base case OS network	ITT population (1+ prior therapies). RCT and observational studies, dose specific, and primary publications	3.11 (1.52, 6.35)
Scenario analysis OS:	ITT population (1+ prior therapies). RCT and observational studies, **dose combined**, and primary publications	3.05 (1.78, 5.22)
Base case ORR network	ITT population (1+ prior therapies). RCT and observational studies, dose specific, and primary publications	2.28 (1.06, 4.93)
Key: BORT, bortezomib; Crl, credible interval; DEX, dexamethasone; LEN, lenalidomide; NMA, network meta analysis; OS, overall survival; ORR, overall response rate; PFS, progression free survival; RCT, randomised controlled trial		

As these data were not available from the NMA due to insufficient evidence for comparators,the ToT for BORT+DEX was assumed equivalent to that of LEN+DEX from the TMM1 clinical trial for the first eight weeks of treatment. Thereafter, no treatment with BORT+DEX was received – in line with the bortezomib summary of product characteristics.[27]

Progression free survival (PFS)

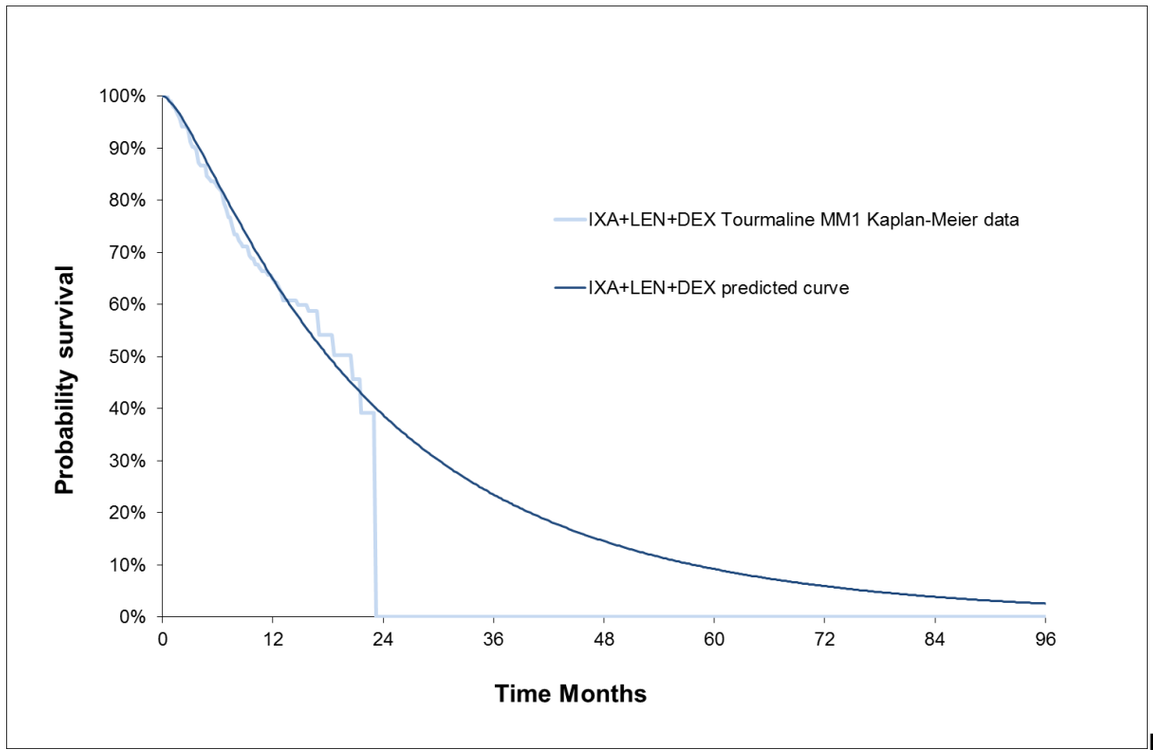
Appendix 11 presents the Kaplan-Meier curves, the LCHPs, the Schoenfeld residual plots, the QQ plots and AIC and BIC estimates for the covariate adjusted PFS associated with LEN+DEX for the 1 prior therapies population. These methods suggest that the generalised gamma provides the most appropriate choice of model; the data satisfy the AFT assumption required when fitting a generalised gamma curve, these curves have relatively low AIC/BIC and provide a good fit to the observed data. Appendix 11 depicts the comparison of fitted covariate-adjusted parametric curves to the underlying data for LEN+DEX. The impact on model results of selecting different parametric curves for PFS was tested in scenario analyses, see Sections 5.8.13 and 5.8.2.3 for the 1 prior and 2 prior therapies populations, respectively.

The applicability of using unstratified models to estimate the treatment effect of IXA+LEN+DEX relative to LEN+DEX for PFS was determined using the LCHP plots, the QQ plots and visual inspection. The QQ curves demonstrate that the AFT assumption is satisfied as the sample quantiles approximate to the 45-degree line. Therefore, a treatment effect was estimated for IXA+LEN+DEX compared with LEN+DEX [treatment effect: 0.94, 95% CI: 0.72 - 1.22] and applied to the LEN+DEX fitted generalised gamma PFS curve.

Within the model the potential for the PFS curve to cross the OS curve was curtailed by applying the minimum of PFS and OS if PFS was greater than OS at a given time point. This was apparent in only early model cycles and was adjusted to attain clinical validity.

Comparisons of the modelled IXA+LEN+DEX curves with the original IXA+LEN+DEX PFS data (Figure 36) indicate a reasonably good visual fit and validate this method of modelling IXA+LEN+DEX PFS estimates. These curves were presented to clinicians, who validated the estimates over time as being clinically plausible for the given population, see Section 5.3.5.

Figure 36: Comparison of the fitted covariate-adjusted PFS curve with unadjusted KM curve for IXA+LEN+DEX in the 1 prior therapy population

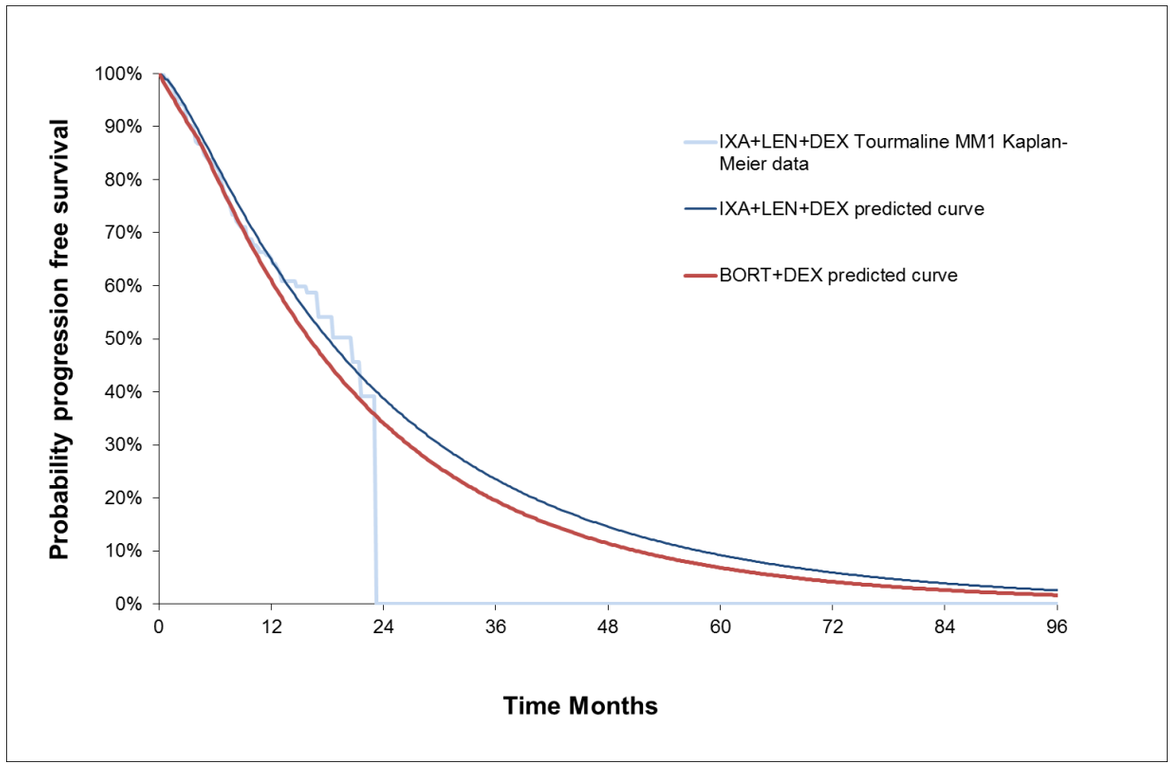


Key: DEX, dexamethasone; IXA, ixazomib; KM, Kaplan-Meier; LEN, lenalidomide; PFS, progression free survival

The NMA, described in Section 4.10, estimated the hazard ratio for PFS [HR: 1.06, 95% CI: 0.61 – 1.85] for BORT+DEX relative to LEN+DEX (see Table 65). This hazard ratio was obtained from a network considering all identified studies (including RCTs and observational data) and across all combined doses (due to te absence

of a network based on specific doses of interest). Figure 37 shows the estimated PFS curve for BORT+DEX relative to IXA+LEN+DEX. These curves were presented to clinicians, who validated the estimates over time as being clinically plausible for the given population, see Section 5.3.5.

Figure 37: Comparison of fitted covariate-adjusted PFS curves for IXA+LEN+DEX and BORT+DEX in the 1 prior therapy**population**



Key: BORT, bortezomib; DEX, dexamethasone; IXA, ixazomib; KM, Kaplan-Meier; LEN, lenalidomide; PFS, progression free survival

Overall survival

Appendix 11 presents the Kaplan-Meier curves, the LCHPs, the Schoenfeld residual plots, the QQ plots and AIC and BIC estimates for OS associated with LEN+DEX for the 1 prior therapy population.

The LCHP plot indicates that the proportional hazards assumption is violated due to the nature of the non-parallel curves; the gap is much wider at first and then narrows over time. The QQ curves demonstrate that the AFT assumption is satisfied as the sample quantiles approximate to the 45-degree line. However, the AFT models (the generalised gamma, Weibull, log-logistic and lognormal functions) result in clinically implausible estimates, for example the generalised gamma curve estimates 13.62% and 17.97% of patients are alive after a 25-year time horizon (52% of patients are over the age of 65 at baseline). As such these curves are considered inappropriate for prediction.

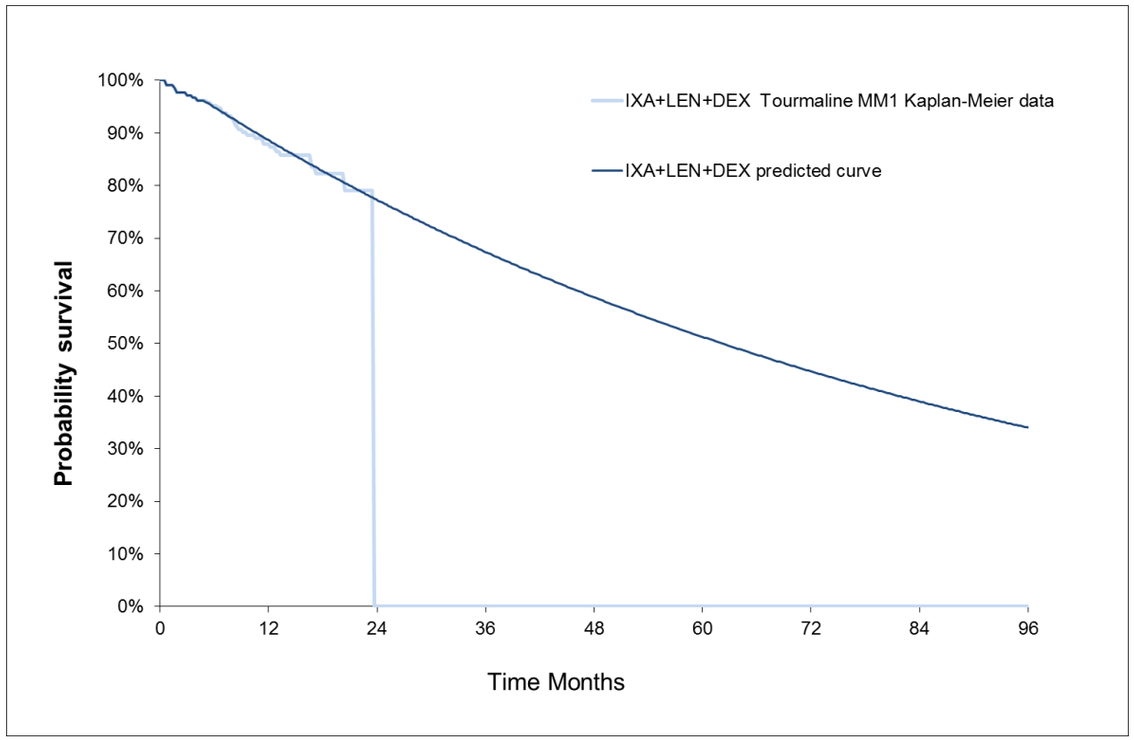
When analysing the LCHP, it is evident that the violation of the proportional hazards assumption exists in the initial stages of the survival data, most notably prior to month 5. For this reason, the model uses Kaplan-Meier data to inform OS from month 0 to month 5; an exponential parametric curve was then fit to the data from month 5 onwards. This approach is provided in more detail in Gelber et al. (1993). [187] The LCHP and the Schoenfeld residual plot, supporting the proportional hazards assumption from month 5 onwards, are shown in Appendix 11 The resulting curve provides a good fit to the observed data for the 1 prior therapy subgroup. The impact on model results of selecting different parametric curves for OS was tested in scenario analyses, see Section 5.3.5.

The applicability of using unstratified models to estimate the treatment effect for IXA+LEN+DEX relative to LEN+DEX for OS was determined using the LCHP plots, QQ curves and visual inspection. The LCHP using the data cut from 5 months supports the assumption of proportional hazards. Therefore, a hazard ratio was estimated for IXA+LEN+DEX compared with LEN+DEX [HR: 0.89, 95% CI: 0.5 - 1.60] and applied to the fitted exponential from 5 months. The model time horizon extends to the point at which 99% of patients have died in the LEN+DEX arm: 25.0-years in the 1 prior therapy population.

At 10 years, 25.83% of patients are expected to still be alive on the IXA+LEN+DEX arm, 13.02% at 15 years and 6.57% at 20-years. These estimates are clinically valid as RRMM is a heterogeneous disease, and while most patients have poor prognosis, a small proportion of patients can experience relatively long survival. Furthermore, it is to be expected that those at second line have a better prognosis than those patients at third line or later.

Comparisons of the modelled IXA+LEN+DEX curves with the original IXA+LEN+DEX OS data (Figure 38) indicate a good fit and validate this method of modelling IXA+LEN+DEX OS estimates. These curves were presented to clinicians, who validated the estimates over time as being clinically plausible for the given population, see Section 5.3.5.

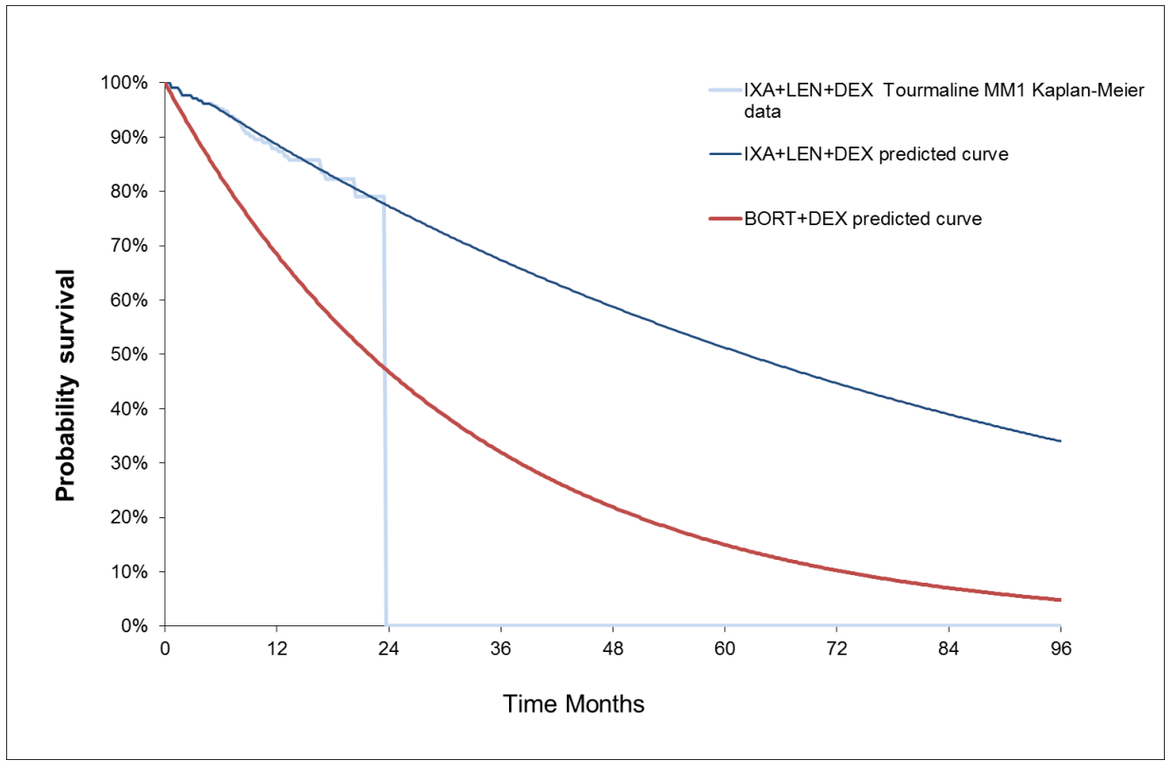
Figure 38: Comparison of the fitted OS curve with unadjusted KM curve for IXA+LEN+DEX in the 1 prior therapy population



Key: DEX, dexamethasone; IXA, ixazomib; KM, Kaplan-Meier; LEN, lenalidomide; OS, overall survival

The NMA, described in Section 4.10, estimated the hazard ratio for OS [HR: 3.11, 95% CI: 1.52 – 6.35] for BORT+DEX relative to LEN+DEX (see Table 65). This hazard ratio was obtained from a network considering all identified studies (including RCTs andobservational data) and for the dose specific to the marketing authorisation for BORT+DEX. A scenario analysis considers the hazard ratio from a network considering all identified studies across combined doses [HR: 3.05, 95% CI: 1.78 – 5.22]. Figure 39 shows the estimated OS curve for BORT+DEX relative to IXA+LEN+DEX. These curves were presented to clinicians, who validated the estimates over time as being clinically plausible for the given population, see Section 5.3.5.

Figure 39: Comparison of fitted OS curves for IXA+LEN+DEX and BORT+DEX in the 1 prior therapy population



Key: DEX, dexamethasone; IXA, ixazomib; KM, Kaplan-Meier; LEN, lenalidomide; PFS, progression free survival

Time on treatment

Appendix 11 presents the Kaplan-Meier curves, the LCHPs, the Schoenfeld residual plots, the QQ plots and AIC and BIC estimates for ToT associated with LEN+DEX for the 1 prior therapy population.

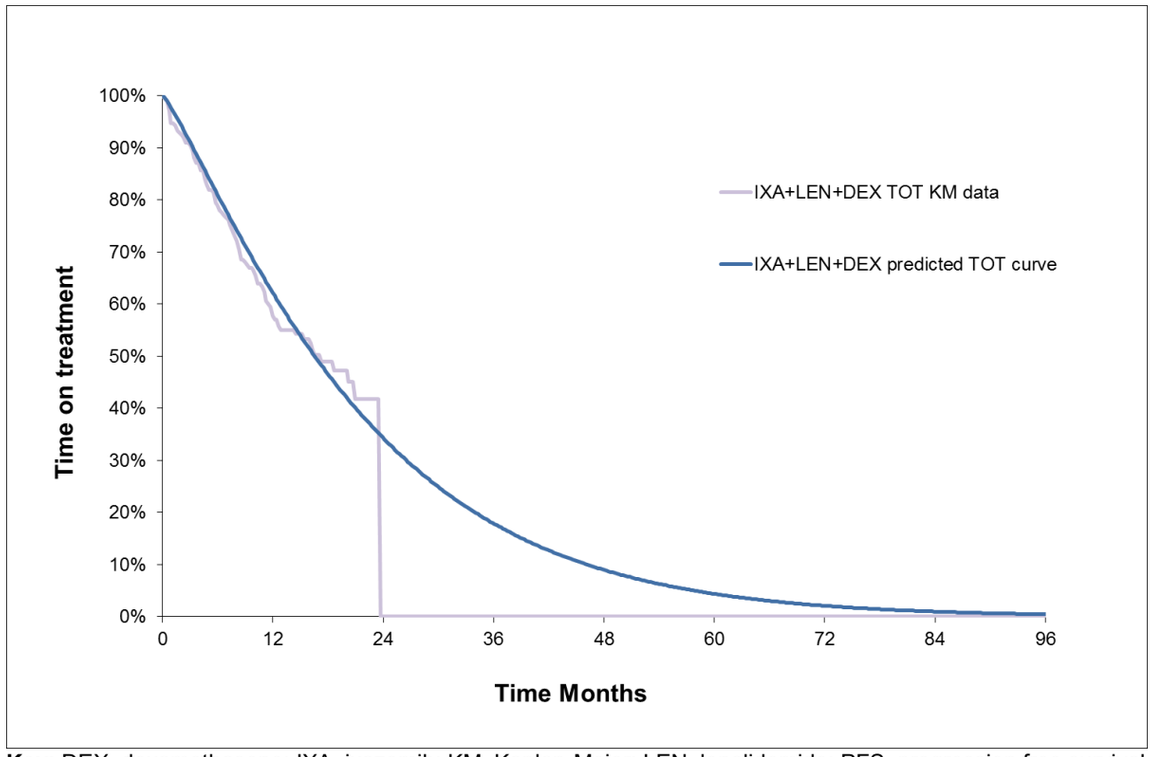
The LCHP indicates a violation of the proportional hazards assumption due to the non-parallelism of the two treatment arms, as well as the overlap which occurs towards the latter part of the follow-up period. The Schoenfeld residual test further provided evidence of a proportional hazards violation with time (with time p=0.04, with log(time) p=0.05 and with time squared p=0.05) which was indicated visually by the negative gradient of the Schoenfeld residual plot. The QQ curves demonstrate that the AFT assumption is satisfied as the sample quantiles approximate to the 45-degree line. These methods, alongside the AIC/BIC statistics, suggest that the Weibull provides the most appropriate choice of model; the data satisfy the AFT assumption required when fitting the Weibull curve, this curve has a relatively low AIC/BIC and provides a good fit to the observed data. Appendix 11 presents the comparison of fitted covariate-adjusted parametric curves to the underlying data for LEN+DEX. The impact on model results of selecting different parametric curves for ToT was tested in scenario analyses, see Sections 5.8.13 and 5.8.2.3 for the 1 prior and 2 prior therapies populations, respectively.

The applicability of using unstratified models for estimating a treatment effect for IXA+LEN+DEX relative to LEN+DEX for ToT was determined using the LCHP plots, the QQ curves and visual inspection. The LCHP demonstrates that the proportional hazard assumption is violated. However, the QQ curve demonstrates that the AFT assumption is satisfied. As such, a treatment effect was estimated for IXA+LEN+DEX compared with LEN+DEX [treatment effect: 1.01, 95% CI: 0.80 - 1.29] and applied to the LEN+DEX fitted Weibull ToT curve.

Comparisons of the modelled IXA+LEN+DEX curves with the original IXA+LEN+DEX ToT data (Figure 40) indicate a good fit and validate this method of modelling IXA+LEN+DEX ToT estimates. These curves were presented to clinicians, who commented that the fitted ToT curves over-estimated the time patients are expected to be on treatment in current UK practice. This has been discussed in detail under the ToT heading for the IXA+LEN+DEX and LEN+DEX comparison for the 2+ prior lines population. In the base case, the data from the TMM1 study was used to model ToT for IXA+LEN+DEX. However, a number of scenarios (described earlier in this section) consider the impact of uncertainty on results.

The potential for the ToT curve to cross the OS curve was curtailed by applying the minimum of ToT and OS if ToT was greater than OS at a given time point. This was apparent in only early model cycles and adjusted to attain clinical validity. The impact on model results of selecting different parametric curves for ToT was tested in scenario analyses, see Sections 5.8.13 and 5.8.2.3 for the 1 prior and 2 prior populations, respectively.

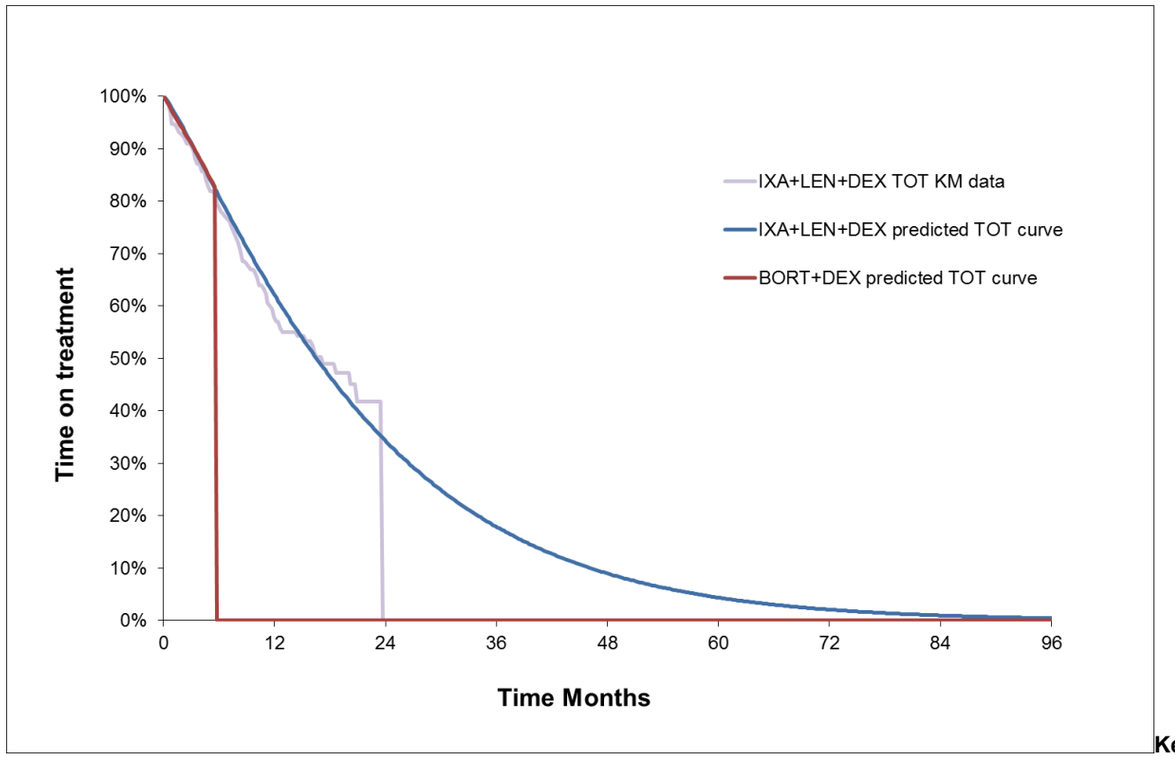
Figure 40: Comparison of fitted covariate-adjusted ToT curve with unadjusted KM curve for IXA+LEN+DEX in the 1 prior line population



Key: DEX, dexamethasone; IXA, ixazomib; KM, Kaplan-Meier; LEN, lenalidomide; PFS, progression free survival

The ToT for BORT+DEX was assumed equivalent to the LEN+DEX ToT arm. However, the summary of product characteristics for BORT+DEX state that the maximum number of treatment cycles is eight. [27] Therefore, after eight 21-day treatment cycles patients in the BORT+DEX arm no longer receive treatment with BORT+DEX. Figure 41 presents the estimated ToT curves for IXA+LEN+DEX and BORT+DEX.

Figure 41: Comparison of fitted adjusted ToT curves for IXA+LEN+DEX and BORT+DEX in the 1 prior therapy population



Key: DEX, dexamethasone; IXA, ixazomib; KM, Kaplan-Meier; LEN, lenalidomide; ToT, time on treatment

5.3.4 Adverse events

Treatment with chemotherapy results in a variety of TRAEs. Furthermore, the type, severity and rate of AEs can vary between chemotherapy treatments leading to differences in overall HRQoL, resource use and costs. All TRAEs grade 3/4 were included in the economic analysis using data from the TMM1 trial dataset. TRAEs associated with IXA+LEN+DEX and LEN+DEX were sourced from the TMM1 trial. As there was no significant difference found between the number of TRAEs occurring in the 1 prior and the 2+ prior therapies subgroups, the patient level data for the ITT population was used in estimating TRAEs. TRAE data for BORT+DEX

were sourced from the pivotal PANORAMA-1 trial.[145] Where TRAE data were not available, differences in the AEs reported across papers, the probability of experiencing a TRAE was assumed equal to LEN+DEX. TRAEs were modelled only for patients on treatment, and it was assumed that TRAEs for all therapies cease once treatment is discontinued. In total, 17 different AEs were included in the analysis as shown in Table 67.

The rate per cycle for each TRAE was estimated for LEN+DEX patients (converted to a probability per person week for implementation in the model). This approach considers both the number of events occurring and the follow-up period or exposure time in person-years (i.e. incidence rate). The average treatment exposure was obtained from the TMM1 data: 11.05 months. All estimates were converted to a probability per cycle. The rate of AEs for IXA+LEN+DEX and BORT+DEX were calculated using the reported percentages of AEs from the TMM1 and PANORAMA-1 studies, respectively. A relative risk (RR) was calculated for each reported AE compared with LEN+DEX which was then applied in the model (Table 66). Where it was not possible for RRs to be calculated (data not reported for all AEs) the rates of AEs observed in the TMM1 study on the LEN+DEX arm were applied. This was the case for three TRAEs: deep vein thrombosis, rash-related AEs and new primary malignancies. The probabilities per cycle for LEN+DEX, IXA+LEN+DEX and BORT+DEX are presented in Table 67.

Table 66: Calculation of AE rates for IXA+LEN+DEX and BORT+DEX

Grade 3+ treatment emergent AEs	Reported % of AEs			Calculated RR vs. LEN+DEX	
	LEN+DEX	IXA+LEN+DEX	BORT+DEX	IXA+LEN+DEX	BORT+DEX
Anaemia	16.39%	11.11%	19.10%	0.66	2.05
Cardiac failure	1.67%	2.22%	1.86%	1.27	1.74
Deep vein thrombosis	0.83%	0.56%	-	0.66	1.00
Diarrhoea	2.22%	7.78%	7.96%	3.45	6.52
Fatigue	2.50%	3.89%	11.94%	1.54	8.69
Upper respiratory tract infection/Pulmonary-related	0.56%	0.83%	1.59%	0.99	3.48
Ischaemic heart disease	0.83%	0.56%	0.00%	0.66	0.00
Nausea	0.07%	1.67%	0.53%	23.69	13.91
Neutropenia	31.67%	41.94%	11.41%	1.23	0.60
Peripheral neuropathy	0.83%	0.28%	14.59%	0.33	31.88
Pneumonia	10.00%	7.50%	10.34%	0.91	1.74
Pulmonary embolism	2.22%	2.22%	0.27%	0.99	0.22
Rash-related	1.39%	4.44%	-	3.95	1.00
Renal failure	4.72%	1.67%	0.00%	0.35	0.00
Thrombocytopaenia	6.11%	20.83%	31.30%	3.41	9.33
Vomiting	0.56%	1.11%	1.33%	1.97	4.35
New primary malignancy	0.56%	1.39%	-	0.49	1.00

Key: AE, adverse event; BORT, bortezomib; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; RR, relative risk

Table 67: TRAEs grade 3/4

Grade 3+ treatment emergent AEs	Average duration of AEs (days)	LEN+DEX			IXA+LEN+DEX cycle probability	BORT+DEX cycle probability
		No of events*	Rate	Cycle Probability		
Anaemia	42.08	61	0.1831	0.0035	0.0023	0.0072
Cardiac failure	11.31	7	0.0210	0.0004	0.0005	0.0007
Deep vein thrombosis	11.40	3	0.0090	0.0002	0.0001	0.0002
Diarrhoea	31.44	8	0.0240	0.0005	0.0016	0.0030
Fatigue	63.33	9	0.0270	0.0005	0.0008	0.0045
Upper respiratory tract infection/Pulmonary-related	15.40	3	0.0090	0.0002	0.0002	0.0006
Ischaemic heart disease	4.20	3	0.0090	0.0002	0.0001	0.0000
Nausea	20.60	0	0.0000	0.0000	0.0000	0.0000
Neutropenia	15.08	124	0.3721	0.0071	0.0088	0.0043
Peripheral neuropathy	50.00	3	0.0090	0.0002	0.0001	0.0055
Pneumonia	19.59	39	0.1170	0.0022	0.0020	0.0039
Pulmonary embolism	56.53	8	0.0240	0.0005	0.0005	0.0001
Rash-related	26.14	5	0.0150	0.0003	0.0011	0.0003
Renal failure	37.05	17	0.0510	0.0010	0.0003	0.0000
Thrombocytopaenia	21.13	22	0.0660	0.0013	0.0043	0.0117
Vomiting	4.75	2	0.0060	0.0001	0.0002	0.0005
New primary malignancy	40.33	2	0.0060	0.0001	0.0001	0.0001
Key: AE, adverse event; BORT, bortezomib; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide						

Costs and utilities were assigned to each AE and multiplied by the cycle probability to get an average cost and disutility per cycle. For the utility calculation, the average durations of AEs were calculated from the patient level data from the TMM1 study and used to weight the disutility associated with each AE (Table 67). The average duration of each specific AE was assumed equal across all comparators in the model.

5.3.5 Validation of clinical parameters and variables

5.3.5.1 Model vs clinical trial validation

The clinical parameters and variables in the model were validated by:

- Comparing the clinical outcomes (OS, PFS, ToT and number of AEs) in the model with those from the TMM1 clinical trial that informed the model
- Clinical validation (see Section 5.3.5.2) and generalisability to current UK practice
- External and internal quality-assured processes

Table 68 shows that the clinical outcomes in the model, after approximately two years (26 treatment cycles with IXA+LEN+DEX). Table 68 highlights that the clinical outcomes in the model after approximately two years closely match the trial outcomes of OS, PFS, ToT and number of AEs for the comparison of IXA+LEN+DEX with LEN+DEX at 1 prior therapy and 2+ prior therapies. In replicating these outcomes, the economic model gives an accurate representation of the clinical outcomes from the TMM1 clinical trial.

The data for the BORT+DEX comparison were obtained from an NMA and so model estimates cannot be directly compared with trial estimates. However, clinical validation of these estimates is ongoing.

Table 68 shows that for IXA+LEN+DEX and LEN+DEX the number of AEs were slightly overestimated by the model – however, this was seen in both treatment arms and so is not thought to bias results.

Table 68: Comparison of clinical outcomes with model outcomes

Outcome	Clinical trial result	Model result	Clinical trial result	Model result
Mean survival (months) 1 prior therapy population (n=425)				
	IXA+LEN+DEX		**BORT+DEX**	
Overall Survival	21.01	20.87	N/A	16.56
Progression-free survival	15.73	15.86	N/A	15.05
Time on treatment	15.17	15.19	N/A	5.15
Mean survival (months) 2+ prior therapies population (n=297)				
	IXA+LEN+DEX		**LEN+DEX**	
Overall Survival	20.89	21.14	19.33	19.77
Progression-free survival	16.56	16.63	12.94	13.87
Time on treatment	15.52	15.86	13.84	13.98

Adverse events (number of events)						
	IXA+LEN+DEX (n=360)		**BORT+DEX (n=377)**		**LEN+DEX (n=360)**	
	Clinical trial result	**Model result (1 prior line, 2+ prior lines)**	**Clinical trial result**	**Model result**	**Clinical trial result**	**Model result**
Anaemia	40	55.79, 58.07	72	57.82	59	77.51
Cardiac failure	8	12.26, 12.76	7	5.64	6	8.91
Deep vein thrombosis	2	2.72, 2.84	-	1.39	3	3.82
Diarrhoea	28	38.11, 39.67	30	24.14	8	10.18
Fatigue	14	19.06, 19.84	45	36.19	9	11.45
Upper respiratory tract infection/Pulmonary-related	3	4.09, 4.25	6	4.83	2	3.82
Ischaemic heart disease	2	2.72, 2.84	0	0	3	3.82
Nausea	6	0.00, 0.00	2	0	0	0.00
Neutropenia	151	210.23, 218.82	43	34.58	114	157.28
Peripheral neuropathy	1	1.36, 1.42	55	44.21	3	3.82
Pneumonia	27	48.99, 50.99	39	31.37	36	49.59
Pulmonary embolism	8	10.90, 11.34	1	0.81	8	10.18

Rash-related	16	27.23, 28.34	-	2.32	5	6.36
Renal failure	6	8.17, 8.51	0	0	17	21.63
Thrombocytopaenia	75	103.31, 107.53	118	94.55	22	27.99
Vomiting	4	5.38, 5.67	5	4.03	2	2.55
New primary malignancy	5	1.36, 1.42	-	0.93	2	2.55
Key: BORT, bortezomib; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; n, number						

Felix et al. (2013) [188] estimated the quantitative relationship between median time-dependent endpoints, including PFS, and median OS in patients with MM. The authors found that for every 2.45 month increase in median PFS one should expect a 2.45 month increase in median OS. This estimate was obtained adjusting for differences in the study demographics, patient type, surrogate endpoint type, publication year, and MM treatments including THAL, BORT, or LEN.

The median PFS was not reached for IXA+LEN+DEX in the IA1 data cut. Therefore, to compare the outcomes of the TMM1 study with the results of the Felix paper the IA2 data cut is considered. This considers the most recent data available from the TMM1 study.

The IA2 data cut reports that the median PFS for IXA+LEN+DEX and LEN+DEX in the 1 prior line population is 18.7 and 17.6 months, respectively. The median PFS for these treatments in the 2+ prior therapies population is 22.0 and 13.0, respectively. In theory, using the results from the Felix paper, this should translate into a median OS of 45.8 and 43.1 months for the 1 prior therapy population, for IXA+LEN+DEX and LEN+DEX, respectively. For the 2+ prior therapies population, this should translate into a median OS of 53.9 and 31.9 months for IXA+LEN+DEX and LEN+DEX, respectively. Given that median OS has not been reached in the IA2 dataset, these results cannot be compared with the clinical outcomes of the TMM1 study.

However, using the Felix paper, it can be predicted that with more mature OS data the OS benefit to be gained could be up to 3 months in the 1 prior therapy population and up to 22 months in the 2+ prior therapies population.

Takeda recognise that these inferences are based on an estimated relationship between time-dependent covariates and OS. However, in the ACD and ERG report published in response to the NICE submission (TA338) the Appraisal Committee and ERG commented that the ratio from the Felix paper could be used to assess the face validity of results.[188] A comparison of the median OS and median PFS estimates obtained from the clinical SLR detailed in Section 4.1 is presented in Table 69. The ratios of median OS to median PFS seen in the literature vary from 1.58 to 5.04 – with an average of 3.16, suggesting that the relationship established in the Felix paper may provide a conservative estimate.

Cartier et al. (2015) [189] consider the relationship between treatment effects on PFS and OS in MM. These results show a strong positive correlation between hazard ratios for PFS and OS, indicating that the treatment effects on PFS and OS in MM are positively associated. These findings also hypothesise that the extended PFS observed in the TMM1 study may lead to an OS benefit.

Therefore, Takeda believe that the OS estimates based on immature interim datacuts do not yet accurately reflect the OS benefit that could be achieved through treatment with IXA+LEN+DEX. Further more mature data is required from the IA3 and potentially final OS data cuts to provide estimates that are more reflective of the observed increases in PFS, as well as reducing the uncertainty within the model.

Table 69: Comparison of the median OS: PFS ratio with those observed in other MM literature

Study	Population	Treatment	Median OS	Median PFS	Ratio
Montefusco et al. (2015)	1+ prior lines population	BORT+DEX	34	14	2.43
Dimopoulos et al. (2016)	RRMM	BORT+DEX	24.3	9.4	2.59
Zagouri et al. (2016)	RRMM	LEN+ intermediate DEX	20	10	2.00
Zagouri et al. (2016)	RRMM	LEN+LD-DEX	41	26	1.58
San Miguel et al. (2014)	RRMM	BORT+DEX	30.39	8.08	3.76
San Miguel et al. (2014)	RRMM	PANO+BORT+DEX	33.64	11.99	2.81
Richardson et al. (2014)	RRMM	POM	13.6	2.7	5.04
Richardson et al. (2014)	RRMM	POM+LD-DEX	16.5	4.2	3.93
San Miguel et al. (2013)	RRMM	HD-DEX	8.1	1.9	4.26
San Miguel et al. (2013)	RRMM	POM+LD-DEX	12.7	4	3.18

Key: BORT, bortezomib; DEX, dexamethasone; HD-DEX, high-dose dexamethasone; LD-DEX, low-dose dexamethasone; LEN, lenalidomide; PANO, panobinostat; POM, pomalidomide; RRMM, relapsed and refractory multiple myeloma

Clinical validation of the parameters and model structure is detailed in the section below. Finally, the model was also quality-assured by internal processes at the company who built the economic model and through an external process by an independent health consultancy. In these processes, an economist not involved in the model's construction reviewed the model for coding errors, inconsistencies and the plausibility of inputs.

5.3.5.2 Clinician validation

Six clinicians were approached for validation of the economic model and associated inputs. These included six haematologists from hospitals across England and Wales.The questions posed to each clinician are presented in Table 70.

Feedback from clinicians performed via semi structured interviews was used to confirm the clinical plausibility of results and to assess the generalisability of model results to current UK practice. It was considered that the OS data were too immature to make valid inferences and that the ToT data were not representative of the

proportion of patients receiving LEN+DEX in UK clinical practice. Clinicians agreed that, given the data, the parametric curves for OS, PFS and ToT fit the data well. However, long term extrapolated estimates for OS were considered to have uncertain clinical plausibility and for ToT not prepresentative of clinical practice, and likely to be overestimates.

The clinical feedback received was that although the mean ToT over the approximate two-year period (26 treatment cycles) presented in Table 68 were clinically plausible, the proportion of patients remaining on treatment after 26 treatment cycles was higher than usually observed in clinical practice in England. This was confirmed by a presentation by Cathy Williams at the 2012 ASH conference, the authors presented results from RWE considering the UK experience with long-term LEN treatment. This study found that 17.59% of patients would remain on treatment after 24 treatment cycles.

Table 70: Clinician validation

Question	Feedback	Learnings for the submission
How is BORT delivered in routine practice?	BORT is commissioned for 32 injections but heterogeneity regarding treatment schedule. BORT is delivered by SC injection.	In line with the SPC, this coincides with the 32 injections (four injections for eight treatment cycles) modelled. The model considers BORT administered by SC.
Is it clinically plausible to model 3rd line treatment using data from patients with 2+ prior therapies?	It was agreed that 4th line was a small proportion of the 2+ therapy group in the TMM1 clinical trial and so outcomes would mostly reflect a 3rd line positioning	The data for 2+ prior lines of therapy is used to proxy 3rd line positioning in this submission
The fit of the Weibull curve to the PFS data for 1 prior line and 2+ prior lines were presented to clinicians. The mean PFS estimated by the model over 26 treatment cycles were presented to clinicians for 1 prior line and 2+ prior lines. Clinicians were asked to comment.	Clinicians responded that the curves provided a sensible fit to the data	
The fit of the delayed exponential and the generalised gamma curve to the OS data for 1 prior line and 2+ prior lines, respectively, were presented to clinicians. The mean OS estimated by the model over 26 treatment cycles were presented to clinicians for 1 prior line and 2+ prior lines. Clinicians were asked to comment.	Clinicians responded that the curves provided a sensible fit to the data	
The fit of the generalised gamma curve and the exponential curve to the ToT data for 1 prior and 2+ prior therapies were presented to clinicians. The mean ToT after 26 treatment cycles with LEN+DEX is estimated to be 13.9 months in the 2+ prior therapies population. The proportion of patients	Clinicians felt that this was high in comparison with current UK practice	A scenario analysis considers using UK real world data to predict ToT representative of UK practice. A proportional decline in ToT is assumed for IXA+LEN+DEX and BORT+DEX.

remaining on treatment after 26 treatment cycles is 31.88%. Clinicians were asked to comment.		
Is it clinically plausible for patients to stop treatment with LEN+DEX for reasons other than progression or TRAEs?	In current UK practice, patients stop treatment with LEN+DEX at progression or at emergence of TRAEs (whichever occurs first). It was estimated that 5-10% of patients would stop before progression due to TRAEs.	In the TMM1 clinical trial patients received treatment past progression – particularly in the LEN+DEX arm. This highlights that the treatment schedule in the TMM1 data is not representative of current UK practice and further emphasises the need of real world evidence for ToT for LEN+DEX and IXA+LEN+DEX. A scenario analysis considers capping ToT by PFS.
Key: BORT, bortezomib; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; OS, overall survival; PFS, progression free survival; SPC, summary of product characteristics; ToT, time on treatment; TRAE, treatment related adverse events		

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality-of-life data from clinical trials

5.4.1.1 Overview of data

Section 3.2 provides an overview of the impact of MM. As well as the physical symptoms associated with MM, MM treatment places a substantial psychological burden on patients, disrupting social activities, decreasing independence, rendering a patient unable to plan for the future and impacting on relationships.

Baz et al. (2015) find that treatment of MM is associated with a decline in HRQL. The authors commented that treatments often cause TRAEs and can have demanding administration and monitoring schedules. Through the use of semi-structured interviews, it was determined that patients receiving oral regimens do not experience any inconvenience associated with treatment relative to those receiving IV or SC regimens.

HRQoL data were collected in the TMM1 clinical trial using the EORTC-QLQ-C30, the EORTC-QLQ-MY20 and the EQ-5D. The EORTC QLQ-C30 assesses the quality of life of cancer patients and the EORTC QLQ-MY20 focuses specifically on patients with MM. HRQoL was measured in the TMM1 study at baseline, every 4 weeks until disease progression and every 12-weeks post-progression until study close.

The EORTC QLQ-C30 and EORTC QLQ-MY20 cannot be used directly in economic evaluation as they do not incorporate preference information required for estimating utility values used to calculate QALYs. In line with the NICE Methods Guide the data from the EQ-5D collection was used in the economic analysis.[185]

Data from the ITT population from the TMM1 study was utilised in this utility analysis to maximise the predictive power of the regression equation; the number of observations significantly reduces when looking at the 1 prior and 2+ prior population subgroups. A repeated measurement mixed model was used to predict EQ-5D utility values based on:

- Response
    - Very good partial response (VGPR+)
    - Partial response (PR)
    - Stable disease (SD)
    - Progressed disease (PD)
- Whether a patient was ≤3 months prior to death
- Hospitalisations
- Grade 3 or 4 TRAEs
- New primary malignancies

These variables were considered relevant to a patient's HRQoL, following feedback from clinicians. The regression model includes both the occurrence of AEs and hospitalisation as covariates. This is appropriate as, although these measures are likely to be correlated, it allows changes in HRQoL to be picked up for AEs that do not results in hospitalisation as well as those that do. By the same measure, it allows for changes in HRQoL to be picked up for hospitalisations that are not caused by TRAEs as well as those that are.

Flags were created for each type of event indicating whether each EQ-5D measurement was affected by the occurrence of an event or not. The flag had a value of 0 if, at the time of the EQ-5D measurement, the event of interest did not occur and a value of 1 if the event occurred. The EQ-5D assessment had to have occurred up to two weeks before or up to 2 weeks after the actual date of the AE for the utility measure to be considered i.e. if any utility assessment fell within these four-week time windows then it was considered as being affected by the event. It was therefore possible that a utility assessment was affected by a disease-related event, by a TRAE, by both, or by none of these.

A mixed effect regression framework took the repeated measures structure of the data into the account. The EQ-5D data were converted into utilities using the EQ-5D UK Tariff values and then transposed into a utility decrement using "decrement = 1 – utility".[190] The decrements were used as dependent variables in the regression model with response status, hospitalisation, TRAEs, new primary malignancy, whether a patient is within 3 months prior to death, treatment allocation and time as independent variables, with interactions between time and response status.

Different variance-covariance structures were fitted to the data and the compound symmetry matrix was found to be the best fitting form. Different distributions and link functions were also compared:

- Normal model: Link = ID, distribution = normal
- Lognormal model: Link = log, distribution = normal
- Gamma model: Link = log, distribution = gamma

These different specifications were tested against each other using the Likelihood Ratio test. The Gamma distribution provided the best fit. Furthermore, the parameterisation of the model was reduced: treatment was found not to have an impact on the EQ-5D estimates, and utilities were found not to change over time. Therefore, a simple model with a Gamma distribution, a log link, a compound symmetry variance matrix and health states as independent variables was used as the final model to predict utility values. The utility coefficients from the regression are displayed in Table 71. Resulting utility values by response status are:

- VGPR+: 0.712
- PR: 0.674
- SD: 0.653
- Post progression: 0.654

Note that the utility value associated with post-progression is higher than that of stable disease. This is likely caused by the fact progressed patients have moved onto subsequent lines of therapy and so may be responding to treatment at next line. The impact of subsequent therapy was not considered in the regression equation due to lack of data once a patient has progressed and moved onto subsequent lines of therapy. Therefore, this represents a conservative estimate of the HRQoL associated with a patient in the progression stage.

Utility decrements associated with hospitalisations, grade 3/4 TRAEs, new primary malignancy and whether a patient was less than 3 months prior to death were estimated as the difference in utility for the VGPR+ health state with and without the events:

- Hospitalisations: -0.071
- TRAEs: -0.016
- New primary malignancy: -0.300
- Within 3 months prior to death: -0.132

The results from this regression show that new primary malignancies and whether a patient is ≤3 months prior to death have the greatest effect on utility. Both new primary malignancies and whether a patient is within 3 months prior to death significantly reduce patient's HRQoL. Variables associated with response status were also found to be significant at the 5% level. Although the coefficients associated with TRAEs and hospitalisations are not significant – these estimates are included in the economic model for completeness.

Table 71: Utility coefficients for parameters obtained using the EQ-5D from the TMM1 trial

Parameter	Coefficient	Standard Error	95% Confidence Limits	95% Confidence Limits	Z	Pr > |Z|
Intercept	-1.245	0.038	-1.319	-1.170	-32.950	<.0001
PD	0.182	0.054	0.077	0.287	3.400	0.001
PR	0.122	0.056	0.012	0.232	2.180	0.029
SD	0.187	0.061	0.068	0.305	3.080	0.002
Hospitalisation	0.219	0.203	-0.178	0.617	1.080	0.279
Grade 3 or 4 TRAE	0.055	0.036	-0.016	0.127	1.52	0.13
New Primary Malignancy	0.713	0.052	0.611	0.815	13.70	<.0001
EOL 0-3 months pre-death	0.378	0.081	0.219	0.537	4.65	<.0001
Key: EOL, end of life; EQ-5D, EuroQol 5 dimensions; PD, progressed disease; PR, partial response; SD, stable disease; TRAE, treatment related adverse events						

In the base case, the aforementioned regression equation was used to estimate HRQoL for patients in the 1 prior therapy and 2+ prior therapies populations. Utilities were estimated by response status and adjusted using the utility decrements accordingly. Scenario analyses considered using the utilities reported in the NICE submission for LEN and POM for the treatment of RRMM (TA171 and TA338, respectively).[25,97] The NICE submission TA171 used utility values from van Agthoven et al. (2004); [182] this study considered a newly diagnosed MM population and did not account for HRQoL loss due to TRAE. The NICE submission TA338 performed a similar regression to this submission, based on data from the MM-003 trial.

Both IXA+LEN+DEX and LEN+DEX are all-oral regimens and so the HRQL captured within the TMM1 clinical trial would not have captured any HRQL loss from IV or SC administrations. Therefore, a utility decrement was applied to patients on treatment with an IV or SC regimen. The utility decrement of 0.025 for IV or SC treatments was obtained from the NICE submissions of erlotinib and gefitinib for the treatment of non-small cell lung cancer. No data were available specific to RRMM.

However, this estimate was considered a conservative estimate due to the relative frailty of RRMM patients. A scenario analysis considered no utility decrement associated with IV or SC treatments.

5.4.1.2 Regression model inputs

Response status

IRC assessed ORR were measured at the end of each treatment cycle in the TMM1 study. Utilities associated with VGPR+, PR and SD were applied to the pre-progression health state in the model and utilities associated with PD were applied to the post-progression health state. For all patients in the pre-progression health state the distribution of patients across VGPR+, PR and SD relevant to each treatment were assumed equal for each cycle. For example, if the data show that of patients in pre-progression 25% have VGPR+, 25% have PR and 50% have SD, then this distribution was assumed for all cycles in pre-progression. The number of patients achieving each response status was obtained from the patient level data from the TMM1 study for the 1 prior and 2+ prior ltherapies populations. Response status was considered by subgroup as data show a significant difference in response status between the 1 prior and 2+ prior therapies populations. Table 72 shows the number of patients experiencing each response status in the TMM1 trial.

Table 72: Response status from the TMM1 trial

Population	Therapy	Missing	PD	SD	PR	VGPR+
All TOURMALINE (n=722)	IXA+LEN+DEX	21	17	40	109	173
	LEN+DEX	24	20	59	118	141
	Total	45	37	99	227	314
1 prior line patients only (n=425)	IXA+LEN+DEX	12	10	27	68	95
	LEN+DEX	9	12	33	66	93
	Total	21	22	60	134	188
2+ prior line patients only (n=297)	IXA+LEN+DEX	9	7	13	41	78
	LEN+DEX	15	8	26	52	48
	Total	24	15	39	93	126
Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; PD, progressed disease; PR, partial response; SD, stable disease; VGPR+, very good partial response						

The number of patients achieving PR+ and PR for BORT+DEX were obtained from the PANORAMA-1 trial. These data were used to estimate the proportion of patients achieving a VGPR+ response. Similarly, the number of patients in PD and the number of patients with SD or worse were obtained from the PANORAMA-1 trial. These data were used to estimate the proportion of patients achieving SD and PD with treatment with BORT+DEX.

To estimate the relative proportion of patients in the PR+ and SD or worse response categories for BORT+DEX an odds ratio, estimated by the NMA described in section 4.10 was applied to the proportion of patients with PR+ in the LEN+DEX arm of the TMM1 trial.

Due to data limitations, no network could be formed incorporating BORT+DEX in the 1 prior therapy population for ORR. Therefore, the odds ratio estimated using the network for the 1+ prior therapies population is assumed in the model. The odds ratio was estimated to be: 2.28 [95% CI: 1.06 – 4.93] relative to the proportion of patients with PR+ in the LEN+DEX arm of the TMM1 trial (see Table 65). The final distribution of patients across response statues is presented in *Table 73.*

In the base case, the model uses the trial data to inform the IXA+LEN+DEX response status in the one prior therapies and 2+ prior therapies populations (Table 70). A scenario analysis considered the impact of using the odds ratio for IXA+LEN+DEX relative to LEN+DEX for the 1+ prior therapies population obtained from the NMA for the proportion of patients with PR+ and estimating the proportion of patients with each response status (as performed for BORT+DEX)), see Table 46 in Section 4.10 This is included in the scenario which considered all relative efficacy estimates for IXA+LEN+DEX vs. LEN+DEX from the NMA, see Sections 5.8.1 and 5.82 for the 1 prior and 2+ prior therapies, respectively.

Table 73: Response status by population subgroup

Proportion	VGPR+	PR	SD	PD	Proportion pre-progression
1 prior therapy population					
IXA+LEN+DEX	47.50%	34.00%	13.50%	5.00%	95.00%
BORT+DEX	3.18%	85.76%	9.74%	1.32%	98.68%
2+ prior therapies population					
IXA+LEN+DEX	56.12%	29.50%	9.35%	5.04%	94.96%
LEN+DEX	35.82%	38.81%	19.40%	5.97%	94.03%
Key: BORT, bortezomib; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; PD, progressed disease; PR, partial response; SD, stable disease; VGPR, very good partial response					

Hospitalisations

Hospitalisations were used in the utility regression analysis, included as a potentially relevant determinant of quality of life; if a patient was hospitalised during the quality of life assessment, we would expect their quality of life to be lower.

The number of hospitalisations for IXA+LEN+DEX and LEN+DEX and for the pre-progression and post-progression health states were obtained from the TMM1 trial data. To avoid double counting, any hospitalisations caused by TRAEs were excluded from the analysis. TMM1 collected hospitalisation episodes for four different types of inpatient care: acute care, ICU care, palliative care, hospice care. No significant difference was found between the 1 prior and 2+ prior therapies populations, as such the hospitalisation episodes were pooled to improve the reliability of the results. The data were stratified by treatment; differences were found between hospitalisation rates for IXA+LEN+DEX compared with LEN+DEX.

The rates of hospitalisations were calculated using the number of events and the patient years of follow up. This was then converted into a probability per cycle in the economic model. This calculation approach considers both the number of events occurring in the trial and the trial follow-up period or exposure time in patient-years. The number of hospitalisations by treatment are presented in Table 74. The probability per patient per cycle is shown in Table 75 for each type of hospitalisation, for each treatment and by progression status. Due to lack of data associated with hospitalisation rate for BORT+DEX, it is assumed that the probability of hospitalisation per patient cycle for BORT+DEX is assumed equal to LEN+DEX.

Table 74: Number of hospitalisations by treatment

	IXA+ LEN+DEX - Number of admissions*		LEN+DEX - Number of admissions*	
	Pre-progression	Post-progression	Pre-progression	Post-progression
Acute care	87	17	96	15
ICU care	7	1	12	3
Palliative care	8	2	5	5
Hospice care	10	0	10	1
Key: ICU, intensive care unit *excluding hospitalisations caused by TRAEs				

Table 75: Probability of hospitalisation by treatment

	IXA+LEN+DEX - Probability per patient per cycle		LEN+DEX - Probability per patient per cycle	
	Pre-progression	Post-progression	Pre-progression	Post-progression
Acute care	0.0043	0.00547	0.0049	0.00363
ICU care	0.0003	0.00032	0.0006	0.00073
Palliative care	0.0004	0.00064	0.0003	0.00121
Hospice care	0.0005	0.00000	0.0005	0.00024
Key: ICU, intensive care unit *excluding hospitalisations caused by TRAEs				

5.4.1.3 Grade 3 or 4 adverse events

The proportion of patients experiencing TRAEs (including new primary malignancies) per cycle is discussed in Section 5.3.4.

5.4.1.4 End of life

The proportion of patients within the final 3 months of life was estimated using the proportion of patients in the death health state. Each cycle the proportion of patients predicted to die over the next 3 months were summed together to approximate the proportion of patients within the final 3 months of life.

5.4.2 Mapping

No mapping has been used for utility elicitation.

5.4.3 Health-related quality-of-life studies

5.4.3.1 Identification of studies

An extensive SLR of health-related quality of life (HRQoL) was conducted between 3rd and 21st August 2015. This has been updated using the same search terms and strategy to provide the evidence base for this submission. Updated searches were carried out in April 2016 and October 2016 to cover the periods of August 2015 to April 2016 and April 2016 to October 2016. Full details of the search strategy are provided in Appendix 10.

The SLR was performed to identify and summarise the relevant HRQoL data evidence available for adult patients with RRMM. Studies considering a newly diagnosed MM population were excluded. Studies that reported on MM in general and did not report the proportion of newly diagnosed patients in the cohort were also excluded. Studies of patients undergoing non-medical therapies, stem cell transplantation, bone marrow transplantation or surgery for bone metastasis were excluded.

Studies were required to report utility values derived from generic HRQoL instruments, such as the SF-36, the EQ-5D and the HUI. Studies reporting utility values derived from disease specific measures were excluded, however, studies mapping from disease specific measures to generic measures were included. Furthermore, visual analogue scales (VAS) measuring pain rather than HRQoL were also excluded. The criteria to include only generic utility measures stems from the NICE Methods Guide which advocates that the generic EQ-5D is the preferred measure of HRQoL.

Reviews (including SLRs), letters, cost-effectiveness analyses and economic evaluations were excluded at the screening stage, the reference lists associated with SLRs were screened to ensure all available evidence is included. Cost-effective and economic evaluations identified were cross-checked with the economic SLR (section 5.1) to ensure these studies had been captured in the economic SLR. Only conference proceedings or abstracts presented within the last year were included, as any high-quality studies should have been reported as journal articles within this time. Any abstracts older that this were excluded at the screening stage. Only conferences with freely available abstracts were included.

5.4.3.2 Description of identified studies

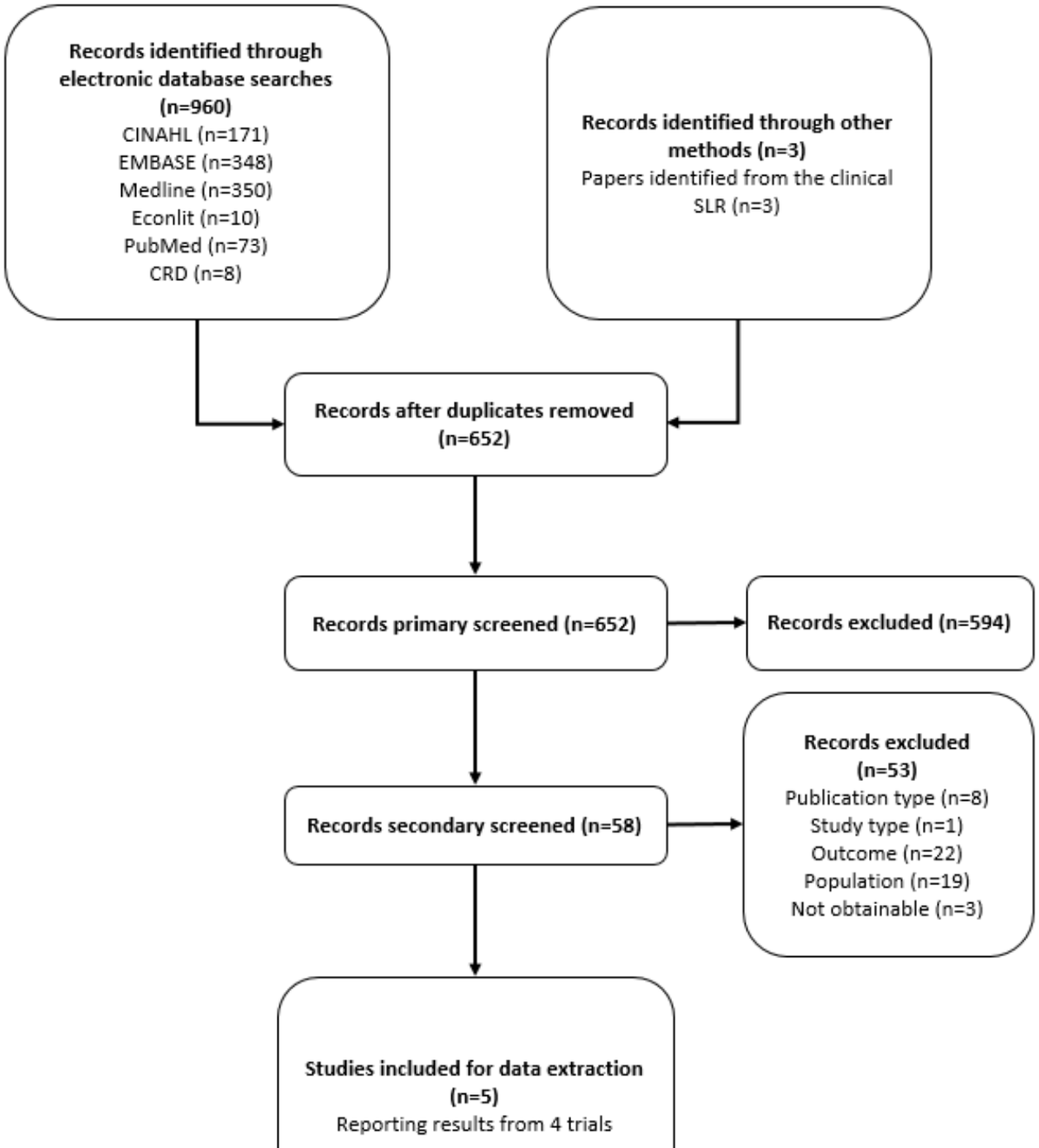
The results of the original HRQoL search and the two updates have been pooled for the purposes of reporting. In total, 963 studies were identified; 960 identified from the systematic databases searched and a further three identified from the clinical SLR. Primary screening of titles and abstracts against the pre-specified inclusion and exclusion criteria (as presented in Appendix 10) was performed for 652 records after removing 311 duplicates. Of these, 58 were included for full text screening. 53 papers were excluded following secondary screening, the most common reasons for exclusion at this stage were outcome (n=22) and population (n=19).

After screening, only five papers were included for data extraction, which reported the results from four different trials:

- Song et al. (2015) and Weisel et al. (2015) detailed results from the MM-003 clinical trial.
- Acaster et al. (2013) report on a cross-sectional survey of patients with RRMM.
- Proskorovsky et al. (2014) discuss a cross-sectional study which used mapping to obtain EQ-5D utilities from the EORTC QLQ-C30 and EORTC QLQ-MY20.
- Kvam et al. (2011) is a prospective study reporting utility values derived from the EQ-5D.

The flow diagram of the economic and cost and resource use SLR is presented in Figure 42.

Figure 42: PRISMA diagram for economic and cost SLR [170]


Records identified through electronic database searches (n=960)
CINAHL (n=171)
EMBASE (n=348)
Medline (n=350)
Econlit (n=10)
PubMed (n=73)
CRD (n=8)
Records identified through other methods (n=3)
Papers identified from the clinical SLR (n=3)
Records after duplicates removed (n=652)
Records primary screened (n=652)
Records excluded (n=594)
Records secondary screened (n=58)
Records excluded (n=53)
Publication type (n=8)
Study type (n=1)
Outcome (n=22)
Population (n=19)
Not obtainable (n=3)
Studies included for data extraction (n=5)
Reporting results from 4 trials

Centre for Reviews and Dissemination; n, number; PRISMA, preferred reporting items for systematic reviews and meta-analyses; SLR, systematic literature review

Table **76** provides a summary of each HRQoL study identified.

Table 76: HRQoL studies

Author, Year	Location	Study design	Population	N	Outcomes for generic HRQoL instrument	
Song et al. (2015) [191] **Weisel et al. (2015)**[192]	International	Open-label randomised phase 3 trial (MM-003 trial)	RRMM patients that had failed at least two previous treatments of BORT and LEN. Median age: 64 years Mean age (SD): 63.6 (9.34)	N=455, n=433 completed HRQoL measurements (n=289 POM+LoDEX arm; n=144 in HiDEX)	**EQ-5D data#:** Change from baseline to cycle 10: POM+LoDEX: 0.05 HiDEX: -0.11 Mean score: POM+LoDEX: Baseline: 0.63 Best Response before progression: 0.73 (p<0.05 vs. baseline) At progression: 0.50 HiDEX: Baseline: 0.58 Best Response before progression: 0.61 At progression: 0.50	
Acaster et al. (2013) [193]	UK	Cross-sectional postal survey	Patients aged >18 years with multiple myeloma. Mean age (SD): First-line treatment: 66.25 (10.15) First treatment free interval: 63.56 (7.80) Second-line treatment: 64.02 (8.83) Second treatment free interval: 64.66 (8.20)	N=370, n=358 (97%) had already received first line MM therapy	**Endpoint**	**Utility value (EQ-5D) Mean (SD)**
					First line treatment	0.63 (.26)
					First treatment free interval	0.72 (.26)
					Second line treatment	0.67 (.25)
					Second treatment free interval	0.63 (.29)

Author, Year	Location	Study design	Population	N	Outcomes for generic HRQoL instrument	
Proskorovsky et al. (2014)[194]	UK and Germany	Cross sectional study	Patients with MM representative of one out of four pre-defined study sub-groups: asymptomatic, mildly symptomatic, moderately symptomatic or severely symptomatic. Mean (SD) age: 66.4 (10.0)	N=154, [n=66 (43%) had received ≥1 prior therapy]: Symptom severity group- n (%) Asymptomatic: 17 (11%) Mildly symptomatic: 48 (31%) Moderately symptomatic: 50 (33%) Severely symptomatic: 39 (25%)	**Utility value (EQ-5D):** Mean (SD): 0.7 (0.3) Median (IQR): 0.73 (0.62-1.00)	
					By symptom group	**Utility value Mean (SD)**
					Asymptomatic	0.923
					Mildly symptomatic	0.806
					Moderately symptomatic	0.675
					Severely symptomatic	0.501
Kvam et al. (2011)[195]	Norway	Prospective study	Patients with MM irrespective of their disease status (newly diagnosed, plateau phase, relapse) or treatment. Median age (range): 66 (36-89)	N=239, n=69 (29%) were relapsed pts.	N=239 Improved: (n=79) Unchanged: (n=111) Deteriorated: (n=49)	Mean change (EQ-5D) (T2-T1)* +0.08 0.00 -0.10
					N= 222 Improved: (n=72) Unchanged: (n=105) Deteriorated: (n=45)	Mean change (15D) (T2-T1)* +0.03 0.00 -0.02

Key: BORT, bortezomib; EQ-5D, EuroQol 5-levels; HiDEX, high dose dexamethasone; HRQoL health related quality of life; LD-DEX, low dose dexamethasone; LEN, lenalidomide; MM, multiple myeloma; n, number; POM, pomalidomide; SD, standard deviation; UK, United Kingdom
Data presented in figures. Data reported in table have been estimated from figures.
*T1: questionnaires completed at inclusion; T2: questionnaires completed after 3 months (+/- 2 weeks)

Song et al. (2015) [191]and Weisel et al. (2015) [192] report HRQoL data from the MM-003 trial published in 2013 (San Miguel et al. (2013)).[150] The MM-003 trial was a multicentre, international, randomised, open-label, phase III trial. The trial compared the efficacy and safety of POM+LD-DEX versus HiDEX alone in RRMM patients. Patients enrolled in the trial had failed at least two previous treatments of BORT and LEN and so HRQoL data reflects a 2+ prior therapies population. As part of the HRQoL assessment, three HRQoL instruments were used: the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC QLQ-MY20 and EQ-5D. Questionnaires were completed at baseline, on day 1 of each treatment cycle and at discontinuation. HRQoL scores were calculated from baseline through to cycle 10. Median follow-up was 10 months. Patients progressing on HiDEX were allowed to receive POM+LD-DEX in a companion MM-003C trial. These patients were not included in the HRQoL analysis after progression. Of the 455 patients enrolled in the trial, 433 completed HRQoL questionnaires and were included in the analysis (POM+LD-DEX; n=289; HiDEX; n=144). Of the 289 patients randomised to POM+LD-DEX, 50 (17.3%) had EQ-5D data available at cycle 10 versus 7 of 144 (4.8%) from the HiDEX arm. Health utility scores are presented in Table 76; change from baseline to cycle 10 was 0.05 for patients in the POM+LD-DEX arm versus -0.11 for patients in the Hi-DEX arm. Mean utility scores for patients at baseline, best response and disease progression for each arm were also reported. Best response utility values improved from baseline in both groups and this improvement was significant ($p<0.05$) in the POM+LD-DEX arm only.

Acaster et al. (2013) [193] reported utility values derived from a survey of UK MM patients (n=402). 32 cases were excluded giving a total for analysis of n=370, the majority of whom had already received first line MM therapy (n=358). The survey comprised of socio-demographic information and three quality of life instruments (the EORTC-QLQ-C30, the EORTC-MY20 and the EQ-5D). Acaster et al. (2013) [193] report utility values as follows: first line treatment (n=12), first treatment free interval (n=177), second line treatment (n=59), second treatment free interval (n=122) see Table 76.

The study by Proskorovsky et al. (2014) [194]was a mapping study to develop a mapping algorithm using HRQoL data from EORTC QLQ-C30 to estimate EQ-5D utility values in patients with MM. Authors used data from a cross-sectional study in MM patients based in the UK and Germany. [196] Eligibility criteria were adult patients with MM. Patients were not eligible if they had undergone an autograft transplantation within the past 3 months or if they had received and experimental treatment. Patients were categorised in four pre-defined groups: asymptomatic, mildly symptomatic, moderately symptomatic or severely symptomatic. Data from three HRQoL questionnaires: EORTC QLQ-C30, EORTC QLQ-MY20 and EQ-5D were collected at the first treatment visit after study enrolment. Of the 154 enrolled patients, 66 (43%) had received ≥1 prior therapy. It should be noted that HRQoL data were collected for the whole population in the trial by severity groups and data for the sub-group of patients who had received ≥1 prior therapy was not available. Details of the patient population and utility data are presented in Table 76.

The final study by Kvam et al. (2011) [195] was a prospective study based in Norway. The aim of the study was to assess HRQoL in MM patients using the EORTC QLQ-C30 questionnaire and two generic preference based instruments: EQ-5D and 15D. Results were compared to evaluate responsiveness and determine minimal importance difference. MM patients regardless of their disease status (newly diagnosed, maintenance therapy or relapsed) were eligible. Patients completed the questionnaires at baseline and after 3 months (+/- 2 weeks). A total of 239 MM patients completed the questionnaires of which n=69 (29%) were RRMM patients. The study reports mean change from baseline for EQ-5D and 15D, results are provided for the total population in the study and not for the sub-group of RRMM patients (see Table 76).

This submission uses data directly from the TOURMALINE-MM1 trial in the base case as this reflects the HRQoL experienced for patients receiving IXA+LEN+DEX and LEN+DEX directly. The resulting utility values by response status are: 0.712 for VGPR+, 0.674 for PR, 0.653 for SD and 0.654 for post-progression. None of the studies identified in the HRQoL SLR were considered relevant for inclusion in the economic model. For completeness, a

comparison of the results with the TOURMALINE-MM1 and reason for exclusion from the economic model is provided for each study below.

Song et al. (2015) and Weisel et al. (2015) report a utility score of 0.61-0.73 for best response before progression and 0.50 at progression. The estimates for best response before progression align with the estimates using the TOURMALINE-MM1 data. However, the post-progression estimate is much lower than observed in the TOURMALINE-MM1 trial. This may be due to differences in trial populations, for example the MM-003 trial considers 2+ prior therapies only and a larger proportion of patients are refractory to treatment. Therefore, these data are not considered representative of patients in the TOURMALINE-MM1 trial.

Acaster et al. (2015) report the utility value associated with second line treatment to be 0.67. This estimate is similar to the estimates obtained from the TOURMALINE-MM1 data. However, no data are provided for post-progression health states. The Proskorovsky et al. (2014) paper reported values ranging from 0.501 to 0.923 based on pre-defined subgroups. All utility estimates from the TOURMALINE-MM1 trial fall within this range, however as similar subgroups were not identified in the TOURMALINE-MM1 dataset these estimates are not comparable. Finally, Kvam et al. (2011) present results for a general MM cohort where only 29% of the patients are relapsed, as such these data are not considered relevant for inclusion within the economic model.

5.4.4 Adverse reactions

In the base case, the regression equation discussed earlier in this section was used to model the HRQL impact associated with AEs. AEs were included as an explanatory variable in the regression equation; the HRQL assessment had to have occurred up to two weeks before or up to 2 weeks after the actual date of the AE for the utility measure to be considered i.e. if any utility assessment fell within these four-week time windows then it was considered as being affected by the AE.

The mixed model initially attempted to estimate the utility decrement associated with individual TRAEs, however, some AEs were too scarce and the resulting utility estimates were unreliable (e.g. renal failure). This was also the case for AEs which had few HRQL assessments fall within their 4-week time window generating results which were counterintuitive, e.g. some AEs resulted in higher utility valuations compared to no AE (e.g. nausea, vomiting and rash). All these cases were problematic, hence, this analysis had several limitations. To address these issues a single value was estimated for any Grade 3 or 4 TRAE (except for new primary malignancy, which was considered separately). Whilst the HRQoL loss associated with TRAEs was assumed to be the same across the TRAEs, the duration of each AE was assumed to differ per type of event.

This method was chosen rather than including utility decrements associated with each event reported in TMM1 to make use of the HRQoL information reported in the TMM1 dataset and due to the lack of published utility decrements for each AE specific to MM patients who have received at least one prior therapy.

It is noted that this approach has limitations – notably that some events may have a more severe HRQoL loss than others which is not captured in this equation. Furthermore, clinical advice indicated that some Grade 3 or 4 haematological issues may be indicated in laboratory tests but may not impact a patients' HRQoL (anaemia, thrombocytopenia or neutropenia). Nevertheless, this approach has been used in previous NICE HTA submissions (for example: TA338)[97] and provides a method with which we can reliably estimate the average impact of TRAEs on HRQoL in the RRMM population.

The utility decrements associated with each treatment were multiplied by the duration of AE, sourced from the TMM1 trial (IA1 data cut). The duration weighted decrements were then multiplied by the probability of grade 3 or 4

TRAEs per cycle to provide overall AE-related utility decrements per cycle. The same utility decrements and durations of AEs were assumed for comparator treatments. The probability of grade 3 or 4 TRAEs per cycle varied for each comparator, see Section 5.3. Table 77 presents the utility decrements associated with each AE and the duration of each AE.

Table **78** presents the per cycle HRQoL utility decrement associated with each comparator.

Table 77: HRQoL utility decrements for each TRAE and mean duration of TRAEs

	Utility decrement	Mean duration (weeks)
Anaemia	-0.016	6.01
Cardiac failure	-0.016	1.62
Deep vein thrombosis	-0.016	1.63
Diarrhoea	-0.016	4.49
Fatigue	-0.016	9.05
Upper respiratory tract infection/Pulmonary-related	-0.016	2.20
Ischemic heart disease	-0.016	0.60
Nausea	-0.016	2.94
Neutropenia	-0.016	2.15
Peripheral neuropathy	-0.016	7.14
Pneumonia	-0.016	2.80
Pulmonary embolism	-0.016	8.08
Rash-related	-0.016	3.73
Renal failure	-0.016	5.29
Thrombocytopenia	-0.016	3.02
Vomiting	-0.016	0.68
New primary malignancy flag	-0.300	5.76
Key: HRQoL, health related quality of life; TRAE, treatment related adverse events		

Table 78: Per cycle utility decrements associated with TRAEs

Treatment	Per cycle HRQoL utility decrement weighted by probability of grade 3 or 4 TRAEs
LEN+DEX	-0.00115
IXA+LEN+DEX	-0.00157
BORT+DEX	-0.00350
Key: HRQoL, health related quality of life; TRAE, treatment related adverse events	

5.4.5 Health-related quality-of-life data used in cost-effectiveness analysis

Within the model, a regression equation (described earlier in this section) estimated utilities based on response status, hospitalisations, TRAEs (including new primary malignancies and whether a patient had ≤3 months to death. The regression equation was estimated using data from the TMM1 clinical trial. Due to lack of data the ITT patient level data were utilised, rather than 1 prior line and 2+ prior line specific data. Subgroup data were considered for

response status and whether a patient had ≤3 months to death and the ITT data were considered for TRAEs and hospitalisations.

The OS and response status data for BORT+DEX relative to LEN+DEX in the 1 prior line population was obtained from a NMA and from the PANORAMA-1 clinical trial for the TRAE data. The rate of hospitalisations for BORT+DEX was assumed the same as for LEN+DEX. No data were available to form a network specifically for the 1 prior line population for the BORT+DEX comparison. Therefore, estimates from the NMA considering ITT data were utilised.

The utility estimates applied in the model by health state are presented in Table 79. Base case utilities are compared with those from TA171 and TA338, which are considered in a scenario analysis.

Table 79: Utility values by health state

	TMM1 data	TA171	TA338
VGPR+ (pre-progression health state)			
VGPR+	0.712 (95% CI: 0.690-0.732)	0.810	0.750
Adverse event	0.696 (95% CI: 0.648-0.737)	0.696	0.696
New primary malignancy	0.412 (95% CI: 0.299-0.507)	0.412	0.412
Hospitalisation	0.641 (95% CI: 0.425-0.776)	0.641	0.612
≤3 months until end of life	0.580 (95% CI: 0.469-0.667)	0.580	0.512
PR (pre-progression health state)			
PR	0.674 (95% CI: 0.609-0.729)	0.810	0.750
Adverse event	0.658 (95% CI: 0.567-0.733)	0.658	0.658
New primary malignancy	0.375 (95% CI: 0.218-0.504)	0.375	0.375
Hospitalisation	0.604 (95% CI: 0.344-0.773)	0.604	0.604
≤3 months until end of life	0.542 (95% CI: 0.388-0.664)	0.542	0.542
SD (pre-progression health state)			
SD	0.653 (95% CI: 0.579-0.714)	0.810	0.650
Adverse event	0.636 (95% CI: 0.537-0.718)	0.636	0.636
New primary malignancy	0.353 (95% CI: 0.188-0.488)	0.353	0.353
Hospitalisation	0.582 (95% CI: 0.315-0.757)	0.582	0.582
≤3 months until end of life	0.521 (95% CI: 0.359-0.648)	0.521	0.521
PD (post-progression health state)			

PD	0.654 (95% CI: 0.587-0.711)	0.640	0.610
New primary malignancy	0.355 (95% CI: 0.196-0.486)	0.355	0.355
Hospitalisation	0.584 (95% CI: 0.322-0.755)	0.584	0.584
≤3 months until end of life	0.522 (95% CI: 0.366-0.646)	0.522	0.522
Key: PD, progressed disease; PR, partial response; SD, stable disease; TA, technology appraisal; VGPR, very good partial disease			

Using the base case method (regression analysis) a patient's HRQL is not constant over time. All explanatory variables included in the regression equation: response status, new primary malignancies, the number of TRAEs, the number of hospitalisations and whether a patient has ≤3 months to death, vary over time. The impact on utility associated with each of the explanatory variables is discussed in detail at the beginning of this section.

5.4.6 Impact of oral vs. non-oral treatments on HRQL

IXA is the first and only oral medication of its kind, a PI, that you can take at home. The use of an oral agent such as IXA reduces the treatment burden on both patients and carers, relative to IV and SC treatments; as discussed in Baz et al. (2015). Clinical experts have emphasised the importance of having access to oral therapies, given that many current treatment options are given IV or SC. AS LEN+DEX is also an oral regimen the utility benefit of oral treatments is likely captured in the utility regression which uses data from the TMM1 clinical trial.

Within the model a utility decrement is applied to patients on treatment for treatment options requiring IV or SC administration (BORT), the utility decrement (0.025) was obtained from two previous NICE appraisals in small-cell lung cancer, and recently accepted as part of the POM TA338 re-submission for the treatment of RRMM. As no MM, specific information is available, this decrement was included within the economic model while patients are receiving treatment with IV or SC therapies to account for the disruption to usual activities, pain and discomfort associated with non-oral therapies.

This decrement is likely to represent an underestimate of the impact in this population as, due to the frailty of patients with MM, greater disruption and impact to daily living is expected from repeated hospital admissions for administration of therapy.

5.5 Cost and healthcare resource use identification, measurement and valuation

Appendix 12 presents a table with all cost and resource use parameters used to evaluate the cost-effectiveness of IXA+LEN+DEX.

5.5.1 Resource identification, measurement and valuation studies

An extensive SLR of cost-effectiveness and cost and resource use studies was conducted between August and December 2015. This has been updated using the same search terms and strategy to provide the evidence base for this submission. Updated searches were carried out from March 2016 through April 2016 and again from

September 2016 to October 2016 to ensure that the latest available evidence is presented in this submission. The details of the search strategy, inclusion/exclusion criteria and associated PRISMA diagram are provided in Appendix 10. This section discusses the results associated with the cost only analyses.

20 cost analyses were identified in the SLR, reported in 23 publications. A summary of these studies is presented in Table 80.

Cost studies were most commonly published from the US perspective, with 8 studies reported in 9 publications. The remaining studies considered a French perspective (n=3; Lassalle et al. (2016), Touati et al. (2016) and Armoiry et al. (2011)), an Italian perspective (n=3; Gonzalez-McQuire et al. (2016), Koleva et al. (2011) and de Portu et al. (2011)), a Dutch perspective (n=2 reported in 4 publications; Gaultney et al. (2013), Franken et al. (2013), Franken et al. (2014) and Groot et al. (2004)), an Australian perspective (n=1; Lingaratnam et al. (2011)), a Chinese perspective (n=1; Zhou et al. (2016)), a Brazilian perspective (n=1; Clark et al. (2011)) and a UK perspective (n=1; Gooding et al. (2015)).

Data were most often obtained from retrospective electronic case files (n=8, reported in 10 publications). Except for one paper considering a Chinese perspective (Zhou et al. (2016)), the retrospective electronic report data were utilised in countries considering a European perspective. Claims data were used in 7 studies, reported in 8 publications; the majority of these studies considered a US perspective (n=6) with the remaining study considering a Brazilian perspective. The remaining studies used prospective data (n=1), published literature (n=1), pharmacy generated list prescriptions (n=1), patient completed questionnaires (n=1) and clinician completed questionnaires (n=1).

Information on hospitalisations was presented in 10 studies, reported in 12 publications. Of these studies, 5 report the cost attributed by hospitalisations only. Whereas, 5 studies provide more detail with regards to the number and/or length of hospitalisations. Gonzalez-McQuire et al. (2016) presented hospitalisation by treatment line, by treatment regimen and by progressed health state. Gooding et al. (2015) provide information on inpatient admissions. Teitelbaum et al. (2013) reports hospitalisation by treatment. Koleva et al. (2011) presents resource use associated with hospitalisation stratified based on age≤65 and age>65. Finally, Ghatnekar et al. (2008) reports hospitalisations by treatment line.

Six cost analyses include data on adverse event management, reported in seven publications. Three studies report uninformative cost data only, whereas three studies present information as to the rate and/or number of adverse events. Roy et al. (2015) presents the proportion of patients receiving each adverse event by treatment, including the following treatments: PANO+BORT+DEX, BORT+DEX, LEN+DEX, LEN+BORT+DEX, CARF+LEN+DEX, CARF and POM+DEX. Gooding et al. (2015) presents the number of adverse events received during the double RRMM period. Durie et al. (2013) reports the proportion of adverse events for LEN+DEX and BORT.

The economic model, as part of this submission, has not used the data from any of the cost and resource use studies identified in the SLR. Gooding et al. (2015) present the only UK specific data relevant to this submission; these results are compared with the model output to validate the inputs and methods used within the model.

Table 80: Cost analyses identified in the economic SLR

	Objective	Country of study	Population	Sample size	Data	Type of cost and resource use data reported	Results
Gonzalez-McQuire et al. (2016) [197]	To use real-world data to assess patient outcomes, and to estimate the healthcare resource utilisation and costs associated with the management of patients with symptomatic MM in Italy.	Italy	Aged 18 years or older with symptomatic MM In the 3 months prior to study initiation, the patient had fulfilled one of the following conditions: (1) had progressed after receiving one of several pre-specified MM treatment regimens (those most commonly prescribed) or (2) had received BSC and subsequently died	N=393	Data were obtained from electronic case report forms completed by oncologists and haematologists using retrospective data.	Outpatient consultations, radiography, scans and other procedures, concomitant medications, hospitalisation and laboratory tests Proportion of patients hospitalised by level of response. Proportion of patients experiencing at least one hospitalisation by therapy line. Distribution of hospitalisations across treatment periods. Treatment periods during which hospitalisations occurred by therapy line.	Total costs for all patients based on treatment and line of treatment for active treatment, treatment free interval and post-progression period. Distribution of costs by treatment period, active treatment/treatment free interval/post-progression (7%/7%/4% outpatient consultations, 10%/8%/15% radiography, scans and other procedures, 29%/19%/29% concomitant medications, 22%/33%/20% hospitalisations and 32%/33%/31% laboratory tests)
Blaudek et al. (2016) [198]	To estimate the economic impact of adding PANO to a U.S. health plan formulary as a treatment option with BORT+DEX	US	Adults aged ≥ 18 years who were initiating salvage therapy for RRMM, having previously been treated with ≥ 2 regimens that must have included a PI and an IMiD.	In a hypothetical commercial plan (1,000,000 covered lives), 72.3% of the population were estimated to be aged ≥ 18 years, and 0% were	Market share data from claims databases. The unit cost of each grade 3/4 AE was based on published literature	Drug, administration, prophylaxis and monitoring including: pharmacy, medical, hydration, complete blood count, oral prophylaxis, deep vein thrombosis/pulmonary	Total annual cost Commercial plan ($): Current=$2,213,703 vs future=$2,167,253, saving $46,450 Total annual cost Medicare plan ($):

	Objective	Country of study	Population	Sample size	Data	Type of cost and resource use data reported	Results
				aged ≥ 65 years.19 In a hypothetical Medicare plan, 17.0% of the population were estimated to be aged ≥ 18 years, and 83% were aged ≥ 65 years.	IV drug cost for commercial and Medicare plans were based on average sales price plus 6% without inflation for commercial costs (whereas the previous model inflated commercial intravenous drug costs to 123.5% of the Medicare rate).	embolism, ECG and grade 3/4 adverse events.	Current=$16,195,283 vs future=$15,853,113, saving $342,169 Per person per year Commercial plan ($): Current=$2.21 vs future=$2.17, saving $0.05 Per person per year Medicare plan ($): Current=$16.20 vs future=$15.85, saving $0.34 Per person per month Commercial plan ($): Current=$0.184 vs future=$0.181, saving $0.004 Per person per month Medicare plan ($): Current=$1.35 vs future=$1.321, saving $0.029
Lassalle et al. (2016)[199]	To assess the cost-effectiveness of home administration of subcutaneous (s.c.) BORT in MM patients	France	All patients with MM living in an 80-km radius of the Department of Haematology of the University Hospital of Nantes, France, and requiring BORT administration	N=50	This was a prospective trial. MM patients received the first administration of s.c. BORT of each cycle in the outpatient unit of the Department of Hematology. All	Cost of a round-trip to hospital, hospital stay, drug costs, preparation and pharmacy costs, personal costs, tax, packaging, retrocession fee, transportation of BORT, nursing fee,	Overall the total cost of one s.c injection of BORT in the outpatient unit was €1510.09 versus €1224.57 for home administration (total reduction: €285.52).

	Objective	Country of study	Population	Sample size	Data	Type of cost and resource use data reported	Results
					subsequent doses of BORT were administered at home when possible by nurses under the responsibilities of the referring physician	coordination cost and extra fee for nurse time	
Touati et al. (2016) [200]	To compare the costs associated with BORT administration in France between hospital care at home (actual data) and outpatient hospital care alone (simulation)	France	Fifty-four consecutive MM patients who received at least one injection of BORT in Hospital care at Home from January 2009 to December 2011 were included in the study.	N=54	Retrospective data using electronic files in hospitals	Transport costs, drug and administration costs. Dosage of drug (mean, SD), number of drug injections at home (mean, SD), number of drug injections in outpatient unit (mean, SD), distance home-hospital round-trip	Mean total cost per patient and per injection, at home: €954.20 and at hospital outpatient: €1,143.42, administration at home was associated with a 16.5% saving. Differences were mainly due to the mean cost of administration and the cost of patient transportation.
Lee et al. (2016) [201]	To assess the out of pocket costs associated with oral medications for the management of MM before and after financial assistance.	US	Patients included were MM patients who received THAL, LEN or POM.	N=6,731	Retrospective study. Data were collected from all oncology pharmacy claims data from a pharmacy claims database.	Out of pocket costs per prescription	Pre-financial assistance out of pocket cost per prescription: $227.23 Post-financial assistance out of pocket cost per prescription: $80.11
Zhou et al. (2016) [202]	To assess the healthcare costs of the treatment of RRMM in Chinese	China	NR	N=93	Data were retrospectively collected using medical charts and	Drug costs and market share across different lines of therapy.	Total monthly costs for second line, third line, fourth line and whole population: $905,

	Objective	Country of study	Population	Sample size	Data	Type of cost and resource use data reported	Results
	patients using real-world data.				electronic records from the time of first relapsed/refractory disease until their date of death or end of the study period All the unit costs of the health resources were estimated using data from the local health system or the National Development and Reform Commission of China	Hospital stays, laboratory tests, diagnostic procedures, concomitant medication, hospital visit, allogeneic-CIK cell infusions reported for each line of therapy and BORT and non-BORT subgroups. Mean total cost for each line of therapy.	$2,638, $2,726 and $1,140
Arikian et al. (2015) [203]	To estimate the total direct costs of care from start of treatment to progression using real-world cost data	US	Patients with newly diagnosed or RRMM receiving LEN or BORT based treatment	N=4,202: First line: n=2,843 Second line: n=1,361	Retrospective cost data from US claim databases: MarketScan Commercial Claims and Encounters (commercial) and Medicare Supplemental and Coordination of Benefits (Medicare) January 2006 to December 2013	Direct healthcare costs: medical and pharmacy costs	The average monthly total costs per patient was $8,364 over the full time to next therapy period (pharmacy costs of $3,491 [42%] and medical costs of $4,873 [58%].
Roy et al. (2015), [204]	To calculate the estimated total Medicare and commercial payer	US	RRMM patients receiving PANO+BORT+DEX, BORT+DEX,	NR	Drug costs were obtained from the Red Book.	Pharmacy costs, medical costs, prophylactic therapy, management of adverse events (includes	Deep vein thrombosis: $31,645 Pneumonia: $14,855

	Objective	Country of study	Population	Sample size	Data	Type of cost and resource use data reported	Results
Abouzaid et al. (2015)[205]	cost per patient to achieve 12 months of PFS with US FDA- approved and/or NCCN recommended therapies for RRMM		LEN+BORT+DEX or CARF+LEN+DEX		For drugs administered by IV infusion, the Medicare drug cost was based on the average sales price plus 6%, whereas for commercial intravenous drugs the cost was estimated at 123.5% of the Medicare cost. The costs of administration were estimated from Current Procedural Terminology (CPT) code 99212 (level 2 established office visit) and CPT code 96409 (chemotherapy administration, iv push, single drug) Costs associated with medical services were obtained from the literature	rate of adverse event per treatment). Medical costs included IV drug administration, hydration and physician office visits.	Febrile neutropenia: $13,261 Renal failure: $12,316 Vomiting: $11,934 Nausea: $11,934 Dyspnea: $10,886 Back pain: $10,728 Diarrhoea: $9,738 Asthenia/fatigue: $8,437 Arrhythmia/atrial fibrillation: $6,998 Upper respiratory infection: $5,220 Hypokalaemia: $1,707 Herpes Zoster: $1,287 Hypocalcaemia: $1,155 Anaemia: $971 Hypomagnesemia: $924 Urinary tract infection: $901 Peripheral neuropathy: $783 Hyperglycaemia: $166 Hyponatremia: $166 Hypophosphatemia: $166 Leukopenia: $166 Lymphopenia: $166 Neutropenia: $166 Thrombocytopenia: $166 Monthly adverse event rates available in the paper

	Objective	Country of study	Population	Sample size	Data	Type of cost and resource use data reported	Results
							Costs associated with Medicare: physician office visit, IV administration, IV administration of hydration: $43.98, $111.20 and $57.92, respectively. Costs associated with commercial insurance: physician office visit, IV administration, IV administration of hydration: $54,31, $137.33 and $71.53, respectively. Total costs of treatment regimens broken down for pharmacy, medical and adverse events are presented in the paper.
Gooding et al. (2015) [206]	To analyse and report medical resource utilization costs, drug costs and outcomes in patients with double RRMM	UK	Patients with double relapsed and/or refractory MM	N=39	Pharmacy-generated lists of all sequential lenalidomide recipients between January 2011 and July 2013 at Oxford University Hospitals and the Royal Berkshire Hospital, Reading, UK	Drug costs, inpatient admissions, attendances (day therapy unit, triage, CT scan), invasive and radiological procedures (MRI scan, X-ray, maxillofacial, other), supportive therapy (bisphosphonate and radiotherapy), transfusion (red blood cells, platelets, full blood count) and	Occurrences of each resource in the double relapsed and/or refractory MM population Total cost per patient: £12,281 Admissions during therapy: 1.3 per patient

	Objective	Country of study	Population	Sample size	Data	Type of cost and resource use data reported	Results
						blood tests (biochemistry, immunology microbiology). Duration of admissions Proportion of patients experiencing adverse events	Duration of admission: 9.3 days
Durie et al. (2013) [207]	To compare the costs of LEN+DEX with BORT for RRMM, from the perspective of a US payer	US	RRMM patients	Per patient costs	Costs and resource use obtained from the literature and claims data.	Drug costs, resource use and adverse event management. Includes: evaluation and management, administration, hydration, laboratory tests, prophylaxis costs and daily medical cost.	Average total cost per month without progression, LEN+DEX and BORT: $8,949 and $10,105, respectively
Teitelbaum et al. (2013) [208]	To assess the health care costs as well as patient burden associated with BORT, THAL and LEN and other chemotherapies used for the treatment of MM	US	Patients with a diagnosis of MM who received at least one course of treatment with BOR, THAL, LEN or other between January 1, 2005 and September 30, 2010	N=2,642 with 4,836 treatment episodes (23.5% second line and 9.2% third line or fourth line)	Retrospective analysis using real-world claims data from a large US plan	Medications, ambulatory care, emergency care, inpatient hospitalisation, other medical and retail pharmacy given as a total and for BORT, THAL, LEN and other. Hazard ratios associated with cost and ambulatory visits of treatment using “other treatments” as the reference case	Total healthcare costs for whole population, BORT, THAL, LEN and other subgroups: $118,354, $133,974, $140,334, $150,544 and $99,175, respectively. Out of pocket costs (adjusted) for BORT, THAL, LEN and other subgroups: $3,846,

	Objective	Country of study	Population	Sample size	Data	Type of cost and resource use data reported	Results
						Mean patient out of pocket costs	$4,666, $4,483 and $3,900, respectively. Rates of resource use for whole population and for treatment subgroups presented in the paper.
Gaultney et al. (2013), Franken et al. (2013), Franken et al. (2014)[209-211]	To investigate the real-world health care costs of RRMM in Dutch daily practice.	The Netherlands	Patients participating in phase III HOVON-50 trial (newly diagnosed patients). Patients relapsing from protocol-based upfront therapy and treated for RRMM in daily practice were included	N=139 (second line) N=90 (third line) N=54 (fourth line)	Retrospective medical chart review Costs based on micro-costing studies. The cost of radiotherapy, surgical procedures and medical imaging services was valued using the fees issued by the Dutch Healthcare Authority. Unit costs for laboratory services were based on a detailed inventory of the resource use of 12 patients (approximately 1000 tests). Unit costs of concomitant treatment costs were acquired from the cost guidelines available from the national	Includes hospital visits, hospital admissions, radiotherapy, surgery, diagnostics, total concomitant medication costs, chronic/prophylactic, therapy and stem cell transplantation	Total monthly costs second, third and fourth line: €3,469, €4,792 and €4,685, respectively Total monthly costs for BORT, THAL and LEN 2L: €4,814, €2,684 and €4,215, respectively Total monthly costs for BORT, THAL and LEN 3L: €5,966, €3,393 and €5,029, respectively Total monthly costs for BORT, THAL and LEN 4L: €6,260, €4,308 and €5,114, respectively

	Objective	Country of study	Population	Sample size	Data	Type of cost and resource use data reported	Results
					pharmaceutical formulary drafted by the Dutch Healthcare Insurance Board.		
Goodwin et al. (2013) [86]	To identify the long-term personal financial effects of MM and its treatment in employment, disability, health/medical and life insurance, retirement and out-of-pocket expenses	US	MM patients who had received intensive treatment	N=762	Patient responded mail questionnaires	Out of pocket expenses on direct costs and indirect costs.	% income spent during first treatment year when treatment began <4 years ago: 40% % income spent during first treatment year when treatment began ≥4 years ago: 33% % income spent during first treatment year when treatment ended <4 years ago: 37% % income spent during first treatment year when treatment ended ≥4 years ago: 29%
Koleva et al. (2011) [212]	To estimate healthcare resource utilisation and costs associated with MM management in an Italian haematological department and to investigate the	Italy	Newly or previously diagnosed MM patients stages II-III	N=90 (n=53 ≤65 years and n=35 >65)	Retrospective observational data Diagnostic tests and non-pharmacological therapy were priced applying the INHS (Italian National Health Service) tariffs. Dispensing prices per	Drugs, new immunomodulatory agents. diagnostic procedures, laboratory tests, specialist consultations, hospital admissions, day-hospital days, non-pharmacological therapy,	Resource consumption per patient per year (whole population): laboratory tests, diagnostic procedures, specialist consultations, hospital admissions, day-hospital days, non-pharmacological therapy, autologous

	Objective	Country of study	Population	Sample size	Data	Type of cost and resource use data reported	Results
	association between costs and age.				unit were used for drugs prescribed in the community; a 50% discount on dispensing prices (i.e. the minimum discount fixed by law for public procurement of drugs in Italy) was applied for drugs purchased by the hospital	autologous transplant and other.	transplant and others: 62.7, 2.7, 4.8, 0.4, 4.2, 1.4, 0.2 and 1.2, respectively. Total cost per patient per year (whole population): €14,053
Armoiry et al. (2011) [213]	To describe the pattern of usual care of RRMM in specialist French Haematological units, and to estimate the direct costs associated with current management of the disease	France	RRMM who had one prior treatment during the period 2004-2005 and had a follow-up of at least 18 months. Results presented for BORT-, THAL- and LEN-based regimens for 2L, 3L and 4L	N=102	Collected using a questionnaire completed by clinicians 2004-2007	Direct costs including: drug, hospital stays, concomitant treatment, adverse events and transport costs	Irrespective of treatment line-order, the mean cost per month was €3,130 with major share of the costs accounted for by drugs (66.1%) and drug administration in day-hospital sessions (15.4%). On this basis and with the average number of 2.75 lines per patient, the total direct cost for RRMM is estimated about €73,000 per patient for the whole period of follow-up of 25.53 months
Clark et al. (2011) [214]	To quantify the reduction of medication waste of different bortezomib vial	Brazil	Patients diagnosed with MM submitted to treatment containing	N=35	Retrospective cost data from Evidencias database (private healthcare database)	Cost of dispensed drug	Average waste per patient/day for 3.5mg, 3mg and 2.5mg vial:

	Objective	Country of study	Population	Sample size	Data	Type of cost and resource use data reported	Results
	presentations used for the treatment of MM in Brazil		BOR for at least one infusion		2007-2009	Resource wasted (costed using the amount of drug wasted in mg) Average waste in mg per patient presented for 3.5mg, 3mg and 2.5mg vials	1.38mg, 0.88mg and 1.05mg, respectively. Average cost wasted per patient per day for 3.5mg, 3mg vial and 2.5mg vial: $926.88, $592.09 and $704.54, respectively.
De Portu et al. (2011) [215]	To assess the incidence, outcome and cost of MM in Italy	Italy	Patients who had a first hospital admission event with diagnosis of MM during the period between 01/01/2001 and 31/12/2005. Results reported for subgroups: <70 years and ≥70 years.	N=517	Retrospective data based on claims of patients enrolled in the administrative database of Friuli Venezia Giulia region of Italy	Hospitalisation costs Drug costs Outpatient care costs	Total healthcare costs during entire follow up and in the first year, <70 years: €76,631 and €42,949, respectively Total healthcare costs during entire follow up and in the first year, <70 years: €22,892 and €14,669, respectively
Cook et al. (2008) [216]	To review the economic impact of MM in the US using a budget impact model comparing across BORT, BORT+DEX, LEN+DEX and THAL+DEX	US	NR	NR	From Fullerton et al. (2007) Drug costs from the 2007 Redbook	Drug costs Medical costs Adverse event costs Prophylaxis cost	Total cost per patient for BORT, BORT+DEX, LEN+DEX and THAL+DEX: $33,966, $47,929, $72,822 and $47,002 (including the cost of prophylaxis)

	Objective	Country of study	Population	Sample size	Data	Type of cost and resource use data reported	Results
Ghatnekar et al. (2008) [217]	To retrospectively investigate the direct hospital resource utilization and costs associated with the treatment of patients with MM in southwest Sweden	Sweden	Patients starting first-line treatment in 2001	N=94 (n=41 2L and n=15 3L)	5-year retrospective data	Drug costs, mean dose, hospital outpatient visits, laboratory tests, inpatient days, diagnostic procedures and radiotherapy sessions given by line of therapy and due to MM or other events	Mean number of hospital outpatient visits per month 2L, 3L and all lines (MM events only): 1.24, 1.12 and 0.69, respectively Mean number of laboratory tests packages per month second line, third line and all lines (MM events only): 0.79, 0.82 and 0.54, respectively Mean number of inpatient days second line, third line and all lines (MM events only): 1.03, 0.40 and 1.47, respectively Mean number of surgical procedures per month second line, third line and all lines (MM events only): 0.01, 0.00 and 0.01, respectively Mean number of diagnostic procedures per month second line, third line and all lines (MM events only): 0.18,

	Objective	Country of study	Population	Sample size	Data	Type of cost and resource use data reported	Results
							0.15 and 0.31, respectively Mean number of radiotherapy sessions per month second line, third line and all lines (MM events only): 0.03, 0.01 and 0.02, respectively Mean cost per line of treatment second line, third line and all lines: €15,828, €6,664 and €88,199, respectively
Groot et al. (2004)[218]	To quantify the medical costs in patients treated for MM with bone lesions in the Netherlands.	The Netherlands	MM patients Durie-Salmon Stage III receiving anticancer therapy.	N=20	Retrospective data from two Dutch hospitals	Hospital days, day care treatment, outpatient visits, laboratory tests, blood components, radiation therapy, autologous SCT, allogenic SCT, radiology, medical interventions, total medication, chemotherapy, antibiotics, growth factors, other medications.	Average cost per patient for age<60 years, first year and after first year: €29,500, €29,572, respectively. Average cost per patient for age ≥60 years, first year and after first year: €12,162 and €17,575, respectively
Key: AE, adverse event; BORT, bortezomib; BSC, best supportive care; CARF, carfilzomib; CPT, Current Procedural Terminology; CT, computed tomography; DEX, dexamethasone; ECG, echocardiogram; FDA, Food and Drug Administration; IMiD, immunomodulatory drug; IV, intravenous; LEN, lenalidomide; MM, multiple myeloma; MRI, magnetic resonance imaging; N, number; NCCN,							

	Objective	Country of study	Population	Sample size	Data	Type of cost and resource use data reported	Results
National Comprehensive Cancer Network; NR, not reported; PANO, panobinostat; PFS, progression free survival; PI, proteasome inhibitor; POM, pomalidomide; RRMM, relapsed and refractory multiple myeloma; SCT, stem cell transplant; SD, standard deviation; THAL, thalidomide; US, United States							

5.5.2 Intervention and comparators' costs and resource use

5.5.2.1 Treatment costs

The unit costs associated with treatment acquisition are shown in Table 81 at list price. The dosing and administration schedule for all included comparators were estimated from the therapy dose reported in pivotal trials, these coincide with the UK marketing authorisation for each of the treatments. The drug unit costs were based on the British National Formulary (BNF),[219] accessed November 2016.

The existing patient access schemes (PASs) were captured in the economic analysis for BORT (manufacturer refunds drug costs for all patients who progress prior to the fourth cycle) and LEN (manufacturer refunds drug costs for all patients receiving treatment after 26 treatment cycles).

The PAS discounts for LEN and BORT were incorporated into the model and were included in the base case. Table 81 details the unit costs of treatment acquisition, based on list prices without PASs.

Table 81: Unit costs for treatment acquisition

Therapy	Administration type	Administration days per cycle	Pack size	Cost per pack	Unit cost (excluding any PAS)	Dosing source
Comparators						
LEN+DEX						
Lenalidomide 25mg	Oral	21 (days 1 through 21 of cycle)	21	£4,368.00	£208.00	TOURMALINE-MM1 trial NCT01564537. Clinical study protocol.[184] BNF accessed November 2016[219]
Dexamethasone 40mg	Oral	4 (days 1, 8, 15, 22 of cycle)	50	£49.00	£0.98	
IXA+LEN+DEX						
Ixazomib 4mg	Oral	3 (days 1, 8, 15 of cycle)	3	£6,336.00	£2,112	TOURMALINE-MM1 trial NCT01564537. Clinical study protocol [184]. BNF accessed November 2016[219]
Lenalidomide 25mg	Oral	21 (days 1 through 21 of cycle)	21	£4,368.00	£208	
Dexamethasone 40mg	Oral	4 (days 1, 8, 15, 22 of cycle)	50	£49.00	£0.98	
BORT+DEX						
Bortezomib 1.3mg/m2	SC	4 (days 1, 4, 8, 11 of cycle)	1	£762.38	£762.38	PANORAMA 1 (Phase 1 treatment).[145] BNF accessed November 2016[219]
Dexamethasone 20mg	Oral	8 (days 1, 2, 4, 5, 8, 9, 11, 12 of cycle	50	£49.00	£0.98	
Subsequent therapies						
BEN+PRED						

Therapy	Administration type	Administration days per cycle	Pack size	Cost per pack	Unit cost (excluding any PAS)	Dosing source
Bendamustine 100mg/m2	IV	Days 1-2 per 28-day cycle	5	£1,379.04	£689.52	Michael (2010) and Knop (2005). BNF accessed November 2016[219]
Prednisolone 100mg/m2	Oral	Days 1-5 per 28-day cycle	100	£2.20	£0.44	
CYC						
Cyclophosphamide 600mg/m2	IV	Days 1-4 per 28-day cycle	1	£10.66	£2.67	Lenhard et al. (1984). BNF accessed November 2016[219]
DOX+BORT						
Pegylated liposomal doxorubicin 30mg/m2	IV	Day 4 of a 21-day cycle	1	£300.52	£300.52	OPTIMUM; Orlowski et al. (2007). BNF accessed November 2016[219]
Bortezomib 1.3mg/m2	SC	Days 1, 4, 8 and 11 per 21-day cycle	1	£762.38	£762.38	
MP						
Melphalan 25mg/m2	IV	Day 1 per 28-day cycle	1	£129.81	£129.81	Petrucci et al. (1989). BNF accessed November 2016[219]
Prednisolone 60mg/m2	Oral	Days 1-7 per 28-day cycle	100	£2.20	£0.31	
THAL+DEX						
Thalidomide 200mg	Oral	Days 1-28 per 28-day cycle	28	£298.48	£10.66	Rajkumar et al. (2006). BNF accessed November 2016[219]
Dexamethasone 40mg	Oral	Days 1-4, 9-12 and 17-20 per 28-day cycle	50	£49.00	£0.98	
PANO+BORT+DEX						

Therapy	Administration type	Administration days per cycle	Pack size	Cost per pack	Unit cost (excluding any PAS)	Dosing source
Panobinostat 20mg	Oral	Days 1, 3, 5, 8, 10 and 12 in a 21-day cycle for 16 cycles	6	£4,656.00	£776.00	PANORAMA-1; San Miguel et al. (2014). BNF accessed November 2016[219]
Bortezomib 1.3mg/m2	SC	Days 1, 4, 8 and 11 in a 21-day cycle for 8 cycles then days 1 and 8 in a 21-day cycle for 8 cycles	1	£762.38	£762.38	
Dexamethasone 20 mg	Oral	Days 1, 2, 4, 5, 8, 9, 11 and 12 in a 21-day cycle for 8 cycles then days 1, 2, 8 and 9 in a 21-day cycle for 8 cycles	50	£49.00	£0.98	

Key: BEN, bendamustine; BORT, bortezomib; CYC, cyclophosphamide; DEX, dexamethasone; DOX, doxorubicin; IXA, ixazomib; LEN, lenalidomide; mg, milligram; PANO, panobinostat; PAS, patient access scheme; PRED, prednisolone; SC, subcutaneous; THAL, thalidomide

5.5.2.2 Dosing

Dosing data for IXA+LEN+DEX and LEN+DEX were taken from the TMM1 trial protocol: [184]

- IXA and placebo were given as single, oral doses of 4 mg weekly (Days 1, 8, and 15) for three weeks in a 28-day treatment cycle.
- LEN was given as a single, daily oral dose of 25 mg for a total of 21 days out of a 28-day treatment cycle (Days 1 – 21).
- DEX was given as a single, oral dose of 40 mg/day weekly on the appropriate days of a 28-day treatment cycle (Days 1, 8, 15, and 22).

The LEN+DEX arm followed the same dosing schedule as the LEN+DEX used in the IXA+LEN+DEX arm of the TMM1 trial.

Dosing data for BORT+DEX were obtained from the PANORAMA-1 trial [145] and based on a patient's body surface area (BSA) in metres squared (m^2). An average BSA of 1.87 was used in the model based on the TMM1 clinical trial:

- BORT was administered at 1.3mg/m^2 on days 1, 4, 8 and 11 every 21-day treatment cycle
- DEX was administered at 20mg on the day of and day after BORT administration (days 1, 2, 4, 5, 8, 9, 11 and 12)

Patients were treated with BORT+DEX for a total of eight 21-day treatment cycles, as per the product's summary of product characteristics. [27]

In the TMM1 clinical trial and in clinical practice, due to toxicity, patients may have their doses reduced or missed doses altogether. Missed doses and dose interruptions were not explicitly modelled. However, dosing intensities were included to capture the impact on costs of potential dose reductions and missed doses. The dose intensity of IXA+LEN+DEX was reported to be 93.10% in the TMM1 clinical trial and for LEN+DEX was reported to be 94.90%. Dose intensity was not reported in the BORT+DEX trial, therefore this was assumed to be 100%.

The dosing regimens and resulting per treatment cycle drug cost for each comparator considered in the model are outlined in Table 82.

Dosing intensities for the subsequent therapies were input according to the literature, where dosing intensities had not been reported 100% dosing intensity was assumed. The dosing regimens for subsequent therapies, average number of treatment cycles and associated sources are reported in Table 83. For subsequent therapies, the cost per treatment cycle was multiplied by the average number of treatment cycles, obtained from the literature.

Table 82: Cost per treatment cycle of chemotherapy (comparator treatments)

Therapy	Administration days per cycle	Unit dose (mg)	Treatment dose (mg)	Dose intensity	Units per treatment cycle (including wastage)	Drug cost per treatment cycle (including dose intensity)	Dosing source
LEN+DEX							
Lenalidomide 25mg	21 (days 1 through 21 per 28-day treatment cycle)	25	25.00	94.90%	21	£4,368.00	TOURMALINE-MM1 trial NCT01564537. Clinical study protocol[184]
Dexamethasone 40mg	4 (days 1, 8, 15, 22 per 28-day treatment cycle)	2	40.00	94.90%	76	£74.48	
IXA+LEN+DEX							
Ixazomib 4mg	3 (days 1, 8, 15 per 28-day treatment cycle)	4	4.00	93.10%	3	£6,336.00	TOURMALINE-MM1 trial NCT01564537. Clinical study protocol[184]
Lenalidomide 25mg	21 (days 1 through 21 per 28-day treatment cycle)	25	25.00	93.10%	21	£4,368.00	
Dexamethasone 40mg	4 (days 1, 8, 15, 22 per 28-day treatment cycle)	2	40.00	93.10%	76	£74.48	
BORT+DEX							
Bortezomib 1.3mg/m2	4 (days 1, 4, 8, 11 per 21-day treatment cycle)	3.5	2.43	100%	4	£3049.52	PANORAMA 1 (Phase 1 treatment)[145]
Dexamethasone 20mg	8 (days 1, 2, 4, 5, 8, 9, 11, 12 per 21-day treatment cycle	2	20.00	100%	80	£78.40	

Key: BORT, bortezomib; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; mg, milligram

Table 83: Cost per treatment cycle of chemotherapy (subsequent treatments)

Therapy	Administration days per cycle	Average duration of treatment (weeks)	Unit dose (mg)	Treatment dose (mg)	Dose intensity	Units per treatment cycle (including wastage)	Drug cost per treatment cycle (£)	Dosing source
BEN+PRED								
Bendamustine 100mg/m2	Days 1-2 per 28-day cycle	15.91	100	187.09	80.00%	4	£1,103.23	Michael et al. (2010) and Knop et al. (2005)
Prednisolone 100mg/m2	Days 1-5 per 28-day cycle	15.91	100	187.09	80.00%	150	£3.30	
CYC								
Cyclophosphamide	Days 1-4 per 28-day cycle	48.03	600	1,122.54	100.00%	8	£85.28	Lenhard et al. (1984)
DOX+BORT								
Pegylated liposomal doxorubicin 30mg/m2	Day 4 in a 28-day cycle	15.00	30	56.13	99.43%	3	£901.56	OPTIMUM; Orlowski et al. (2007)
Bortezomib 1.3mg/m2	Days 1, 4, 8 and 11 in a 28-day cycle	15.00	1.3mg/m2	2.43	98.46%	4	£3,049.52	
MP								
Melphalan 25mg/m2	Day 1 per 35-day cycle	48.00	25mg/m2	46.77	100.00%	1	£129.81	Petrucci et al. (1989)
Prednisolone 60mg/m2	Days 1-7 per 35-day cycle	48.00	60mg/m2	140.32	100.00%	203	£4.47	

THAL+DEX								
Thalidomide 200mg	1-28 days per 28-day cycle	17.39	200	200	100.00%	112	£1,193.92	Rajkumar et al. (2006)
Dexamethasone 40mg	Days 1-4, 9-12 and 17-20 per 28-day cycle	17.39	40	40	100.00%	240	£235.20	
PANO+BORT+DEX								
Panobinostat 20mg	Days 1, 3, 5, 8, 10 and 12 in a 21-day cycle for 16 cycles	21.74	20	20	80.70%	6	£4,656.00	PANORAMA-1; San Miguel et al. (2014)
Bortezomib 1.3mg/m2	Days 1, 4, 8 and 11 in a 21-day cycle for 8 cycles then days 1 and 8 in a 21-day cycle for 8 cycles	21.74	1.3mg/m2	2.43	75.80%	4 (2 for final 8-cycles)	£3,049.52 (£1,524.76 for final 8-cycles)	
Dexamethasone 20mg	Days 1, 2, 4, 5, 8, 9, 11 and 12 in a 21-day cycle for 8 cycles then days 1, 2, 8 and 9 in a 21-day cycle for 8 cycles	21.74	20	20	87.50%	72 (36 for final 8-cycles)	£70.56 (£35.28 for final 8-cycles)	
Key: BEN, bendamustine; BORT, bortezomib; CYC, cyclophosphamide; DEX, dexamethasone; DOX, doxorubicin; IXA, ixazomib; LEN, lenalidomide; mg, milligram; PANO, panobinostat; PAS, patient access scheme; PRED, prednisolone; SC, subcutaneous; THAL, thalidomide								

5.5.2.3 Administration costs

It was assumed that only IV treatments incurred administration costs. No administration costs were assumed for oral or SC treatments. Given that IXA, LEN and DEX are administered as oral therapies and BORT is administered as a SC injection, no administration costs were included in the model for first-line treatments.

It is noted that in the recent NICE submission appraising PANO+BORT+DEX for the treatment of RRMM, the NICE Appraisal Committee advised that BORT should be administered via SC injection rather than IV infusion.[220] Therefore, BORT was assumed to be administered via SC injection for cost calculations.

In the post-progression health state, for patients who receive subsequent therapies, a weighted cost of treatment was applied. Administration costs were included for IV treatments, including: BEN, CYC, DOX and MP. The administration cost was calculated per treatment cycle and then multiplied by the average number of treatment cycles sourced from available literature. Administration costs were sourced from the English and Welsh NHS reference costs.[221] The NHS reference costs 2014/2015 provides a number of tariffs for each type of chemotherapy administration, as outlined in Table 84. Costs were provided for first attendance and subsequent elements of a chemotherapy cycle. The administration cost for the first treatment cycle was weighted based on one first attendance cost and the remaining number of administrations multiplied by the subsequent administration cost. Administration costs for the first and subsequent treatment cycles are shown in Table 85.

Table 84: Unit costs for IV chemotherapy administration

Administration costs	Code	Unit cost	Source
Deliver Complex Chemotherapy, including Prolonged Infusion Treatment, at First Attendance	SB14Z	£413.58	NHS Reference Costs 2014-2015 [221] Chemotherapy*
Deliver subsequent elements of a chemotherapy cycle	SB15Z	£362.37	NHS Reference Costs 2014-2015 Chemotherapy*
*** Weighted average of Day case and Regular Day/Night, Outpatient, Other** **Key: NHS, National Health Service**			

Table 85: Administration costs

Treatment	Administration cost per treatment cycle	Source
IXA+LEN+DEX	£0.00	Assumption – oral and SC treatments are associated with no administration costs
LEN+DEX	£0.00	Assumption – oral and SC treatments are associated with no administration costs
BORT+DEX	£0.00	Assumption – oral and SC treatments are associated with no administration costs
BEN+PRED	£775.95	NHS reference costs 2014/15
CYC	£1,500.69	NHS reference costs 2014/15
DOX	£413.58	NHS reference costs 2014/15
LEN+DEX	£0.00	Assumption – oral and SC treatments are associated with no administration costs
MP	£413.58	NHS reference costs 2014/15
THAL+DEX	£0.00	Assumption – oral and SC treatments are associated with no administration costs

PANO+BORT+DEX	£0.00	Assumption – oral and SC treatments are associated with no administration costs
Key: BEN, bendamustine; BORT, bortezomib; CYC, cyclophosphamide; DEX, dexamethasone; DOX, doxorubicin; IXA, ixazomib; LEN, lenalidomide; mg, milligram; MP, melphalan and prednisolone; NHS, National Health Service; PANO, panobinostat; SC, subcutaneous; THAL, thalidomide		

5.5.2.4 Medical resource use costs

Routine care resource use

The resources used as part of routine care were estimated based on international multiple myeloma treatment and patient's follow-up guidelines (International Myeloma Foundation, Multiple Myeloma: Patient Handbook [222]). Routine care costs were applied to all patients on treatment. Patients who move onto active subsequent therapy continued to receive routine care, and thus incurred the routine care costs. Those patients who do not move onto active subsequent therapies were assumed to receive an anti-cancer treatment plan.

Routine care costs are split into:

- Immediate care at initiation of chemotherapy treatment
- Follow-up and monitoring during comparator and subsequent treatment.

Unit costs associated with routine care were sourced from the NHS reference costs 2014/15 then multiplied by the amount of resource use and the proportion of patients on treatment. The resource use for each treatment, both comparator treatments and subsequent therapies, was assumed to be the same with the exception of PANO, where all patients also received a transthoracic echocardiogram each treatment cycle due to associated TRAEs. This led to a cost of £1,081 at the initiation of chemotherapy (£1,165 for PANO+BORT+DEX) and a cost of £167 for subsequent administrations (£251 for PANO+BORT+DEX).

The resource use comprising routine care are summarised in Table 86.

Table 86: Resource use in routine care

Administration costs	Number for first treatment cycle	Number for subsequent treatment cycles	Unit cost (£)	Code	Source
Outpatient visit to oncologist	3	1	158.54	370	NHS Reference Costs 2014-2015 [221] Outpatient visits
Complete blood count	1	2	3.01	DAPS05	NHS Reference Costs 2014-2015 Haematology
Blood testing-chemistry panel	1	2	1.19	DAPS04	NHS Reference Costs 2014-2015 Clinical Biochemistry
Blood testing-FREELITE® test	1	0	5.49	DAPS06	NHS Reference Costs 2014-2015 Immunology
Blood testing-immunofixation	1	0	5.49	DAPS06	NHS Reference Costs 2014-2015 Immunology
Blood testing-serum protein electrophoresis	1	0	1.19	DAPS04	NHS Reference Costs 2014-2015 Clinical Biochemistry
Bone testing - X-rays	1	0	69.03	RA15Z	NHS Reference Costs 2014-2015 Dexa Scan
Bone marrow aspirate / biopsy *	1	0	497.23	SA33Z	NHS Reference Costs 2014-2015 Diagnostic Bone Marrow Extraction
C-reactive protein	1	0	5.49	DAPS06	NHS Reference Costs 2014-2015 Immunology
Serum albumin	1	0	1.19	DAPS04	NHS Reference Costs 2014-2015 Clinical Biochemistry
Serum lactate dehydrogenase	1	0	1.19	DAPS04	NHS Reference Costs 2014-2015 Clinical Biochemistry
Serum ß2 microglobulin (S ß2M)	1	0	1.19	DAPS04	NHS Reference Costs 2014-2015 Clinical Biochemistry
Urine testing - immunofixation	1	0	6.99	DAPS01	NHS Reference Costs 2014-2015 Cytology
Urine testing - protein electrophoresis	1	0	6.99	DAPS01	NHS Reference Costs 2014-2015 Cytology
Transthoracic echocardiogram (applied to patients receiving PANO+BORT+DEX only)	1	0	83.94	RD51A	NHS Reference Costs 2014-2015 Diagnostic imaging
Key: BORT, bortezomib; DEX, dexamethasone; NHS, National Health Service; PANO, panobinostat					

The resource use associated with routine care was validated by clinicians. Resource use was assumed to be the same for all chemotherapy treatments with the exception of PANO, which is a more toxic treatment, and therefore patients receive a transthoracic echocardiogram each treatment cycle. For patients in the post-progression health state, the routine care costs were weighted by the proportion of patients moving onto subsequent therapy in each arm and multiplied by the average number of treatment cycles obtained from the literature. This estimate was then applied as an average cost per subsequent therapy.

In the pre-progression health state when patients were not receiving any active therapy, it was assumed that no routine care was required.

Hospitalisations

Hospitalisations were included in the model to capture non-routine health care use in the pre- and post-progression health states.

The number of hospitalisations were obtained from the patient-level data from the TMM1 clinical trial for the IXA+LEN+DEX and LEN+DEX arm. No significant difference was found between the number of hospitalisations across the 1 prior and 2+ prior lines populations and so to improve the reliability of the estimates (by increasing the number of events) the data were pooled across the patient populations. A difference was found across the treatment arms and progression status and so hospitalisation rates are considered by treatment arm and progression status. Four different types of inpatient care were captured: acute care, ICU care, palliative care and hospice care. Only data considering hospitalisation resource use for events unrelated to TRAEs were analysed; any events due to "treatment toxicity" were excluded from the analysis. The rate per cycle for each type of hospitalisation was estimated for all patients and converted to a probability per patient week for implementation in the model. This approach considers both the number of hospitalisations occurring and the follow-up period or exposure time in person-years (i.e. incidence rate). The probability per patient cycle for each hospitalisation are presented in Table 87.

Table 87: Rate of hospitalisation for pre- and post-progression

Description	Number of Events	Rate	Probability per patient cycle
Pre-progression – IXA+LEN+DEX			
Acute care unit admission	87	0.2269	0.0043
Palliative care unit admission	7	0.0183	0.0003
ICU admissions	8	0.0209	0.0004
Hospice admission	10	0.0261	0.0005
Pre-progression – LEN+DEX			
Acute care unit admission	96	0.2583	0.0049
Palliative care unit admission	12	0.0323	0.0006
ICU admissions	5	0.0135	0.0003
Hospice admission	10	0.0269	0.0005
Post-progression – IXA+LEN+DEX			
Acute care unit admission	17	0.2861	0.0055
Palliative care unit admission	1	0.0168	0.0003
ICU admissions	2	0.0337	0.0006
Hospice admission	0	0.0000	0.0000
Post-progression – LEN+DEX			
Acute care unit admission	15	0.1897	0.0036
Palliative care unit admission	3	0.0379	0.0007
ICU admissions	5	0.0632	0.0012
Hospice admission	1	0.0126	0.0002
Key: ICU, intensive care unit			

Costs associated with hospitalisations were sourced from the NHS reference costs 2014/2015. [221] Hospitalisation costs for acute, palliative and ICU care were provided as cost per event, whereas the cost of hospice care was provided as a daily cost. This was multiplied by the average length of stay per admission calculated using the Ns (n=5) and the total length of stay (18.32 days) provided in the NHS reference costs 2014/15 to give the average length of stay (3.66 days). Table 88 details the costs of hospitalisation.

Table 88: Hospitalisation unit costs

Item Name	Reference	Source	Cost
Acute ward - cost per event	SA17G-H	NHS Reference Costs [221] 2014-2015;	£1,119.89
ICU ward - cost per event	XC01Z-XC07Z	NHS Reference Costs 2014-2015; Critical care: weighted average of inpatient codes	£1,306.16
Palliative ward - cost per event	SD01A & SD03A	NHS Reference Costs 2014-2015; Palliative care: weighted average of inpatient codes for adults	£186.56
Hospice - cost per day	SD02A	NHS Reference Costs 2014-2015; Palliative care day/night care	£160.46
End of Life Care per decedent	PSSRU	PSSRU 2015,[223] section 8.13: End of Life care	£10,670.00
Key: ICU, intensive care unit; NHS, National Health Service; PSSRU, Personal Social Services Research Unit			

The probability of each hospitalisation was multiplied by the cost and the proportion of patients in either pre- or post-progression each cycle, respectively.

5.5.2.5 Concomitant medications

The TMM1 clinical trial captured concomitant therapy use up to 30-days post-progression. No significant difference was found between the IXA+LEN+DEX and LEN+DEX treatment arms for concomitant medication. Therefore, the model used the pooled data for concomitant medications where at least 7.5% of patients received the medication.

Unit costs associated with each concomitant therapy were based on list prices (where available) reported in the BNF. The total cost of concomitant therapies per week (£30.93) was multiplied by the proportion of patients in the pre-progression health state. Due to lack of data, the weekly cost of concomitant medications was assumed equal for all comparators. Furthermore, due to lack of data on concomitant medications associated with post-progression therapies, the cost of concomitant medications was applied to patients in the post-progression health state.

Table 89: Overview of concomitant medications

Treatment	Description	Cost / pack (£)*	Units cycle)	Drug cost cycle (£)	N	Proportion of patients from the TMM1 study	Total cost /wk. (£)
ACETYLSALICYLIC ACID	Tablets, aspirin 300 mg, 32-tab pack, 75 mg daily	3.35	7	0.73	554	76.7%	0.56
ACICLOVIR	Tablets, aciclovir 200 mg, 56-tab pack 4 times daily	3.02	14	0.76	287	39.8%	0.30
ALLOPURINOL	Tablets, allopurinol 100 mg, 28-tab pack, once daily	0.87	7	0.22	129	17.9%	0.04
AMLODIPINE	Tablets amlodipine 5 mg, 28-tab pack, 5 mg once daily	0.73	7	0.18	64	8.9%	0.02
BACTRIM (CO-TRIMOXAZOLE)	Tablets co-trimoxazole 960 mg, 100 tab-pack, 960 mg every 12 hours	2.29	7	0.57	198	27.4%	0.16
CALCIUM CARBONATE	Tablet calcium carbonate 1.25 g (calcium 500 mg or Ca2+ 12.5 mmol); WHO DDD A12AA04 = 3g	9.46	21	1.99	27	3.7%	0.07
COLECALCIFEROL	Tablets 20 mcg, 30-tab pack= £3.60; WHO DDD A11CC05 = 20 mcg	3.60	7	0.84	33	4.6%	0.04
ENOXAPARIN	Injection, enoxaparin sodium 100 mg/mL, 40 mg (4000 units) every 24 hours	30.27	7	21.19	144	19.9%	4.23
ESOMEPRAZOLE	Capsules, enclosing e/c pellets, esomeprazole, 20 mg 28-cap pack, 20 mg daily when required	2.97	7	0.74	30	4.2%	0.03
FENTANYL	Tablet (sublingual) fentanyl (as citrate) 100 micrograms, 10-tab pack, 100 micrograms, repeat if necessary after 15-30 minutes	57.86	2.33	27.00	70	9.7%	2.62
FUROSEMIDE	Tablets furosemide 20 mg, 28-tab pack, 20-40 mg daily	0.74	7	0.19	28	3.9%	0.01
IBUPROFEN	Tablets, ibuprofen 200 mg 84-tab pack, maintenance dose of 0.6–1.2 g daily may be adequate	3.40	21	0.85	57	7.9%	0.07
LANSOPRAZOLE	For acid-related dyspepsia: 15-30mg daily for 2-4 wks; caps encl e/c granules 30 mg, 28-cap pack	1.26	0.06	0.00	31	4.3%	0.00

Treatment	Description	Cost / pack (£)*	Units cycle)	Drug cost cycle (£)	N	Proportion of patients from the TMM1 study	Total cost /wk. (£)
LEVOTHYROXINE	Tablets, levothyroxine sodium 50 micrograms, 28-tab pack, usual maintenance dose 50–200 micrograms once daily	1.65	7	0.41	60	8.3%	0.03
METFORMIN	Tablets, coated metformin hydrochloride 500 mg 28-tab pack, 500 mg with breakfast, lunch and evening meal	0.86	21	0.65	28	3.9%	0.03
METOPROLOL	Tablets, metoprolol tartrate 50 mg, 28-tab pack, 50 mg 2-3 times daily	1.25	14	0.63	29	4.0%	0.03
MORPHINE	Tablets, morphine sulphate 5 mg, 60-tab pack, 5 mg every 4 hours adjusted per response	3.29	42	2.30	73	10.1%	0.23
NADROPARIN	Injection, enoxaparin sodium 100 mg/mL, 40 mg (4000 units) every 24 hours	3.03	7	21.21	36	5.0%	1.06
OMEPRAZOLE	Capsules, omeprazole 10 mg, 28-cap-pack, 10 mg daily	5.96	7	1.49	242	33.5%	0.50
ONDANSETRON	Tablets, ondansetron 8 mg, 10-tab pack, 8 mg 1-2 hours before treatment	2.28	1	0.23	30	4.2%	0.01
OXYCODONE	Capsules, oxycodone hydrochloride 5 mg, 56-cap pack	6.26	28	6.74	98	13.6%	0.92
PAMIDRONIC ACID	IV infusion, powder for reconstitution, pamidronate disodium, 90 mg vial, 90 mg every four weeks	170.45	0.25	42.61	160	22.2%	9.44
PANTOPRAZOLE	Tablets pantoprazole 20 mg, 28-tab pack, 20 mg daily	0.99	7	0.25	105	14.5%	0.04
PARACETAMOL	Tablets, paracetamol 500 mg, 32-tab pack	0.73	56	1.28	306	42.4%	0.54
POTASSIUM	Tablets, diclofenac potassium 25 mg, 28-tab pack; Rheumatic disease, musculoskeletal disorders, acute gout, 75–150 mg daily in 2–3 divided doses	3.23	35	4.04	30	4.2%	0.17
SIMVASTATIN	Prevention of cardiovascular events, initially 20-40mg once daily at night 20mg, 28-tab pack	66.00	14	33.00	28	3.9%	1.28
TRAMADOL	Capsules, tramadol hydrochloride 50 mg 30-cap pack, 50 mg every 4-6 hours, adjust per response	1.20	28	1.12	111	15.4%	0.17
VALACICLOVIR	Tablets, valaciclovir 500 mg, 10-tab pack, 500 mg twice daily for 3-5 days	3.18	1.5	0.48	133	18.4%	0.09
ZOLEDRONIC ACID	Concentrate for IV infusion, zoledronic acid, 800 micrograms/mL, 5 ml (4 mg) vial, 4 mg over at least 15 minutes every 3-4 weeks	174.17	0.25	43.54	137	19.0%	8.26
						Total cost (£) per patient week	30.93

Key: IV, intravenous; mg, milligram; mL, millilitre; N, number; tab, tablet; Tx, treatment
*** BNF accessed November 2016**

5.5.2.6 Subsequent therapies

Patients who progress in the economic model move to the post-progression health state; in line with the TMM1 clinical trial it was assumed that a proportion of progressed patients receive active subsequent therapy. It was assumed that the treatment effect of any subsequent line of therapy was captured in TMM1 OS estimates; hence, efficacy associated with post-progression therapy was not explicitly modelled.

The TMM1 clinical trial provides the proportion of progressed patients who go on to receive active subsequent therapy (n=176, 24.4%) and the treatments these patients move on to: BEN regimens (n=18), cyclophosphamide regimens (n=63), doxorubicin regimens (n=16), BORT regimens (n=99), CARF regimens (n=13), LEN regimens (n=27), melphalan regimens (n=24), POM regimens (n=25) and THAL regimens (n=28). The total patients receiving each subsequent therapy sums to more than the initial 176, this is because some patients go on to receive multiple lines of subsequent therapy.

As BORT, CARF and POM are not authorized for use in the UK (statement dated: October 2016), it was considered that modelling these costs would not reflect clinical practice in the UK. Following feedback from UK clinical experts, it was considered that patients receiving these treatments after IXA+LEN+DEX or LEN+DEX would likely receive PANO+BORT+DEX at next line in a UK setting. Therefore, in the economic model these patients (n=137) were assumed to receive PANO+BORT+DEX as subsequent therapy and the costs reflect this.

The cost of active subsequent therapy includes: the one-off costs associated with initiation of chemotherapy, the therapy costs (including administration costs), TRAE costs and routine management costs. These costs are estimated based on a weekly cost (or a treatment cycle cost) and multiplied by the average number of weeks (or the average number of treatment cycles) for each respective subsequent therapy. The average number of weeks were obtained from the literature, see Table 90, and the number of treatment cycles were obtained from the product's SPC.

The resulting cost of subsequent therapy was calculated as a weighted cost across all included active subsequent therapies; the proportion of patients receiving each subsequent therapy as reported in the TMM1 clinical trial multiplied by the average cost associated with each treatment. This was then multiplied by the proportion of patients receiving active subsequent therapy (24.4%) and applied as a one-off cost to patients moving to the post-progression health state. Table 90 details the post-progression active subsequent therapies and the corresponding costs.

Table 90: Post-progression resource use for patients receiving active anti-cancer therapy

Therapy	Duration of treatment in weeks	One off Costs Initiation of Therapy	Therapy Costs £	TRAE cost £	Routine Management Costs £	Total
BEN regimens (assumed to be BEN+PRED)	15.91	£1,081.29	£7,485.38	£654.29	£663.76	£1,010.94
CYC	48.03	£1,081.29	£19,042.76	£773.40	£2,004.30	£8,197.78
DOX regimens (assumed to be DOX+BORT)	15.00	£1,081.29	£21,823.32	£1,668.97	£834.64	£2,309.84
LEN regimens (assumed to be LEN+DEX)	48.03	£1,081.29	£53,340.88	£773.40	£2,004.30	£8,774.98
Melphalan regimens (assumed to be MP)	48.00	£1,081.29	£5,259.46	£1,643.18	£1,602.51	£1,307.24
THAL regimens (assumed to be THAL+DEX)	17.39	£1,081.29	£8,285.49	£748.89	£967.78	£1,763.28
PANO+BORT+DEX*	21.74	£1,081.29	£56,353.44	£1,519.47	£1,209.73	£46,832.15
Total one-off active subsequent therapy cost						£70,196.20
Key: BEN, bendamustine; BORT, bortezomib; CYC, cyclophosphamide; DEX, dexamethasone; DOX, doxorubicin; LEN, lenalidomide; MP, melphalan and prednisolone; PANO, panobinostat; PRED, prednisolone; TRAE, treatment related adverse event						

It was assumed that patients in the post-progression health state who do not receive active subsequent treatment (n=546, 75.6%) instead receive a follow up treatment plan comprising of:

- At first-week initiation of progressive disease treatment plan – one outpatient visit, one blood test and one chemistry panel (£162.73 in the first week)
- Subsequent progressive disease treatment plan – one outpatient visit, one blood test and one chemistry panel every four weeks (£40.68 for subsequent weeks)

5.5.3 Health-state unit costs and resource use

Table 91 describes the costs associated with each health state for IXA+LEN+DEX compared with LEN+DEX and BORT+DEX.

In each health state the model calculates the proportion of patients in each health state and applies the appropriate costs and resource use associated with that health state. This method is the same for all health states, but costs are weighted differently according to the proportion of patients in the respective health states.

The weighted average cost per week of end-of-life care is applied to all patients who enter the death health state as a one-off cost. This is therefore not strictly incurred in the death state, but upon entry into the death state; but it detailed under the death state in Table 91.

Table 91: Cost breakdown for each health state

Health state	Items	Value	Reference in report
Pre-progression	Technology (cost per treatment cycle) Please note that these costs are adjusted for dose intensity	IXA+LEN+DEX (28-day treatment cycle) = £8,492.48 BORT+DEX (21-day treatment cycle) = £3,127.92 LEN+DEX (28-day treatment cycle) = £4,442.48	Section 5.5.2.1
	Administration per treatment	IXA+LEN+DEX = £0 BORT+DEX = £0 LEN+DEX = £0	Section 5.5.2.3
	Routine care (cost per cycle)	At treatment initiation = £1,081.29 Subsequent cycles = £166.93	Section 5.5.2.4
	Hospitalisation (pre-progression; cost per cycle)	Acute ward = £1.77 Palliative care = £0.05 ICU admission = £0.04 Hospice = £0.07 Total = £1.93 (Equal for all comparators)	Section 5.5.2.5
	Concomitant medications (cost per cycle)	£30.93	Section 5.5.2.6
	Adverse events (cost per cycle)	IXA+LEN+DEX = £16.65 BORT+DEX = £35.40 LEN+DEX = £16.10	Section 5.5.4
	Indirect costs (not included in the base case)	IXA+LEN+DEX = £303.19 (initiation of chemotherapy) and £25.27 during follow up LEN+DEX = £303.19 (initiation of chemotherapy) and £25.27 during follow up	Section 5.5.2.8

		BORT+DEX = £303.19 (initiation of chemotherapy) and £33.69 during follow up	
Post-progression	Subsequent active therapies (24.40% of patients; one off cost)	£70,196.20 (Equal for all comparators)	Section 5.5.2.7
	Progressive disease treatment plan (75.60%)	£162.73 at initiation of progressive disease treatment plan £40.68 in subsequent cycles (Equal for all comparators)	Section 5.5.2.7
	Hospitalisation	Acute ward = £3.34 Palliative care = £0.29 ICU admission = £0.37 Hospice = £0.08 Total = £4.09 (Equal for all comparators)	Section 5.5.2.5
	Concomitant medications (cost per cycle)	£30.93	Section 5.5.2.6
Death	End of life care (one-off cost applied on transition to the death health state)	£2,134.00 (Equal for all comparators)	Section 5.5.5
Key: BORT, bortezomib; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide			

5.5.4 Adverse reaction unit costs and resource use

Section 5.3 describes the inclusion of AEs in the economic model. To capture the cost impact of AEs on each arm, a cost was assigned to each AE and multiplied by the cycle probability of that event occurring.

It was found for some AEs that patients were not necessarily treated; and that patients who were treated would receive a mix of primary care and secondary care. The proportion of patients treated and the proportion treated in a primary care vs. secondary care setting was obtained from the manufacturer's submission to NICE for TA171. Where no data were available, assumptions were reviewed by a UK clinical expert. It was assumed that 100% of renal failure and pulmonary embolisms would be treated in secondary care. Nausea and rashes were assumed to be treated in primary care and 50% of upper respiratory infections and ischaemic heart disease cases were assumed to be treated in primary care and the remaining 50% in secondary care.

The unit costs for TRAEs treated in a secondary care setting were sourced from the NHS reference costs 2014/2015. The unit costs for TRAEs treated in a primary care setting were sourced from the PSSRU (per patient contact lasting 11.7 minutes - £46). The proportion of patients actively treated by treatment setting and unit cost is displayed in Table 92.

Table 92: Proportion of AEs actively treated, by treatment setting and unit cost

	Cost of AE by treatment setting		% actively treated	Cases by treatment setting		Weighted average cost
TRAE	Secondary Care	Primary Care		Secondary Care	Primary Care	
Anaemia	£1,145	£46	96%	94%	6%	£1,036
Cardiac failure	£2,038	£46	100%	100%	0%	£2,038
DVT	£627	£46	100%	99%	1%	£622
Diarrhoea	£1,120	£46	98%	99%	1%	£1,087
Fatigue	£1,120	£46	100%	0%	100%	£46
Upper respiratory tract infection/Pulmonary-related	£1,127	£46	100%	50%	50%	£586
Ischemic heart disease	£1,700	£46	100%	50%	50%	£873
Nausea	£1,120	£46	98%	0%	100%	£45
Neutropenia	£715	£46	57%	98%	2%	£400
Peripheral neuropathy	£1,253	£46	82%	98%	2%	£1,008
Pneumonia	£2,066	£46	100%	100%	0%	£2,066
Pulmonary embolism	£1,571	£46	100%	100%	0%	£1,571
Rash-related	£1,120	£46	100%	0%	100%	£46
Renal failure	£1,571	£46	100%	100%	0%	£1,571
Thrombocytopenia	£643	£46	63%	99%	1%	£402
Vomiting	£1,120	£46	98%	99%	1%	£1,087
New primary malignancy flag	£1,927	£46	100%	100%	0%	£1,927
Key: AE, adverse event; DVT, deep vein thrombosis; TRAE, treatment related adverse event						

Costs were weighted based on treatment setting and multiplied by the proportion of patients suffering each AE, see Section5.3. Weighted weekly costs are displayed in Table 93.

Table 93: Weight per-cycle costs of AEs

Treatment	Weighted per cycle cost of AE
LEN+DEX	£14.17
IXA+LEN+DEX	£14.38
BORT+DEX	£35.26
PANO+BORT+DEX	£69.62
THAL+DEX	£43.06
CYC	£16.10
DOX+BORT	£111.26
BEN+PRED	£40.06
MP	£32.75
Key: AE, adverse event; BEN, bendamustine; BORT, bortezomib; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; MP, melphalan and prednisolone; PANO, panobinostat; PRED, prednisolone	

5.5.5 Miscellaneous unit costs and resource use

5.5.5.1 Terminal care costs

End of life care costs were captured as a one-off cost applied when a patient moves to the death health state. The cost of end of life care per decedent was sourced from the PSSRU (2015): £10,670 per decedent. [224] It was assumed that 20% of patients receive end of life care (consistent with previous submissions in RRMM - TA338 and TA171), resulting in a one-off cost of £2,134 per decedent.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of base-case de novo analysis inputs

The variables applied in the economic model are summarised in Appendix 12, along with the section in the submission where each variable is explained in more detail.

The model followed the NICE reference case and adopted a UK NHS and PSS perspective and discounts both costs and effects at a rate of 3.5%. Results are presented over a lifetime horizon which equates to 25.0 years in the 1 prior line population and 18.7 years in the 2+ prior lines population.

For the 1 prior therapy population, comparing IXA+LEN+DEX with BORT+DEX, the model used data from the TMM1 clinical trial for IXA+LEN+DEX and hazard ratios estimated by the NMA relative to LEN+DEX (discussed further in section 5.3.1) for OS, PFS and ORR associated with BORT+DEX. For the comparison of IXA+LEN+DEX with LEN+DEX in the 2+ prior therapies population all clinical data was taken from the TMM1 clinical trial.

Where possible, data specific to the 1 prior therapy or 2+ prior therapies populations were used: i.e. OS, PFS, ToT and ORR for IXA+LEN+DEX and LEN+DEX. However, due to lack of a significant difference or lack of data the following inputs used the ITT data as a proxy: TRAEs, hospitalisations and concomitant medications. For the comparison with BORT+DEX, hazard ratios for OS, PFS and ORR relative to LEN+DEX were estimated from an ITT population due to lack of subgroup data.

5.6.2 Assumptions

Table 94 details the assumptions used in the economic model and provides a justification for each one. Section 5.8.1.3 and section 5.8.1.4 detail the scenario analyses for the 1 prior and 2 prior therapies population, respectively, considering the impact of these assumptions on results.

Table 94: Base case assumptions

	Assumption	Justification	Reference in submission
Comparators	We assume that the only relevant comparators for the 1 prior line population are IXA+LEN+DEX and BORT+DEX and the only relevant comparators for the 2+ prior lines population are IXA+LEN+DEX and LEN+DEX.	This is in line with the CARF submission to NICE.[3] Furthermore, it was confirmed with clinical experts in the UK that IXA+LEN+DEX would most likely replace BORT+DEX at second line and LEN+DEX at third line.	Section 5.2
Time horizon	The analysis considers a lifetime perspective based on 99% of patients predicted to have died within the LEN+DEX arm. As a maximum, the model considers 25 years.	Due to the treatment pathway and incurable nature of RRMM a lifetime horizon is the most appropriate.	Section 5.2
Relative efficacy	We assume that the differences in patient characteristics between the IXA+LEN+DEX and LEN+DEX arms from the TMM1 clinical trial can be accounted for via covariate adjustment	Although the trial is an RCT, several significant imbalances were found between variables for OS, PFS and ToT. Covariate adjustment adjusted for these differences.	Section 5.3
Relative efficacy	We assume that the proportional hazards assumption allows for fitting a single parametric model to the LEN+DEX data and estimation of relative efficacy for IXA+LEN+DEX compared with LEN+DEX for: OS (2 + prior lines), PFS (1 prior line and 2+ prior lines) and ToT (2+ prior lines). Proportional hazards did not found to hold for OS (1 prior lines) and ToT (1 prior lines). The delayed exponential fit to the 1 prior lines population satisfied the proportional hazards assumption. An AFT model was fit to the ToT for 1 prior lines.	Followed the NICE Methods Guide for fitting parametric curves to the data. Where the proportional hazards assumption was violated a delayed model was fit to the data which satisfied the proportional hazards assumption or an AFT model was fit to the data.	Section 5.3

	Assumption	Justification	Reference in submission
Relative efficacy	We assume that proportional hazards hold within the NMA and that trial characteristics are comparable.	This assumption is made due to the lack of data. It is recognised that the trials have heterogenous populations but due to the lack of covariate data no adjustment could be made to account for this.	Section 5.3
Relative efficacy	We assume that the hazard ratios obtained for BORT+DEX from the NMA for 1+ prior therapies can be used used as a proxy for the 1 prior therapy population	This assumption is made as no subgroup data are available for BORT+DEX after 1 prior therapy. The 1+ prior therapy population data is from a larger evidence base, hence can be considered to be relatively robust	Section 5.3
Relative efficacy	In the base case, NMA data were obtained from a network connecting all relevant studies (including RCTs and observational evidence) and data considering the specific dose of treatment used in the model.	The NMA estimates utilised all available studies to make the most of all available data. Analysis using RCT studies alone in the NMA showed little differences ton the base case (see section 4.10) The NMA estimates considered dose specific studies where possible in line with the marketing authorisations for the treatments.	Section 5.3
Relative efficacy	It was assumed that the treatment effect post-trial was equal to the IXA+LEN+DEX within trial estimate for PFS and OS	This assumption is validated by the validation of proportional hazards and AFT functionality through the use of LCHPs and Q-Q curves. These assumptions meant that a constant treatment effect or hazard ratio could be estimated for IXA+LEN+DEX compared to LEN+DEX – by nature, this is a constant treatment effect/hazard ratio and therefore extends beyond the trial period. More mature data from IA3 (Q2 2017) and potentially final OS analysis (Q3 2019) will provide more information on whether this assumption can be expected to hold over a patient's lifetime.	Section 5.3

	Assumption	Justification	Reference in submission
TRAEs	Where no TRAE data were reported for comparators, the rate of AE occurrence was assumed to be the same as LEN+DEX	There was evidence of a publication bias in some studies, in particular older or smaller studies, which failed to report AE rates for AEs of interest. Assuming AE rates equal to LEN+DEX was a conservative approach, rather than assuming no AEs occurred.	Section 5.3
Utility	It was assumed that HRQL associated with RRMM could be captured by the regression equation estimated using the TMM1 patient level data. It was assumed that utility values would change over time based on response status, TRAEs, hospitalisation and proximity to death.	Using data directly from the TMM1 clinical trial aligns with efficacy estimates used within the model. Therefore, this is an appropriate reflection of HRQL expected for these patients.	Section 5.4.1
Utility	HRQoL loss associated with TRAEs was assumed to be the same across TRAEs, but the duration of the AE was assumed to differ per type of event.	Due to limited data individual HRQL decrements for each AE could not be reliably estimated. Therefore, the HRQL data for each TRAE were pooled to provide the model with reliable estimates.	Section 5.4.4
Treatment costs	The PASs for LEN and BORT are included in the model.	LEN and BORT each have an associated PAS which is currently used in UK practice.	Section 5.5.2.1
Administration costs	We assume BORT is administered via SC injection for cost calculations, rather than IV.	It is noted that in the recent NICE PANO submission (TA380),[98] the NICE Appraisal Committee advised that BORT should be assumed to be administered via SC injection rather than IV infusion.	Section 5.5.2.3
Administration costs	No administration costs were assumed for oral and SC regimens.		Section 5.5.2.3
Hospitalisations	It was assumed that the probability of hospitalisation was the same for all treatments, stratified based on pre-progression and post-progression	Due to lack of available data from the TMM1 clinical trial, hospitalisations were not provided for IXA+LEN+DEX and LEN+DEX separately. Therefore, the model uses the pooled data across the treatment arms. Further analysis is being conducted to obtain treatment specific hospitalisation rates.	Section 5.5.2.5

	Assumption	Justification	Reference in submission
Concomitant medications	It is assumed that all patients receive concomitant medications, whether on treatment, off treatment or in the post-progression health state. The per cycle cost of concomitant medications is assumed the same across all comparators	No statistically significant difference was found between the IXA+LEN+DEX and LEN+DEX treatment arms in the TMM1 clinical trial. As such, it is assumed that the per cycle cost of concomitant medication is the same for all comparator arms, including subsequent therapy.	Section 5.5.2.6
Subsequent therapy	Subsequent therapy was assumed to be initiated upon progression for a proportion of patients. For the remaining patients, a progressive disease treatment plan was initiated.	The patient level data from TMM1 recorded the patients who went onto receive active subsequent therapy with other chemotherapy regiments (24.4%). The remaining patients would receive palliative care in clinical practice which is proxied in the model by the progressive disease treatment plan. The resource use associated with the treatment plan was validated by clinical experts.	Section 5.5.2.7
Subsequent therapy	Any patient who received CARF, POM or BORT in the TMM1 trial data as active subsequent therapy were assumed to instead receive PANO+BOR+DEX within the model.	CARF and POM are not authorised in UK (statement dated October 2016). RRMM patient not eligible for BORT in later lines of therapy hence BORT costs excluded from UK post-progression anti-cancer therapy costs. It was confirmed by clinicians that these patients would likely receive PANO+BORT+DEX in this setting.	Section 5.5.2.7
End of life care costs	A one-off cost of end of life care was applied to patients upon transition to the death health state. The end of life care per decedent is reported in the PSSRU (2015). It was assumed that 20% of patients received this cost.	Assuming 20% of patients required end of life care was consistent with assumptions made in the previous NICE submissions in RRMM - TA338 and TA171.	Section 5.5.2.7

5.7 Base-case results

5.7.1 Base-case incremental cost effectiveness analysis results

Two sets of base case model results comparing IXA+LEN+DEX with BORT+DEX (for patients who have had one prior therapy, to support a 2nd line positioning in the RRMM treatment pathway) and with LEN+DEX (for patients who have had at least two prior therapies, to support a 3rd line positioning in the RRMM treatment pathway) are presented in Section 5.7.2 and Section 5.7.3, respectively.

Full incremental analysis is not presented for IXA+LEN+DEX, BORT+DEX and LEN+DEX as the comparators for IXA+LEN+DEX differ depending on patient population (1 prior therapy or 2+ prior therapies). The efficacy data used in the model is specific to the patient population and so comparison is not appropriate across the different populations.

5.7.2 IXA+LEN+DEX compared with BORT+DEX - 1 prior therapy

5.7.2.1 Base-case incremental cost effectiveness analysis results (1 prior therapy)

The base case results for IXA+LEN+DEX compared with BORT+DEX are shown in Table 95 for the patient population that have had one prior therapy, used to represent a 2nd line treatment positioning for ixazomib. Results were subject to a discount rate of 3.5% per annum and are presented over a lifetime horizon (25 years).

IXA+LEN+DEX is associated with a gain of 2.34 QALYs per patient and an incremental cost of [redacted] per patient compared with BORT+DEX. The resulting ICER is [redacted] per QALY gained.

Table 95: Base-case results – comparison with BORT+DEX (1 prior therapy)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
BORT+DEX	£38,770	2.452	1.596	-	-	-	-
IXA+LEN+DEX	[redacted]	5.943	3.932	[redacted]	3.491	2.336	[redacted]
Key: BORT, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; LYG, life years gained; QALYs, quality-adjusted life years							

5.7.2.2 Clinical outcomes from the model (1 prior therapy)

Table 96 displays the clinical outcomes and the model outcomes for the three main measures: OS, PFS, ToT, as well as AEs for the one prior line population. Clinical outcomes are presented for all comparisons assuming the base case parametric curve fits and adjusting covariates using the mean of covariates method (see Section 5.3).

The mean OS, PFS and ToT are comparable and consistent with the respective observed clinical outcomes reported in the TMM1 (IXA+LEN+DEX) and PANORAMA-1 (BORT+DEX) clinical trials.

Table 96 - Comparison of clinical outcomes with model outcomes for 1 prior therapy

Outcome	Clinical trial result	Model result	Clinical trial result	Model result
Mean survival (months) 1 prior therapy population (n=425)				
	IXA+LEN+DEX		**BORT+DEX**	
Overall Survival	21.01	20.87	N/A	16.56
Progression-free survival	15.73	15.86	N/A	15.05
Time on treatment	15.17	15.19	N/A	5.15
Adverse events (number of events)				
	IXA+LEN+DEX (n=360)		**BORT+DEX (n=377)**	
	Clinical trial result	**Model result**	**Clinical trial result**	**Model result**
Anaemia	40	55.79	72	57.82
Cardiac failure	8	12.26	7	5.64
Deep vein thrombosis	2	2.72	-	1.39
Diarrhoea	28	38.11	30	24.14
Fatigue	14	19.06	45	36.19
Upper respiratory tract infection/Pulmonary-related	3	4.09	6	4.83
Ischaemic heart disease	2	2.72	0	0
Nausea	6	0.00	2	0
Neutropenia	151	210.23	43	34.58
Peripheral neuropathy	1	1.36	55	44.21
Pneumonia	27	48.99	39	31.37
Pulmonary embolism	8	10.90	1	0.81
Rash-related	16	27.23	-	2.32
Renal failure	6	8.17	0	0
Thrombocytopaenia	75	103.31	118	94.55
Vomiting	4	5.38	5	4.03
New primary malignancy	5	1.36	-	0.93
Key: BORT, bortezomib; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; N, number.				

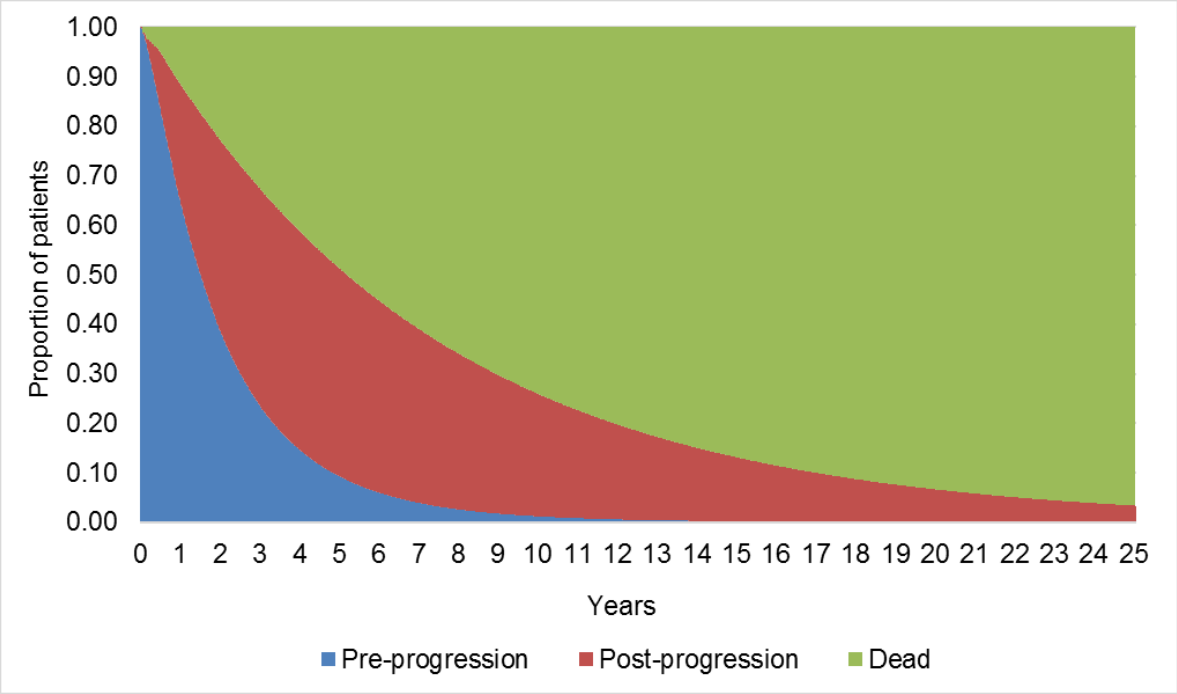
Markov traces

Markov traces are presented for the IXA+LEN+DEX and BORT+DEX comparison in Figure 43 and

Figure 44, respectively. These graphs depict how patients move through the model health states over time when treated with IXA+LEN+DEX and BORT+DEX, respectively. At baseline 100% of patients are in the pre-progression health state then over time patient's transition to the post-progression and death health states.

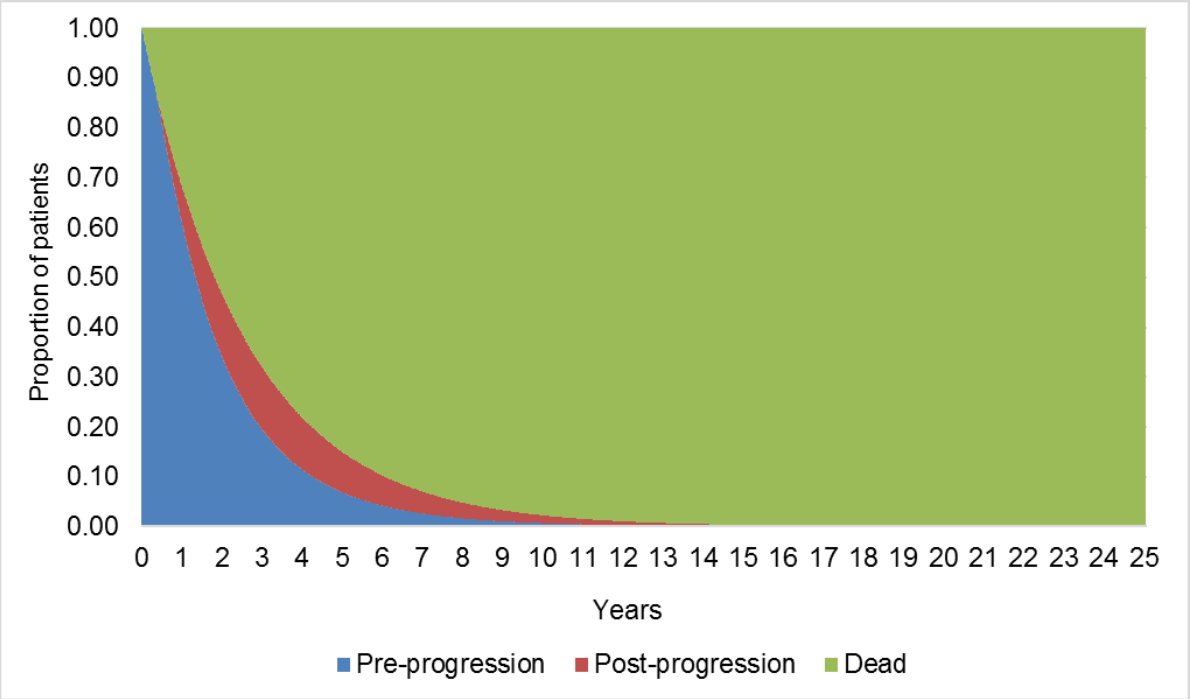
The Markov traces show that patients remain in the progression free and post-progression health states for longer when treated with IXA+LEN+DEX.

Figure 43: Patient distribution over time for patients who have received one prior therapy and are receiving IXA+LEN+DEX



Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide

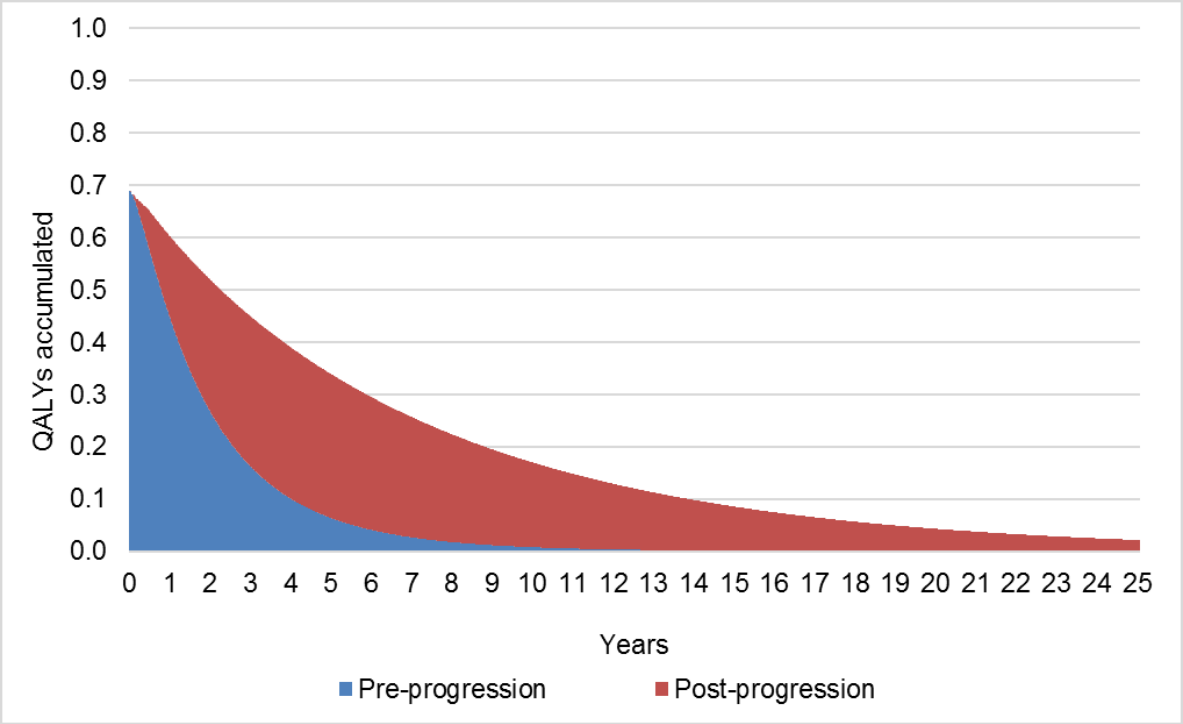
Figure 44: Patient distribution over time for patients who have received one prior therapy and are receiving BORT+DEX



Key: BORT, bortezomib; DEX, dexamethasone

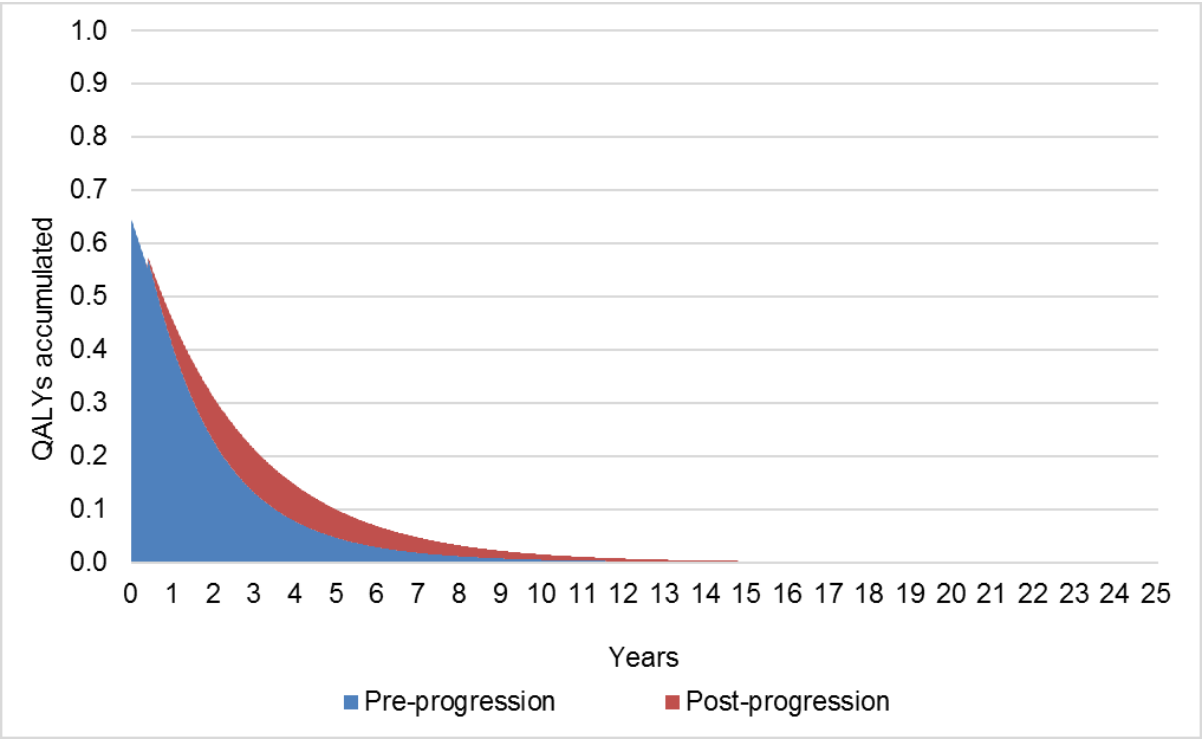
The accumulation of QALYs over time is shown in Figure 45 for IXA+LEN+DEX and Figure 46 for BORT+DEX for the pre-progression and post-progression health states over the lifetime horizon. QALYs are initially primarily accrued in the pre-progression health state; as time continues, the QALYs are increasingly accrued in the post-progression health state. Compared with BORT+DEX, the number of QALYs associated with IXA+LEN+DEX at each cycle are consistently higher.

Figure 45: Markov trace for QALYs accrued – IXA+LEN+DEX



Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; QALYs, quality adjusted life years

Figure 46: Markov trace for QALYs accrued – BORT+DEX



Key: BORT, bortezomib; DEX, dexamethasone; QALYs, quality adjusted life years

5.7.2.3 Disaggregated results of the base case incremental cost effectiveness analysis (1 prior therapy)

Life years

The total life years gained by patients in each health state for IXA+LEN+DEX versus BORT+DEX are detailed in Table 97. Life years are not discounted in the table below in line with the NICE reference case. Table 97 shows that treatment with IXA+LEN+DEX produces an incremental gain in life years compared with BORT+DEX for each of the model health states. The majority of these gains are accumulated whilst a patient is in the post-progression health state (93.58%).

Table 97: Summary of life years by health state

Health state	IXA+LEN+DEX	BORT+DEX	Increment	% increment
Pre-progression: Life Years	2.050	1.826	0.224	6.42%
Post-progression: Life Years	3.893	0.626	3.267	93.58%
Total life years	5.943	2.452	3.491	100.00%
Key: BORT, bortezomib; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide				

QALYs

Table 98 details the incremental QALYs gained in each health state for IXA+LEN+DEX compared with BORT+DEX. These values are from the base case where QALYs are calculated using utilities estimated using the regression equation derived from the TMM1 clinical trial. QALYs were discounted using a 3.5% annual rate. Treatment with IXA+LEN+DEX results in higher QALYs across all health states, with the largest increment seen in the post-progression health state suggesting a continued treatment effect after treatment. There is uncertainty associated with the survival and QALY gains post progression due to immaturity of the OS data from the TOURMALINE MM-1 trial, although patient follow-up is ongoing and so it is expected that the uncertainty associated with the extrapolated treatment effect will be reduced with later data cuts from the TMM1 clinical trial (a third datacut for OS analysis is expected in mid 2017, with a final OS analysis datacut planned for Q3 2019).

Table 98: Summary of QALYs by health state

Health state	IXA+LEN+DEX	BORT+DEX	Increment	% Increment
Pre-progression QALYs	1.415	1.219	0.196	8.38%
Post-progression QALYs	2.547	0.410	2.138	91.62%
Total	3.932	1.596	2.336	100.00%
Key: BORT, bortezomib; DEX, dexamethasone; LEN, lenalidomide; QALYs, quality-adjusted life years				

Costs

The discounted total costs associated with each health state for IXA+LEN+DEX and BORT+DEX are shown in Table 99. The majority of costs incurred by IXA+LEN+DEX occur in the pre-progression health state, primarily associated with drug costs. This is evident in Table 100, showing the summary of predicted resource use by category of cost in the base case analysis, where the costs incurred by IXA+LEN+DEX patients are primarily driven by drug costs.

The costs associated with treatment, disease management, concomitant medications and TRAEs are shown to be greater for patients treated with IXA+LEN+DEX. This is primarily because patients are living longer and treated for longer in the IXA+LEN+DEX arm, reflected by the life year breakdown shown above. BORT+DEX is associated with greater terminal care costs which shows that more patients are dying when receiving treatment with BORT+DEX compared with IXA+LEN+DEX.

Table 99: Summary of costs by health state

Health state	IXA+LEN+DEX	BORT+DEX	Increment	% Increment
Pre-progression costs	[redacted]	£32,369	[redacted]	92.25%
Post-progression costs	[redacted]	£6,402	[redacted]	7.75%
Total costs	[redacted]	£38,770	[redacted]	100.00%
Key: BORT, bortezomib; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; QALY, quality-adjusted life year				

Table 100: Summary of predicted resource use by category of cost

Health state	IXA+LEN+DEX	BORT+DEX	Increment	% absolute increment
Drug costs and therapy specific resource use	[redacted]	£28,057	[redacted]	91.71%
Concomitant medication	£9,590	£3,957	£5,633	2.62%
Adverse events	£1,512	£789	£724	0.34%
Disease management	£15,715	£3,981	£8,480	5.46%
Terminal care	£1,702	£1,987	-£285	-0.13%
Total costs	[redacted]	£38,770	[redacted]	100.00%
Key: BORT, bortezomib; DEX, dexamethasone; LEN, lenalidomide; QALY, quality-adjusted life year				

5.7.3 IXA+LEN+DEX compared with LEN+DEX – 2+ prior therapies

5.7.3.1 Base-case incremental cost effectiveness analysis results (2+ prior therapies)

The base case results for IXA+LEN+DEX compared with LEN+DEX are shown in Table 101 based on the data for the patient population who have had at least two prior therapies, used to represent a 3rd line treatment positioning for IXA. Results were subject to a discount rate of 3.5% per annum and are presented over a lifetime horizon (18.74 years).

IXA+LEN+DEX is associated with a gain of 0.97 QALYs per patient and an incremental cost of [redacted] per patient compared with LEN+DEX. The resulting ICER is [redacted] per QALY gained.

Table 101: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
LEN+DEX	£91,428	3.324	2.2041	-	-	-	-
IXA+LEN+DEX	[redacted]	4.708	3.1736	[redacted]	1.385	0.9694	[redacted]
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; LYG, life years gained; QALYs, quality-adjusted life years							

5.7.3.2 Clinical outcomes from the model (2+ prior therapies)

Table 102 displays the clinical outcomes and the model outcomes for the three main measures: OS, PFS, ToT, as well as AEs for the 2+ prior therapies population. Clinical outcomes are presented for all comparisons assuming the base case parametric curve fits and adjusting covariates using the mean of covariates method (see Section 5.3).

The mean OS, PFS and ToT are comparable and consistent with the respective observed clinical outcomes reported in the TMM1 clinical trial.

Table 102 Comparison of clinical outcomes with model outcomes for the 2+ prior lines population

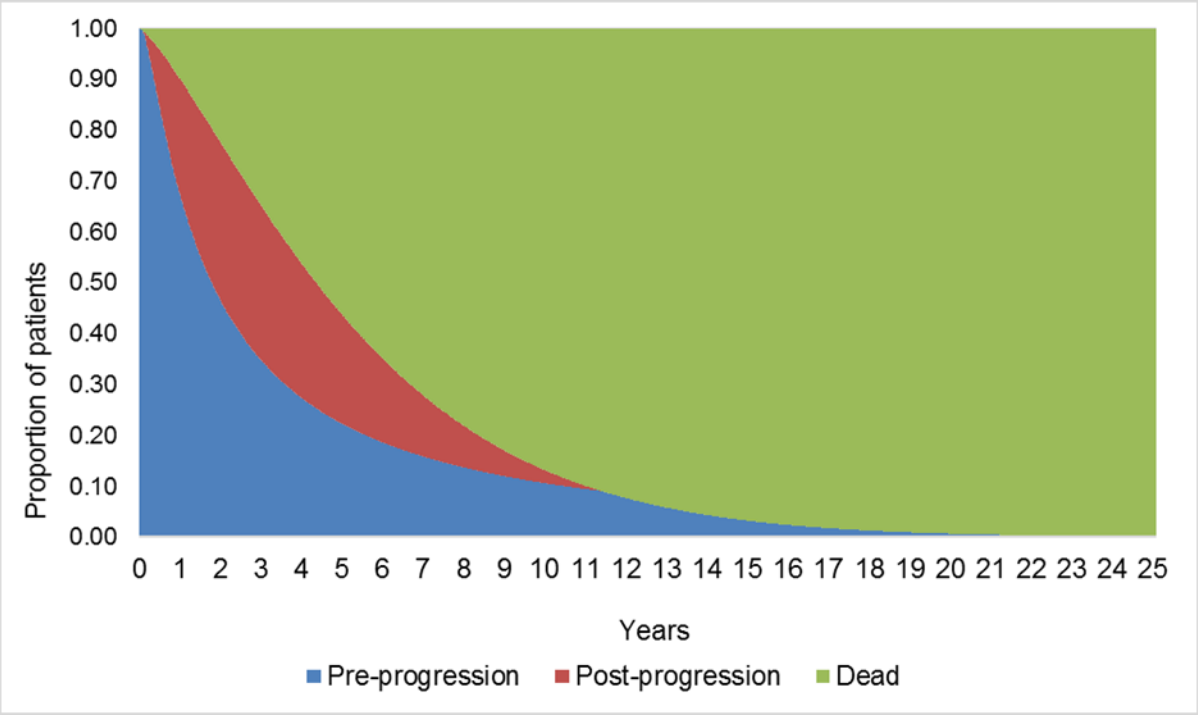
Outcome	Clinical trial result	Model result	Clinical trial result	Model result
Mean survival (months) 2+ prior lines population (n=297)				
	IXA+LEN+DEX		**LEN+DEX**	
Overall Survival	20.89	21.14	19.33	19.77
Progression-free survival	16.56	16.63	12.94	13.87
Time on treatment	15.52	15.86	13.84	13.98
Adverse events (number of events)				
	IXA+LEN+DEX (n=360)		**LEN+DEX (n=360)**	
	Clinical trial result	**Model result**	**Clinical trial result**	**Model result**
Anaemia	40	58.07	59	77.51
Cardiac failure	8	12.76	6	8.91
Deep vein thrombosis	2	2.84	3	3.82
Diarrhoea	28	39.67	8	10.18
Fatigue	14	19.84	9	11.45
Upper respiratory tract infection/Pulmonary-related	3	4.25	2	3.82
Ischaemic heart disease	2	2.84	3	3.82
Nausea	6	0.00	0	0.00
Neutropenia	151	218.82	114	157.28
Peripheral neuropathy	1	1.42	3	3.82
Pneumonia	27	50.99	36	49.59
Pulmonary embolism	8	11.34	8	10.18
Rash-related	16	28.34	5	6.36
Renal failure	6	8.51	17	21.63
Thrombocytopaenia	75	107.53	22	27.99
Vomiting	4	5.67	2	2.55
New primary malignancy	5	1.42	2	2.55
Key: BORT, bortezomib; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; N, number.				

Markov traces

Markov traces are presented for the IXA+LEN+DEX and LEN+DEX comparison in Figure 47 and Figure 48, respectively. These graphs depict how patients move through the model health states over time when treated with IXA+LEN+DEX and LEN+DEX, respectively. At baseline 100% of patients are in the pre-progression health state, over time patient's transition to the post-progression and death health states.

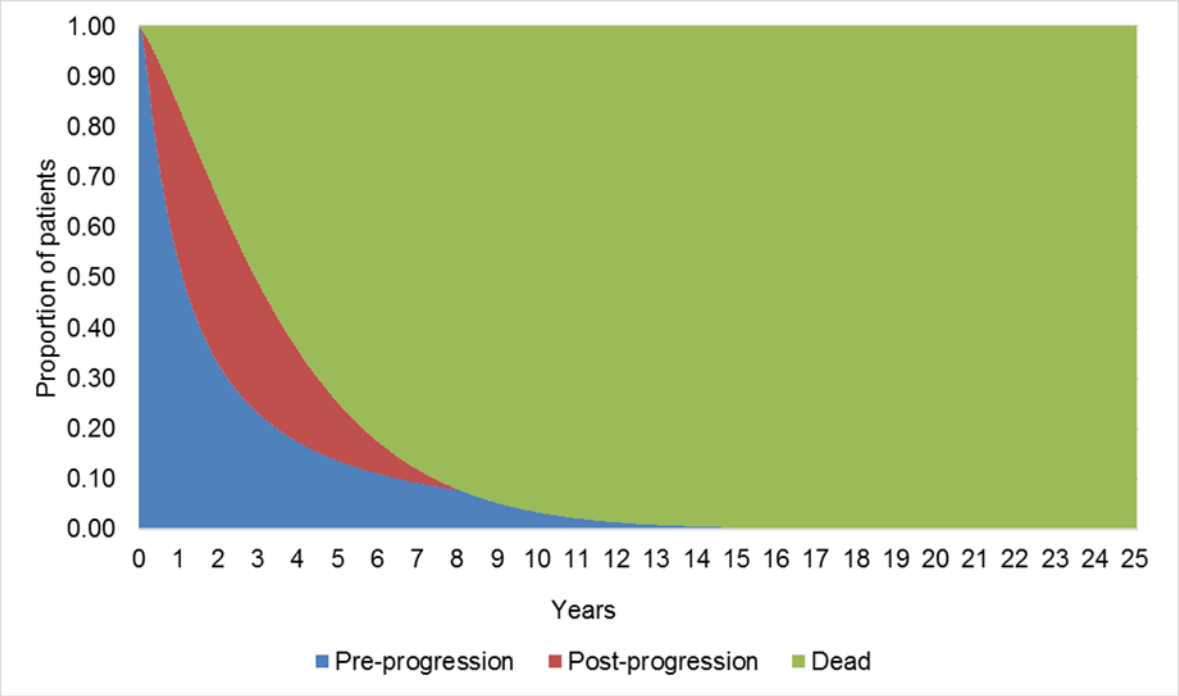
At first glance, the Markov traces show that patients remain in the progression free health state for longer when treated with IXA+LEN+DEX.

Figure 47: Patient distribution over time for patients who have received 2+ prior therapies and are receiving IXA+LEN+DEX



Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide

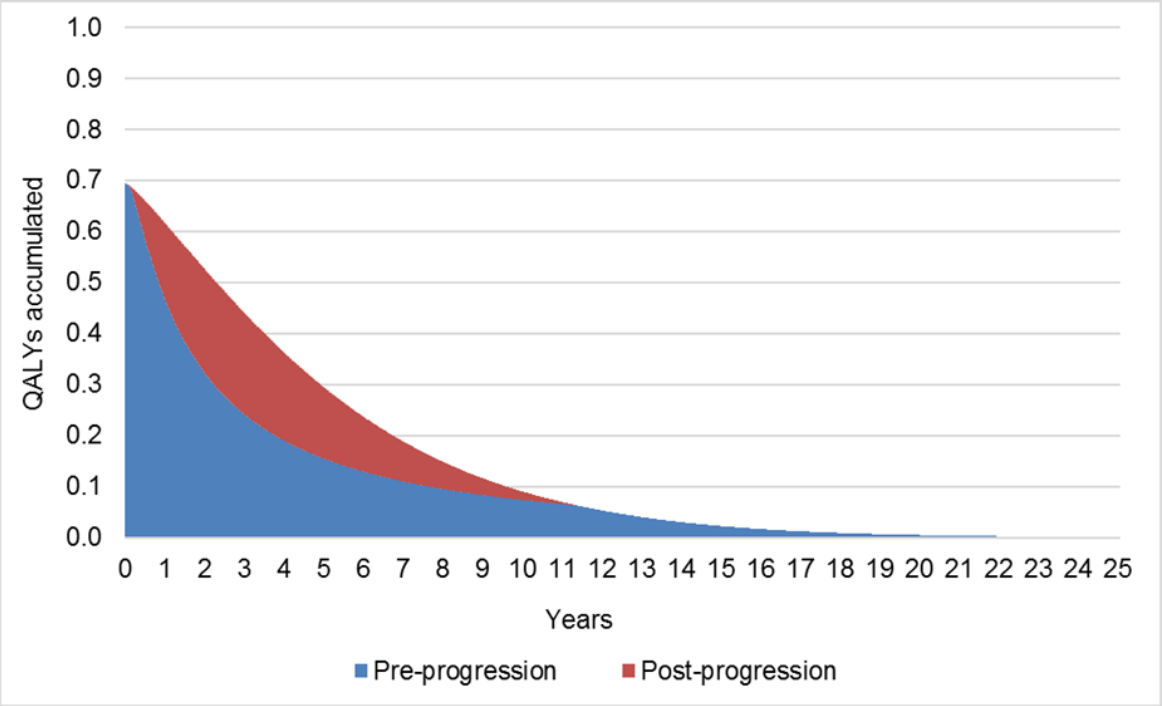
Figure 48: Patient distribution over time for patients who have received 2+ prior therapies and are receiving LEN+DEX



Key: DEX, dexamethasone; LEN, lenalidomide

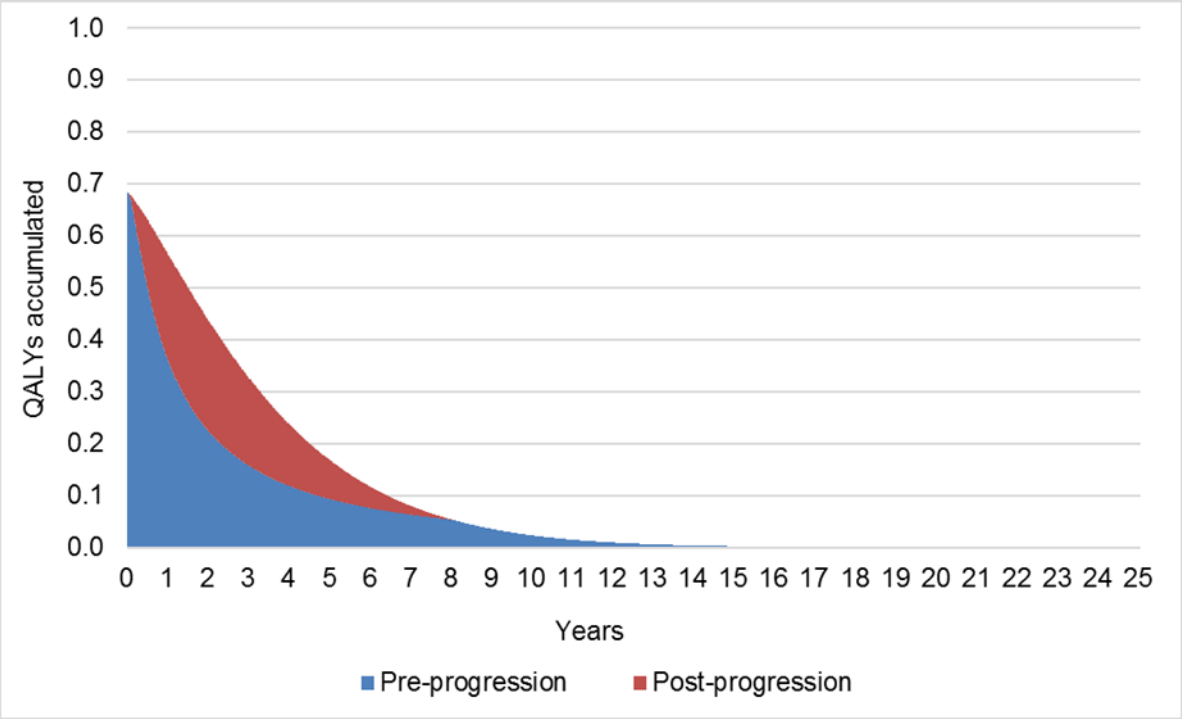
The accumulation of QALYs over time is shown in Figure 49 for IXA+LEN+DEX and Figure 50 for LEN+DEX for the pre-progression and post-progression health states over the lifetime horizon. QALYs are initially primarily accrued in the pre-progression health state; as time continues, the QALYs are increasingly accrued in the post-progression health state. Compared with LEN+DEX, the number of QALYs associated with IXA+LEN+DEX at each cycle are consistently higher.

Figure 49: Markov trace for QALYs accrued – IXA+LEN+DEX



Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; QALYs, quality adjusted life years

Figure 50: Markov trace for QALYs accrued –LEN+DEX



Key: DEX, dexamethasone; LEN, lenalidomide; QALYs, quality adjusted life years

5.7.3.3 Disaggregated results of the base case incremental cost effectiveness analysis (2+ prior therapies)

Life years

The total life years gained by patients in each health state for IXA+LEN+DEX versus LEN+DEX are detailed in Table 103. Life years are not discounted in the table below in line with the NICE reference case. Table 103 shows that treatment with IXA+LEN+DEX produces an incremental gain in life years compared with LEN+DEX for each of the model health states. The majority of these gains are accumulated whilst a patient is in the pre-progression health state (74.02%).

Table 103: Summary of life years by health state

Health state	IXA+LEN+DEX	LEN+DEX	Increment	% increment
Pre-progression: Life Years	3.130	2.105	1.025	74.02%
Post-progression: Life Years	1.579	1.219	0.360	25.98%
Life Years: On treatment	4.708	3.324	1.385	100.00%
Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide				

QALYs

Table 98 details the incremental QALYs gained by health state for IXA+LEN+DEX compared with LEN+DEX. These values are from the base case where QALYs were calculated using utilities estimated using the regression equation derived from the TMM1 clinical trial. QALYs are discounted using a 3.5% annual rate. Treatment with IXA+LEN+DEX results in higher QALYs across all health states, with the largest increment in the pre-progression health state.

Table 104: Summary of QALYs by health state

Health state	IXA+LEN+DEX	LEN+DEX	Increment	% Increment
Pre-progression QALYs	2.174	1.440	0.733	75.70%
Post-progression QALYs	1.033	0.798	0.235	24.30%
Total	3.174	2.204	0.969	100.00%
Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; QALY, quality-adjusted life year				

Costs

The discounted total costs associated with each health state for IXA+LEN+DEX and LEN+DEX are shown in Table 105. The majority of costs incurred by IXA+LEN+DEX occur in the pre-progression health state, primarily caused by the drug costs. This is evident in Table 106, showing the summary of predicted resource use by category of cost in the base case analysis, where the costs incurred by IXA+LEN+DEX patients are primarily driven by drug costs.

The costs associated with treatment, disease management, concomitant medications and TRAEs are shown to be greater for patients treated with IXA+LEN+DEX. This is primarily because patients are living longer and treated for longer in the IXA+LEN+DEX arm, reflected by the life year breakdown shown above. LEN+DEX is associated with greater terminal care costs which shows that more patients are dying when receiving treatment with LEN+DEX compared with IXA+LEN+DEX.

Table 105: Summary of costs by health state

Health state	IXA+LEN+DEX	LEN+DEX	Increment	% Increment
Pre-progression costs	[redacted]	£79,396	[redacted]	99.64%
Post-progression costs	[redacted]	£12,032	[redacted]	0.36%
Total costs	[redacted]	£91,428	[redacted]	100.00%
Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; QALY, quality-adjusted life year				

Table 106: Summary of predicted resource use by category of cost

Health State	IXA+LEN+DEX	LEN+DEX	Increment	% absolute increment
Drug costs and therapy specific resource use	[redacted]	£73,941	[redacted]	98.37%
Concomitant medication	£7,598	£5,363	£2,234	1.13%
Adverse events	£1,916	£1,394	£523	0.26%
Disease management	£9,378	£8,805	£573	0.29%
Terminal care	£1,812	£1,925	-£112	-0.06%
Total costs	[redacted]	£91,428	[redacted]	100.00%
Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; QALY, quality-adjusted life year				

5.8 Sensitivity analyses

5.8.1 Sensitivity analysis results – 1 prior therapy

5.8.1.1 Probabilistic sensitivity analysis – 1 prior therapy

To characterise uncertainty in the model inputs a probabilistic sensitivity analysis (PSA) was performed for the comparison of IXA+LEN+DEX with BORT+DEX. A PSA varies all inputs simultaneously based upon distributional information (see Section 5.6) and records each set of results to estimate a probabilistic ICER which may conceivably be the "true" underlying ICER.

Figure 51 presents the cost-effectiveness plane (CEP) for IXA+LEN+DEX compared with BORT+DEX based on 1,000 PSA iterations. CEPs show the incremental QALYs and costs of IXA+LEN+DEX relative to the comparator BORT+DEX, and CEACs show the likelihood of IXA+LEN+DEX being cost-effective compared to BORT+DEX at different WTP thresholds (Figure 52).

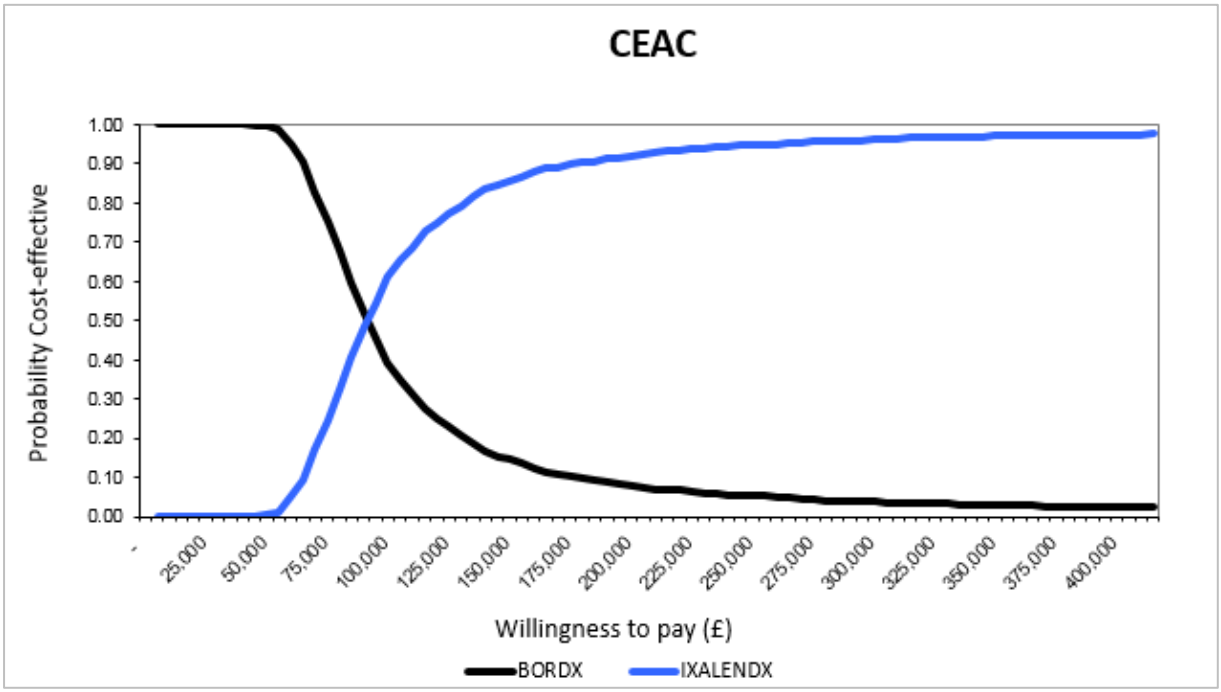
Mean incremental QALYs gained from IXA+LEN+DEX compared to BORT+DEX for the one prior therapy patient population was 2.31 (95% CI: [0.44 – 3.90]). Mean incremental costs were [redacted] The resulting probabilistic ICER was [redacted] which is comparable to the deterministic base case ICER of [redacted] indicating that the deterministic result is a good approximation of the mean probabilistic value. In the majority of simulations (99.00%), IXA+LEN+DEX provided a QALY gain compared to BORT+DEX.

Figure 51 Cost-effectiveness plane from 1,000 PSA iterations for IXA+LEN+DEX compared with BORT+DEX – 1 prior line

[redacted]

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

Figure 52: CEAC for IXA+LEN+DEX compared with BORT+DEX – 1 prior line



Key: BORT, bortezomib; CEAC, cost effectiveness acceptability curve; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years; WTP, willingness to pay

5.8.1.2 Deterministic sensitivity analysis – 1 prior therapy

A series of one-way sensitivity analyses were performed to evaluate the sensitivity of the model ICER to individual inputs, holding all else constant. Distribution information used in the model is provided in Appendix 12. Model results were recorded after changing each input to its upper and lower bound value in turn, upper and lower bounds were derived based on 95% confidence intervals estimated using distributional information presented in Appendix 12.

Table 107 presents the ten most influential parameters, shown in descending order of ICER sensitivity.

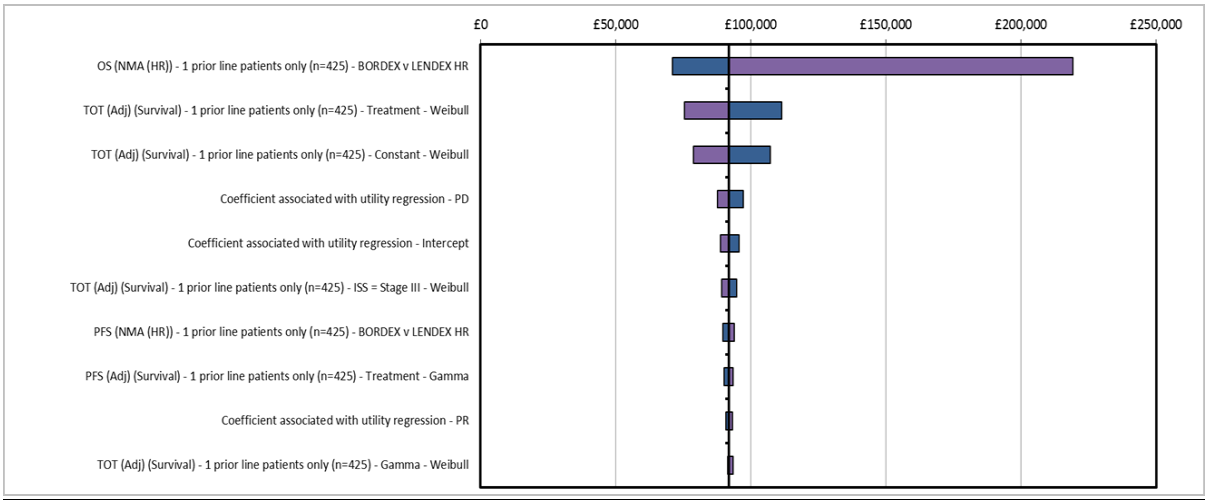
Figure **53** represents a tornado diagram presenting these results visually. The parameters with the greatest impact on model outcomes included in the OWSA were the hazard ratio applied to the LEN+DEX data to obtain the OS for BORT+DEX as well as the coefficients for the adjusted ToT parametric curve. The hazard ratio for OS directly impacts the incremental life years associated with IXA+LEN+DEX and BORT+DEX, and therefore is a driver of the ICER. Furthermore, modelled ToT has a significant impact on costs within the model (a larger ToT results in larger costs) and so this is also a driver of the results.

Table 107: OWSA: ten most influential parameters for IXA+LEN+DEX compared with BORT+DEX - 1 prior therapy

Variable	Lower Bound	Upper Bound	Difference
OS (NMA (HR)) - 1 prior line patients only (n=425) - BORDEX v LENDEX HR	[redacted]	[redacted]	[redacted]
TOT (Adj) (Survival) - 1 prior line patients only (n=425) - Treatment - Weibull	[redacted]	[redacted]	[redacted]
TOT (Adj) (Survival) - 1 prior line patients only (n=425) - Constant - Weibull	[redacted]	[redacted]	[redacted]
Coefficient associated with utility regression - PD	[redacted]	[redacted]	[redacted]
Coefficient associated with utility regression - Intercept	[redacted]	[redacted]	[redacted]
TOT (Adj) (Survival) - 1 prior line patients only (n=425) - ISS = Stage III - Weibull	[redacted]	[redacted]	[redacted]
PFS (NMA (HR)) - 1 prior line patients only (n=425) - BORDEX v LENDEX HR	[redacted]	[redacted]	[redacted]
PFS (Adj) (Survival) - 1 prior line patients only (n=425) - Treatment - Gamma	[redacted]	[redacted]	[redacted]
Coefficient associated with utility regression - PR	[redacted]	[redacted]	[redacted]
TOT (Adj) (Survival) - 1 prior line patients only (n=425) - Gamma - Weibull	[redacted]	[redacted]	[redacted]

Key: Adj, adjusted; BORT, bortezomib; DEX, dexamethasone; ISS, International Staging System; IXA, ixazomib; LEN, lenalidomide; N, number; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; ToT, time on treatment

Figure 53: Results of the one-way sensitivity analysis for IXA+LEN+DEX compared with BORT+DEX – 1 prior therapy



Key: Adj, adjusted; BOR, bortezomib; BORDEX, bortezomib + dexamethasone; DEX, dexamethasone; EOL, end of life; HR, hazard ratio; LEN, lenalidomide; LENDEX, lenalidomide + dexamethasone; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; PR, partial response; TOT, time on treatment

5.8.1.3 Scenario analysis – 1 prior therapy

The uncertainty around the structural assumptions has been included in the model through a number of scenario analyses (Table 108). In addition, an exploratory scenario has been performed to explore the paradox associated with a hypothetical zero cost for IXA.

Table 108: Scenario analyses for 1 prior therapy

Structural assumption in the base case	Scenario analysis
Lifetime horizon	15-year time horizon 20-year time horizon
Covariate adjusted clinical endpoints (see Section 5.3)	Non-covariate adjusted clinical endpoints
Modelled ToT independent of PFS i.e. patients may be treated beyond progression	Cap ToT by PFS i.e. ToT cannot exceed PFS
PFS parametric curve = gamma	PFS parametric curve = exponential, Weibull, gompertz, log-normal and log-logistic
OS parametric curve = delayed exponential from month 5	OS parametric curve = exponential, Weibull, gompertz, log-normal, log-logistic and gamma
ToT parametric curve = Weibull	ToT parametric curve = exponential, gompertz, log-normal, log-logistic and gamma
ToT for IXA+LEN+DEX vs LEN+DEX as estimated via extrapolation of duration of treatment data in the TMM1	Due to uncertainty in relative duration of treatment in clinical practice due to immaturity of TMM1 data exploration of the impact that a 25% relative reduction in ToT vs LEN+DEX.
ToT for IXA+LEN+DEX vs LEN+DEX as estimated via extrapolation of duration of treatment data in the TMM1	ToT based on duration of treatment observed in the TMM1 trial
First interim datacut used (IA1) from TMM1 (primary analysis of PFS) for PFS,	Later interim datacut used from TMM1 for PFS, OS and ToT (IA2 - July 2015, 23 months' follow-up). Relative efficacy estimates for BORT+DEX were

OS and ToT (Oct 2014 – 15 months follow-up)	obtained from the NMA discussed in Section 4.10 – for this scenario the NMA results from the networks considering the 1+ prior population and including the later data cut (IA2) of the TMM1 clinical trial were used for OS and PFS, 2.30 (95% CI: 1.17, 4.51) and 1.06 (95% CI: 0.61, 1.85), respectively. No ORR data were available from the later data cut of the TMM clinical trial and so the odds ratios obtained using the IA1 data were used from the 1+ prior therapies population, see Table 65). The hazard ratios and odds ratios estimated from the NMA for BORT+DEX were applied relative to LEN+DEX in the model.
Utility modelled using the regression equation fit to the data from the TMM1 clinical trial	Health state specific utilities obtained from the TA171 and TA338 NICE submissions. [96,97]
Efficacy data for IXA+LEN+DEX were obtained directly from the TMM1 clinical trial	Efficacy data (OS, PFS and ORR) for IXA+LEN+DEX sourced from the NMA base case for the 1+ prior therapy population (as a proxy for 1 prior therapy patients, see Table 44, Table 45 and Table 46 for PFS, OS and ORR, respectively, in Section 4.10). This scenario used hazard ratio/odds ratio from the network considering all studies (RCTs and obersvational data) using doses specific to the marketing authorisation for OS and ORR. To maintain consistency with the BORT+DEX comparison, this scenario used a hazard ratio from the network considering all studies (RCTs and observational data) pooling all doses observed across studies for PFS.
The list price of Ixazomib was £6,336 per cycle	***Exploratory scenario:*** The price of Ixazomib was set to £0, to explore the paradox that the cost-effectiveness of the regimen is adversely affected by the incremental costs of lenalidomide in the additional PFS time patients experience with ixazomib, such that it is difficult to demonstrate cost-effectiveness of ixazomib even at zero price.
Key: BORT, bortezomib; DEX, dexamethasone; ITT, intention to treat; IXA, ixazomib; LEN, lenalidomide; NMA, network meta-analysis; ORR, overall response rate; OS, overall survival; PFS, progression free survival; RCTs, randomised controlled trials; RWE, real world evidence; ToT, time on treatment	

The results from each of these scenarios are given in Table 109 below for IXA+LEN+DEX compared with BORT+DEX. Section 5.8.2.3 discusses the scenario analyses for IXA+LEN+DEX compared with LEN+DEX for the 2-prior line population.

Table 109: Scenario analysis results - 1 prior therapy

Scenario	Incremental costs	Incremental QALYs	ICER
Base case	[redacted]	2.336	[redacted]
Time horizon 15 years	[redacted]	2.094	[redacted]
Time horizon 20 years	[redacted]	2.263	[redacted]
Discount rate costs and QALYs: 0%	[redacted]	3.024	[redacted]
Non-covariate adjusted clinical endpoints	[redacted]	2.324	[redacted]
Cap ToT by PFS	[redacted]	2.336	[redacted]
PFS parametric curve: Exponential	[redacted]	2.341	[redacted]
PFS parametric curve: Weibull	[redacted]	2.332	[redacted]
PFS parametric curve: Gompertz	[redacted]	2.329	[redacted]
PFS parametric curve: Log-normal	[redacted]	2.353	[redacted]
PFS parametric curve: Log-logistic	[redacted]	2.348	[redacted]
PFS parametric curve: Gamma	[redacted]	2.336	[redacted]
OS parametric curve: Exponential	[redacted]	2.360	[redacted]
OS parametric curve: Weibull	[redacted]	1.586	[redacted]
OS parametric curve: Gompertz	[redacted]	0.980	[redacted]
OS parametric curve: Log-normal	[redacted]	3.120	[redacted]
OS parametric curve: Log-logistic	[redacted]	2.222	[redacted]
OS parametric curve: Gamma	[redacted]	2.676	[redacted]
OS parametric curve: Delayed exponential	[redacted]	2.336	[redacted]
ToT parametric curve: Exponential	[redacted]	2.335	[redacted]
ToT parametric curve: Weibull	[redacted]	2.336	[redacted]
ToT parametric curve: Gompertz	[redacted]	2.336	[redacted]
ToT parametric curve: Log-normal	[redacted]	2.334	[redacted]
ToT parametric curve: Log-logistic	[redacted]	2.335	[redacted]
ToT parametric curve: Gamma	[redacted]	2.336	[redacted]
25% reduction in ToT on IXA+LEN+DEX	[redacted]	2.337	[redacted]
Duration of treatment based on observed data in TMM1 study	[redacted]	2.337	[redacted]
Later interim datacut used from TMM1 (July 2015 – 23 months follow-up)	[redacted]	1.842	[redacted]

Utility source: TMM1 clinical trial	[redacted]	2.336	[redacted]
Utility source: TA171	[redacted]	2.283	[redacted]
Utility source: TA338	[redacted]	2.164	[redacted]
Efficacy data for IXA+LEN+DEX sourced from NMA (see Table 44, Table 45 and Table 46 for PFS, OS and ORR, respectively, in Section 4.10)	[redacted]	2.969	[redacted]
Exploratory scenario: setting the cost of IXA to £0	[redacted]	2.336	[redacted]
Key: BORT, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; ITT, intention to treat; IXA, ixazomib; LEN, lenalidomide; NMA, network meta-analysis; ORR, overall response rate; OS, overall survival; PFS, progression free survival; QALYs, quality adjusted life years; RCTs, randomised controlled trials; RWE, real world evidence; ToT, time on treatment			

The results appear sensitive to the choice of parametric curve fit to the OS data, with ICERs ranging from [redacted] to [redacted]. The ICER associated with the gompertz distribution is a notable outlier. However, the gompertz distribution is not a statistically plausible fit to the data as the proportional hazards assumption does not hold and thus invalidates this curve choice. Removing statisitically implausible parametric curves, ICERs range from [redacted] to [redacted]. This high uncertainty from the extrapolation of OS is associated with the immaturity of this data from the TMM1 clinical trial, and therefore a large amount of uncertainty is incorporated into the parametric curve fitting.

The results are also sensitive to the choice of parametric curve fit to the ToT data, with ICERs ranging from [redacted] to [redacted]. The fit of parametric curves to the ToT data is also an expected driver of model results as the cost of treatment makes up a large proportion of the total costs in the model. ToT data from the TMM1 trial is also immature with a large proportion of patients still on treatment at end of follow-up; 42.18 % and 34.75% remain on treatment with IXA+LEN+DEX and LEN+DEX, respectively. Feedback from clinicians and RWE indicated that the ToT for LEN+DEX observed in the TMM1 clinical trial surpassed what might be expected in UK clinical practice, and so by inference there is also uncertainty that the duration of IXA+LEN+DEX is also above that which would be expected in clinical practice (see Section 5.3.5.1). The immaturity of the ToT data for IXA+LEN+DEX, means there is high uncertainty associated with any extrapolation with subsequently a significant impact on the ICER associated with different durations of treatment, with the results senstive to lower duration of treatment assumed for clinical practice. In scenario analysis, a 25% reduction in estimated ToT associated with IXA+LEN+DEX produces an ICER of [redacted] (Table 109 above). A large part of the uncertainty is associated with the impact of extrapolation of ToT data, which is illustrated by scenario analysis in which no extrapolation is performed (ie the observed data for IXA+LEN+DEX from TMM1 is used for duration of treatment), which produces an ICER of [redacted]

The scenario analysis using the later datacut for IXA+LEN+DEX increased the ICER to [redacted], and the results were not highly sensitive to an alternative source for utility estimates.

Using the NMA data for IXA+LEN+DEX reduces the ICER to [redacted], this indicates that the data utilised from the NMA provides different efficacy estimates for IXA+LEN+DEX from those in the TMM1 clinical trial, with an improved QALY gain estimate (see Table 44, Table 45 and Table 46 for PFS, OS and ORR, respectively, in Section 4.10). There may be a number of factors contributing to this which could be explored when more data becomes available from the TMM1 clinical trial.

In the base case, efficacy data for BORT+DEX was obtained from hazard ratios and an odds ratio derived from the NMA presented in Section 4.10. The relative efficacy estimates for OS and ORR were obtained from the 1+ prior therapies population pooling all studies (RCTs and observational data) across studies considering the doses specific to marketing authorisations only (Table 65). Due to lack of data, the relative efficacy estimates for PFS were obtained from the 1+ prior therapies population pooling all studies (RCTs and observational data) and pooling across different doses (Table 65). Section 4.10 (Table 44, Table 45 and Table 46) presents the results from scenarios for BORT+DEX compared with IXA+LEN+DEX, these show little difference between the scenarios and the base case and, as such, no scenario analyses were conducted in the economic model.

An exploratory scenario was performed in which the cost of ixazomib was set at zero, which was designed to explore the paradox that when a new drug such as this is used in combination with another expensive treatments (i.e. lenalidomide) that may have bordeline cost-effectiveness, [225] then even at very low prices, ixazomib may struggle to show cost-effectiveness. This is demonstrated by the fact that at zero price/cost the ICER is still only just below the conventional threshold of cost-effectiveness at [redacted].

5.8.1.4 Summary of sensitivity analyses results – 1 prior therapy

Model results were reasonably robust to sensitivity analyses with the key areas of uncertainty surrounding the hazard ratio associated with OS for BORT+DEX relative to LEN+DEX, and uncertainty associated with absolute and relative ToT for IXA+LEN+DEX vs BORT +DEX.

The hazard ratio for OS associated with BORT+DEX is applied to the LEN+DEX data from the TMM1 clinical trial. The ToT data was obtained directly from the TMM1 clinical trial. The uncertainty associated with both OS and ToT estimates are related to the immaturity of the OS and ToT data in TMM1, and the limitations of the data for BORT+DEX from the NMA. . More mature clinical trial data when available should increase the robustness of model findings and reduce uncertainty in the model.

The PSA indicated that simultaneous variation of parameter values resulted in IXA+LEN+DEX having an incremental QALY gain compared to BORT+DEX in the majority of iterations (99.00%). This is illustrated by Figure 51, which shows most of the PSA points lay in the north-east quadrant of the cost-effectiveness plane.

5.8.2 Sensitivity analysis results – 2+ prior therapies

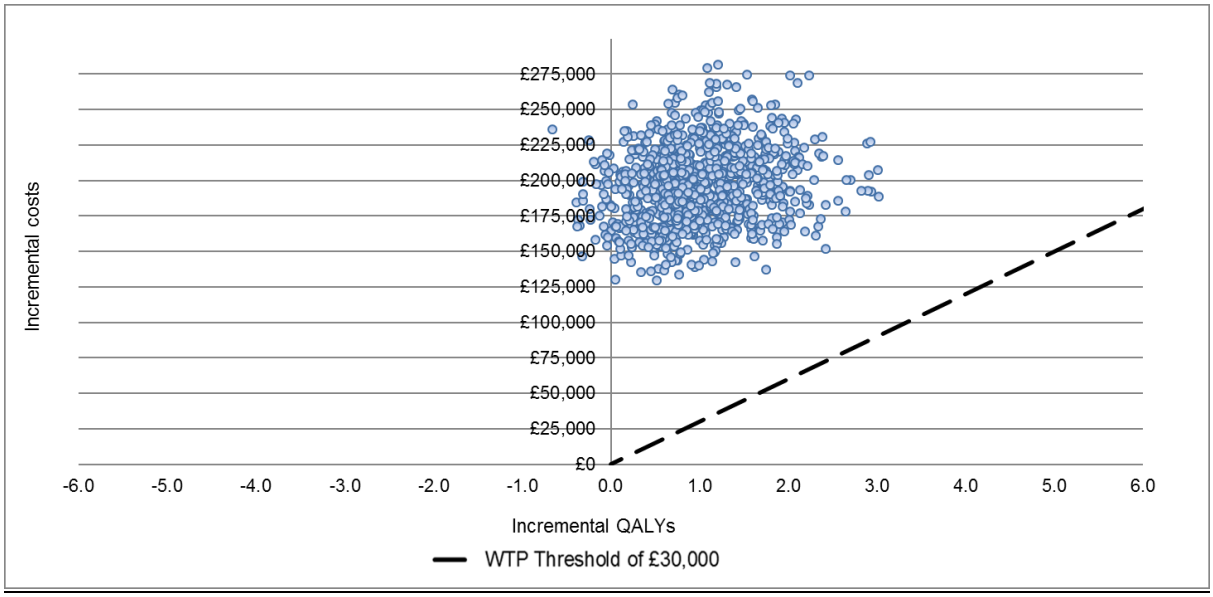
5.8.2.1 Probabilistic sensitivity analysis – 2+ prior therapies

To characterise uncertainty in the model inputs a PSA was performed for the comparison of IXA+LEN+DEX with LEN+DEX for the two prior therapies patient population. A PSA varies all inputs simultaneously based upon distributional information (see Section 5.6) and records each set of results to estimate a probabilistic ICER which may conceivably be the "true" underlying ICER.

The results of 1,000 PSA iterations are presented in Figure 54 and

Figure 55 as a CEP and a CEAC. Mean incremental QALYs gained from IXA+LEN+DEX compared to LEN+DEX for the two prior therapies patient population were 1.01 (95% CI: [-0.06 – 2.23]). Mean incremental costs were [redacted]The resulting probabilistic ICER was [redacted]which is comparable to the deterministic base case ICER of [redacted]indicating that the deterministic result is a good approximation of the mean probabilistic value. In the majority of simulations (96.60%), IXA+LEN+DEX provided a QALY gain compared to LEN+DEX.

Figure 54: Cost-effectiveness plane from 1,000 PSA iterations for IXA+LEN+DEX compared with LEN+DEX – 2 prior therapies

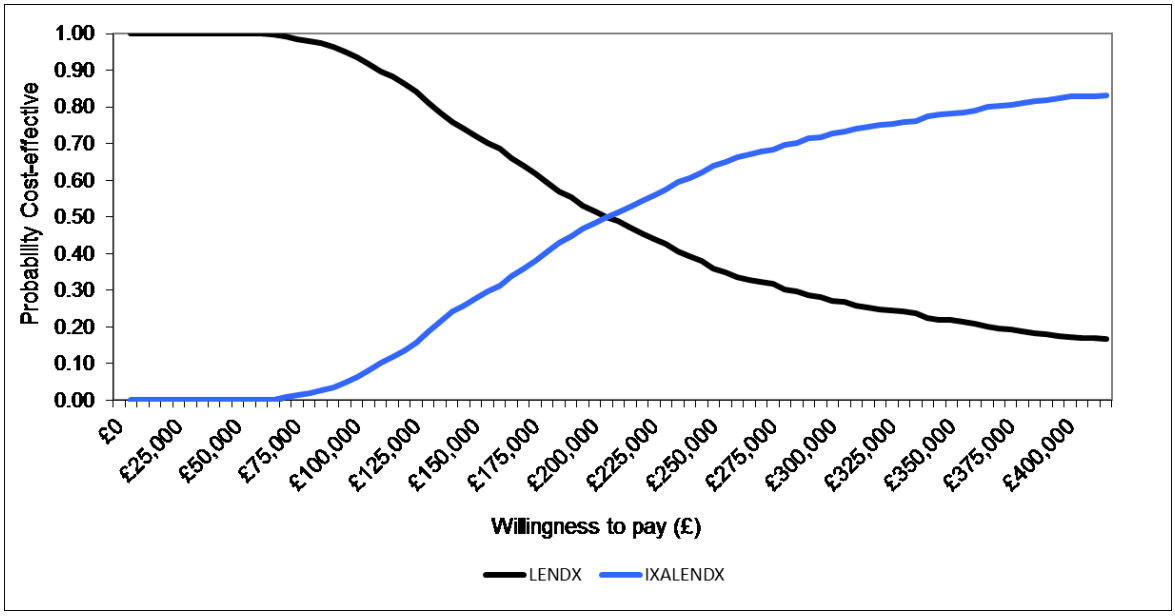


Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years; WTP, willingness to pay

The CEAC for IXA+LEN+DEX compared with LEN+DEX is presented in

Figure 55.

Figure 55: Cost-effectiveness acceptability curve for IXA+LEN+DEX compared with LEN+DEX – 2 prior therapies



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

5.8.2.2 Deterministic sensitivity analysis – 2+ prior therapies

A series of one-way sensitivity analyses were performed to evaluate the sensitivity of the model ICER to individual inputs, holding all else constant. Distribution information used in the model is provided in Appendix 12. Model results were recorded after changing each input to its upper and lower bound value in turn, upper and lower bounds were derived based on 95% confidence intervals estimated using distributional information presented in Appendix 12.

Table 110 presents the ten most influential parameters, shown in descending order of ICER sensitivity. OS directly impacts the incremental life years associated with IXA+LEN+DEX and LEN+DEX, and therefore is expected to be a driver of the ICER. Furthermore, modelled ToT has a significant impact on costs within the model (a larger ToT results in larger costs) and so this is also expected to be a driver of the results.

Table 110: OWSA: ten most influential parameters for IXA+LEN+DEX compared with LEN+DEX – 2+ prior lines

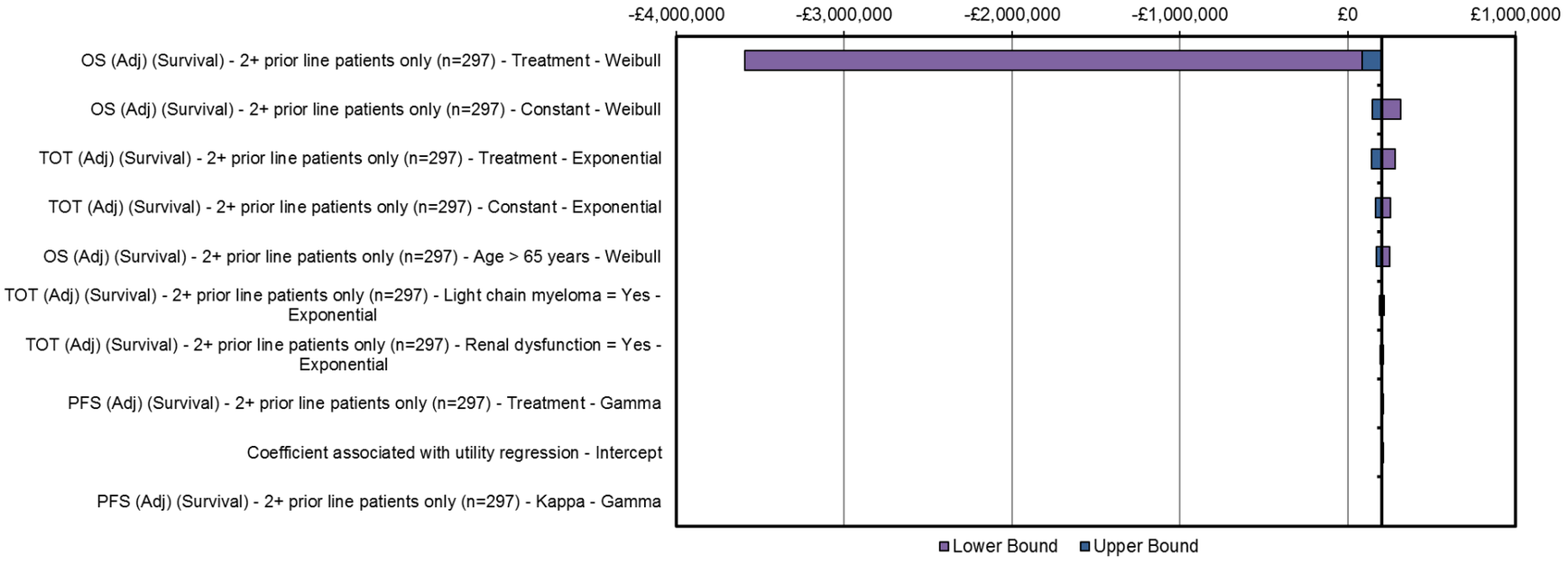
Variable	Lower Bound	Upper Bound	Difference
OS (Adj) (Survival) - 2+ prior line patients only (n=297) - Treatment - Weibull	[redacted]	[redacted]	[redacted]
OS (Adj) (Survival) - 2+ prior line patients only (n=297) - Constant - Weibull	[redacted]	[redacted]	[redacted]
TOT (Adj) (Survival) - 2+ prior line patients only (n=297) - Treatment - Exponential	[redacted]	[redacted]	[redacted]

TOT (Adj) (Survival) - 2+ prior line patients only (n=297) - Constant - Exponential	[redacted]	[redacted]	[redacted]
OS (Adj) (Survival) - 2+ prior line patients only (n=297) - Age > 65 years - Weibull	[redacted]	[redacted]	[redacted]
TOT (Adj) (Survival) - 2+ prior line patients only (n=297) - Light chain myeloma = Yes - Exponential	[redacted]	[redacted]	[redacted]
TOT (Adj) (Survival) - 2+ prior line patients only (n=297) - Renal dysfunction = Yes - Exponential	[redacted]	[redacted]	[redacted]
PFS (Adj) (Survival) - 2+ prior line patients only (n=297) - Treatment - Gamma	[redacted]	[redacted]	[redacted]
Coefficient associated with utility regression - Intercept	[redacted]	[redacted]	[redacted]
PFS (Adj) (Survival) - 2+ prior line patients only (n=297) - Kappa - Gamma	[redacted]	[redacted]	[redacted]
Key: Adj, adjusted; DEX, dexamethasone; ISS, International Staging System; IXA, ixazomib; LEN, lenalidomide; N, number; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; ToT, time on treatment			

Figure 56 depicts a tornado diagram presenting these results visually. The parameters with the greatest impact on model outcomes included in the OWSA are the coefficients associated with the adjusted OS and ToT parametric curves. When the OS treatment effect for IXA+LEN+DEX relative to LEN+DEX is set to its lower bound the ICER falls into the north-west quadrant of the cost-effectiveness plane and LEN+DEX dominates IXA+LEN+DEX; LEN+DEX is less costly and accumulates more QALYs than IXA+LEN+DEX. However, the OS data from the IA1 data cut of the TMM1 clinical trial is extremely immature (with events recorded for less than 20% of patients). As such, there is a large amount of uncertainty associated with the extrapolation of these data. We believe that more mature data from the later data cuts (i.e. IA3 due Q2 2017) will reduce the uncertainty in the model and improve the robustness of results.

Both parametric curves were fit to patient level data obtained from the TMM1 clinical trial, data cut IA1. OS directly impacts the incremental life years associated with IXA+LEN+DEX and LEN+DEX, and therefore is a driver of the ICER. Furthermore, modelled ToT has a significant impact on costs within the model (a larger ToT results in larger costs) and so this is also a driver of the results.

Figure 56: Results of one-way sensitivity analysis – 2+ prior therapies – IXA+LEN+DEX vs LEN+DEX



Key: Adj, adjusted; BOR, best overall response; DEX, dexamethasone; EOL, end of life; HR, hazard ratio; LEN, lenalidomide; LENDEX, lenalidomide + dexamethasone; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; PR, partial response; SD, stable disease; TOT, time on treatment

5.8.2.3 Scenario analysis – 2+ prior therapies

The uncertainty around the structural assumptions has been included in the model through a number of scenario analyses (Table 111). In addition, an exploratory scenario has been performed to explore the paradox associated with a hypothetical zero cost for IXA.

Table 111: Scenario analyses for 2+ prior therapies

Structural assumption in the base case	Scenario analysis
Lifetime horizon	15-year time horizon 20-year time horizon
Discount rate for costs and QALYs set to 3.5%	Discount rate for costs and QALYs set to 0.0%
Covariate adjusted clinical endpoints (see Section 5.3)	Non-covariate adjusted clinical endpoints
Modelled ToT independent of PFS i.e. patients may be treated beyond progression	Cap ToT by PFS i.e. ToT cannot exceed PFS
PFS parametric curve = gamma	PFS parametric curve = exponential, Weibull, gompertz, log-normal and log-logistic
OS parametric curve = Weibull	OS parametric curve = exponential, gompertz, log-normal, log-logistic and gamma
ToT parametric curve = exponential	ToT parametric curve = Weibull, gompertz, log-normal, log-logistic and gamma
ToT for IXA+LEN+DEX vs LEN+DEX as estimated via extrapolation of duration of treatment data in the TMM1 study	Due to uncertainty in relative duration of treatment in clinical practice due to immaturity of TMM1 data exploration of the impact that a 25% relative reduction in ToT vs LEN+DEX.
ToT for IXA+LEN+DEX vs LEN+DEX as estimated via extrapolation of duration of treatment data in the TMM1	ToT based on duration of treatment observed in the TMM1 trial
First interim datacut used from TMM1 (primary analysis of PFS) for PFS, OS and ToT (Oct 2014 – 15 months follow-up)	Later interim datacut used from TMM1 for PFS, OS and ToT (July 2015 – 23 months follow-up)
Utility modelled using the regression equation fit to the data from the TMM1 clinical trial	Health state specific utilities obtained from the TA171 and TA338 NICE submissions. [96,97]
The list price of Ixazomib was £6,336	***Exploratory scenario 1:*** The price of Ixazomib was set to £0, to explore the paradox that the cost-effectiveness of the regimen is adversely affected by the incremental costs of lenalidomide in the additional PFS time patients experience with ixazomib, such that it is difficult to demonstrate cost-effectiveness of ixazomib even at zero or low prices/cost for the drug.
Efficacy data for IXA+LEN+DEX were obtained directly from the TMM1 clinical trial	Efficacy data (OS, PFS and ORR) for IXA+LEN+DEX sourced from the NMA base case for the 1+ prior therapy population (as a proxy for 1 prior therapy patients, see Table 44, Table 45 and Table 46 for PFS, OS and ORR, respectively, in Section 4.10). This scenario used hazard ratio/odds ratio from the network considering all studies (RCTs and obersvational data) using doses specific to the marketing authorisation for OS and ORR. To maintain consistency with the BORT+DEX comparison, this scenario used a hazard ratio from the network considering all studies (RCTs and observational data) pooling all doses observed across studies for PFS.
LEN+DEX costed in the IXA+LEN+DEX regimen as per standard methods using ToT and UK cost references	***Exploratory scenario 2:*** Only additional LEN+DEX costed in the IXA+LEN+DEX regimen, over and above what is received in the LEN+DEX regimen. This scenario captures the additional cost of LEN+DEX required due to the increase in ToT associated with IXA+LEN+DEX

	Exploratory scenario 3: Additional LEN+DEX over and above what is received in the LEN+DEX regimen is not costed. This scenario only captures the cost of the LEN+DEX that would be received in current practice anyway.
Key: DEX, dexamethasone; ITT, intention to treat; IXA, ixazomib; LEN, lenalidomide; NMA, network meta-analysis; ORR, overall response rate; OS, overall survival; PFS, progression free survival; RCTs, randomised controlled trials; RWE, real world evidence; ToT, time on treatment	

The results from each of these scenarios are given in Table 112 below for IXA+LEN+DEX compared with LEN+DEX. Section 5.8.1.3 discusses the scenario analyses for IXA+LEN+DEX compared with BORT+DEX for the 1-prior therapy population.

Table 112: Scenario analysis results for 2+ prior therapies

Scenario	Incremental costs	Incremental QALYs	ICER
Base case	[redacted]	0.964	[redacted]
Time horizon 15 years	[redacted]	0.943	[redacted]
Time horizon 20 years	[redacted]	0.973	[redacted]
Discount rate costs and QALYs: 0%	[redacted]	1.194	[redacted]
Non-covariate adjusted clinical endpoints	[redacted]	0.886	[redacted]
Cap ToT by PFS	[redacted]	0.969	[redacted]
PFS parametric curve: Exponential	[redacted]	0.964	[redacted]
PFS parametric curve: Weibull	[redacted]	0.951	[redacted]
PFS parametric curve: Gompertz	[redacted]	0.946	[redacted]
PFS parametric curve: Log-normal	[redacted]	0.966	[redacted]
PFS parametric curve: Log-logistic	[redacted]	0.964	[redacted]
PFS parametric curve: Gamma	[redacted]	0.969	[redacted]
OS parametric curve: Exponential	[redacted]	1.486	[redacted]
OS parametric curve: Weibull	[redacted]	0.969	[redacted]
OS parametric curve: Gompertz	[redacted]	0.521	[redacted]
OS parametric curve: Log-normal	[redacted]	1.028	[redacted]
OS parametric curve: Log-logistic	[redacted]	1.130	[redacted]
OS parametric curve: Gamma	[redacted]	1.155	[redacted]
ToT parametric curve: Exponential	[redacted]	0.969	[redacted]
ToT parametric curve: Weibull	[redacted]	0.969	[redacted]
ToT parametric curve: Gompertz	[redacted]	0.969	[redacted]
ToT parametric curve: Log-normal	[redacted]	0.969	[redacted]
ToT parametric curve: Log-logistic	[redacted]	0.969	[redacted]
ToT parametric curve: Gamma	[redacted]	0.969	[redacted]
25% reduction in ToT on IXA+LEN+DEX	[redacted]	0.970	[redacted]
Duration of treatment based on observed data in TMM1 study	[redacted]	0.970	[redacted]
Later interim datacut used from TMM1(July 2015 – 23 months follow-up)	[redacted]	0.992	[redacted]
Utility source: TMM1 clinical trial	[redacted]	0.969	[redacted]
Utility source: TA171	[redacted]	1.056	[redacted]

Utility source: TA338	[redacted]	1.001	[redacted]
Efficacy data for IXA+LEN+DEX and LEN+DEX sourced from NMA	[redacted]	0.873	[redacted]
Exploratory scenario 1: setting the cost of IXA to £0	[redacted]	0.969	[redacted]
Exploratory scenario 2: Only additional LEN+DEX costed in the IXA+LEN+DEX regimen, over and above what is received in the LEN+DEX regimen. This scenario captures the additional cost of LEN+DEX required due to the increase in ToT associated with IXA+LEN+DEX	[redacted]	0.969	[redacted]
Exploratory scenario 3: Additional LEN+DEX over and above what is received in the LEN+DEX regimen is not costed. This scenario only captures the cost of the LEN+DEX that would be received in current practice anyway.	[redacted]	0.969	[redacted]
Key: DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; ITT, intention to treat; IXA, ixazomib; LEN, lenalidomide; NMA, network meta-analysis; ORR, overall response rate; OS, overall survival; PFS, progression free survival; QALYs, quality adjusted life years; RCTs, randomised controlled trials; RWE, real world evidence; ToT, time on treatment			

The results are sensitive to the choice of parametric curve fit to the OS data, with ICERs ranging from [redacted] to [redacted]. The high uncertainty from the extrapolation of OS is associated with the immaturity of these data from the TMM1 clinical trial, and therefore a large amount of uncertainty is incorporated into the parametric curve fitting.

The results are also sensitive to the choice of parametric curve fit to the ToT data, with ICERs ranging from [redacted] to [redacted] The log-normal and log-logistic curve fits to the ToT data result in high ICERs (much higher than the base case). However, these curves were deemed clinically implausible by clinicians (see section 5.3.5); the large tails associated with these curves resulted in a large proportion of patients remaining on treatment over the lifetime horizon which is not plausible for a relapsing disease like MM. Removing clinically implausible parametric curves, ICERs range from [redacted] to [redacted]. The fit of parametric curves to the ToT data is an expected driver of model results as the cost of treatment makes up a large proportion of the total costs in the model. ToT data from the TMM1 trial is also immature with a large proportion of patients still on treatment at end of follow-up; 42.18 % and 34.75% remain on treatment with IXA+LEN+DEX and LEN+DEX in the ITT (1+ prior therapies) population, respectively. Feedback from clinicians and RWE indicated that the ToT for LEN+DEX observed in the TMM1 clinical trial surpassed what might be expected in UK clinical practice, and so by inference there is also uncertainty that the duration of IXA+LEN+DEX is also above that which would be expected in clinical practice (see section 5.3.5.1). The immaturity of the ToT data for IXA+LEN+DEX, means there is high uncertainty associated with any extrapolation with subsequently a significant impact on the ICER associated with different durations of treatment, with the results senstive to lower duration of treatment assumed for clinical practice. In scenario analysis, a 25% reduction in estimated ToT associated with IXA+LEN+DEX produces an ICER of [redacted] (Table 112 above). A large part of the uncertainty is associated with the impact of extrapolation of ToT data, which is illustrated by scenario analysis in which no extrapolation is performed (ie the observed data for IXA+LEN+DEX from TMM1 is used for duration of treatment), which produces an ICER of [redacted]

The scenario analysis using the later datacut for IXA+LEN+DEX and LEN+DEX reduced the ICER from [redacted] to [redacted], indicating that the outcomes of treatment with IXA+LEN+DEX are still being realised within the TMM1 clinical trial for the 2+ prior therapies population. Results were not highly sensitive to alternative sources for utility estimates.

Using the NMA data for IXA+LEN+DEX increases the ICER to [redacted], this indicates that the data utilised from the NMA provides different efficacy estimates for IXA+LEN+DEX from those in the TMM1 clinical trial, with an impact on QALY outcomes (see Table 44, Table 45 and Table 46 for PFS, OS and ORR, respectively, in Section 4.10). There may be a number of factors contributing to this which could be explored when more data becomes available from the TMM1 clinical trial.

It is recognized that new technologies (i.e. IXA) that are administered in combination with existing treatments (i.e. LEN+DEX) may struggle to demonstrate cost-effectiveness if those existing treatments (i.e. LEN+DEX) are themselves not cost-effective or if their cost-effectiveness falls very close to the WTP threshold. [225] An exploratory scenario 1 was performed in which the cost of IXA was set at zero, which was designed to explore the paradox that when a new drug such as this is used in combination with another expensive treatment (i.e. LEN) which may have bordeline cost-effectiveness, [225] then even at very low prices, IXA may struggle to show cost-effectiveness. This is demonstrated by the fact that at zero price/cost the ICER is below the conventional threshold of cost-effectiveness at [redacted]To reach a WTP threshold of £30,000 a discount of 91.7% would be required, this translates to a reduction from list price of £2,112 per capsule to £175 per capsule.

In order to explore the impact of the cost of LEN+DEX in the IXA+LEN+DEX regimen further, two additional exploratory scenarios were considered, which could be argued to be more plausible in terms of NHS policy relevance:

- Costing only the additional LEN+DEX in the IXA+LEN+DEX regimen, over and above that received in the LEN+DEX regimen (Exploratory scenario 2).
- Additional LEN+DEX over and above that received in the LEN+DEX regimen is not costed (Exploratory scenario 3).

The first of these scenarios captures the additional cost of LEN+DEX required due to the increase in ToT associated with treatment with IXA+LEN+DEX. The IXA+LEN+DEX is expected to displace LEN+DEX in the 3rd line treatment setting and, as such, patients would already be receiving LEN+DEX as standard care. For this reason, the economic impact of IXA+LEN+DEX could be considered to include only the costs above that which would already be received as part of standard care and hence already funded from the NHS budget. The second scenario captures only the cost of the LEN+DEX that would be received in current UK practice. This scenario aims to demonstrate the impact of the additional ToT observed in the IXA+LEN+DEX arm on results. These scenarios resulted in ICERs of [redacted]and [redacted]per QALY gained respectively (Table 112), and show that the cost-effectiveness of Ixazomib is being reduced significantly through the additional costs associated with high cost drugs (i.e. lenalidomide) that may have borderline cost-effectiveness but are already being funded by the NHS.

5.8.2.4 Summary of sensitivity analyses results – 2+ prior therapies

As with the one prior therapy analysis the ICERs for IXA+LEN+DEX vs LEN +DEX for the 2+ prior therapies population were sensitive to uncertainty associated with relative OS estimates, which impacts on QALY outcomes, and the absolute and relative time on treatment which primarily impacts on relative costs. The uncertainty is related to the immaturity of this data and the extensive extrapolation beyond the TMM1 trial follow-up.

The PSA indicated that simultaneous variation of parameter values resulted in IXA+LEN+DEX having an incremental QALY gain compared to LEN+DEX in the majority of iterations (97.20%). This is illustrated by Figure 54, which shows most of the PSA points lay in the north-east quadrant of the cost-effectiveness plane.

In clinical practice, IXA would be administered with LEN+DEX and as such standard modelling techniques require the costing of all treatments for the duration of time on treatment. The NICE DSU [225] guidance recognises the

challenges associated with showing the cost-effectiveness of a regimen like IXA+LEN+DEX when the existing regimen LEN+DEX is itself only of borderline cost-effectiveness. A number of scenarios have been performed to explore the impact of the costs associated with LEN+DEX in the IXA+LEN+DEX arm. These scenarios demonstrate that the cost of the additional LEN+DEX has a substantial upward impact on the ICER.

5.9 Subgroup analysis

The base case results consider two independent populations: patients who have received 1 prior line and patients who have received 2+ prior lines. No further subgroups are considered within this submission.

5.10 *Validation*

5.10.1 Validation of de novo cost-effectiveness analysis

5.10.1.1 Internal validation

The model was quality-assured by the internal processes of the health economists who constructed the de-novo economic model. Furthermore, a health economist not involved in model adaptation reviewed the model for coding errors, inconsistencies and the plausibility of inputs. The model was also put through a checklist of known modelling errors, and questioning of the assumptions based upon the Phillips checklist. [226]

5.10.1.2 External validation of efficacy inputs

External validation included:

- Semi-structured interviews with five UK clinical experts (see section 5.3.5.2)
- Clinical outcomes were compared with those from the TMM1 clinical trial
- Efficacy outcomes were compared with other cost-effectiveness studies identified as part of the economic SLR (see Section 5.1)

Semi-structured interviews were conducted with five UK clinical expertsin the treatment of RRMM. Interviews were conducted during model construction to validate model specification and inputs as well as when the model had been finalised to validate any updated inputs or assumptions. Clinicians were each asked the same questions, detailed in Section 5.3.5, and asked to comment on results in terms of clinical plausibility and generalisability to UK clinical practice. Detailed responses are provided in Section 5.3.5. In summary, clinicians agreed that the extrapolated parametric curves for OS, PFS and ToT provided a reasonable fit given the data available. It was emphasised that valid inferences could not be obtained from the OS data due to its immaturity, and so long term OS outcomes remained uncertain for IXA+LEN+DEX. Furthermore, it was commented that the proportion of patients remaining on treatment with LEN+DEX beyond 26 treatment cycles exceeded what might be expected in current UK practice, and this was supported by a presentation of real world use of LEN+DEX in the UK presented at the ASH conference in 2012. [123,227] Both comments on the OS and ToT data applied to the observed Kaplan-Meier data from the TMM1 trial, rather than specifically to the extrapolated curves. This suggests that more mature data is required from the TMM1 to draw conclusive inferences for OS and further RWE is required to support the duration of treatment likely to occur in UK practice.

It was commented that the efficacy observed in the TMM1 clinical trial for the LEN+DEX treatment arm was more efficacious than estimates previously seen in MM-009 and MM-010. For example, the ORR of LEN+DEX in the TMM1 clinical trial was 71.5% compared to 60.6% in the MM-009 and MM-010 trials. Furthermore, the median PFS and median ToT observed in the TMM1 clinical data exceeded those estimates observed in the MM-009 and MM-010 clinical trials. There may be a number of factors causing these differences. However, it should be noted that patients receiving LEN+DEX in the TMM1 clinical trial seem to be achieving particularly good results. Ongoing assessment of the use of a pooled hazard ratio for LEN+DEX relative to IXA+LEN+DEX is being conducted to adjust for potential within trial differences and to analyse the impact of this on results.

In terms of innovation, clincial expert feedback was that IXA+LEN+DEX can be considered innovative as the first oral-PI for the treatment of RRMM. The benefits of oral dosing, combined with IXA's favourable tolerability profile, means that patients can receive continuous treatment for longer. This is supported by the TMM1 clinical trial which demonstrated longer ToT for IXA+LEN+DEX compared to LEN+DEX.

The efficacy estimates for each of the comparators were compared with other published NICE submissions considering the treatment of RRMM as identified in the economic SLR (section 5.1), Table 113. No studies were identified that considered the outcomes associated with IXA+LEN+DEX, as such the results from this model for IXA+LEN+DEX cannot be validated by the literature. No studies report results for the 1 prior population specifically and so the efficacy associated with BORT+DEX can only be compared with 2+ prior lines populations or ITT populations. Life years for BORT range from 2.25-3.14 in the literature, the estimate of 2.45 falls within this range. Likewise, for QALYs, the range for BORT is from 1.48-2.95.

No studies report results for the 2+ prior population specifically and so the efficacy associated with LEN+DEX can only be compared with the ITT population. Life years for LEN+DEX range from 4.20-5.84, the estimate of 3.32 does not fall within this range. For QALYs, the range for LEN+DEX is from 3.77-4.21. The estimated life years and QALYs from the model are slightly less than the values observed in the literature, this is likely because this submission considers LEN+DEX placed at 3rd line and not an ITT population.

Table 113: Comparison of this submission efficacy estimates with identified literature

	Population	Life years	QALYs
This submission	IXA+LEN+DEX (1 prior line)	5.94	3.93
	BORT+DEX (1 prior line)	2.45	1.60
	IXA+LEN+DEX (2+ prior lines)	4.71	3.17
	LEN+DEX (2+ prior lines)	3.32	2.20
NICE submission TA380, PANO for treating MM after at least 2 previous treatments	PANO+BORT+DEX	2.29	1.52
	BORT+DEX	2.25	1.48
NICE submission TA338, POM for RRMM previously treated with LEN and BORT	POM+LD-DEX	2.23	1.29
	Comparator	1.17	0.68
NICE submission TA171, LEN for the treatment of MM in people who have received at least one prior therapy and pre-existing peripheral neuropathy	LEN+DEX	4.20	3.77
	DEX	1.65	1.53
	POM+DEX	2.33	1.39

Borg et al. (2016), uses data from MM-003 (2+ prior therapies)	HD-DEX	1.12	0.66
Jakubowiak et al. (2016), RMM 1-3 prior therapies	CARF+LEN+DEX	7.83	5.88
	LEN+DEX	5.84	4.21
Brown et al. (2013), RRMM 1+ prior therapies	LEN+DEX	5.37	3.69
	DEX	2.15	1.49
Fragoulakis et al. (2013), RRMM	LEN+DEX	4.14	3.01
	BORT	3.14	2.22
Hornberger et al. (2010) and Ishak et al. (2011), RRMM	BORT	NR	2.95
	DEX	NR	2.26
	LEN+DEX	NR	2.91
Moller et al. (2011), RRMM	BORT	3.11	2.19
	LEN+DEX	4.06	2.95
Key: DEX, dexamethasone; BORT, bortezomib; CARF, carfilzomib; HD-DEX, high-dose dexamethasone; LEN, lenalidomide; PANO, panobinostat; POM, pomalidomide; QALYs, quality adjusted life years; RRMM, relapsed and refractory multiple myeloma			

5.10.1.3 External validation of utility inputs

Limited data are available for health state specific utilities in RRMM. The NICE methods guide states that the preferred source of utilities is from the relevant clinical trial and that the preferred measure is the EQ-5D. Therefore, this submission uses the data from the TMM1 clinical trial to model utility by response status.

Weisel et al. (2015) and Song et al. (2015) [191,192]report that the utility of patients receiving POM+LD-DEX for best response before progression is 0.73. This is similar to the estimate obtained for VGPR+ within this submission. Furthermore, Acaster et al. (2013) [193] find that the utility associated with second line treatment is 0.67 and for the second line treatment free interval utility is 0.63. These estimates are similar to the pre-progression utility estimates derived from the TMM1 patient level data: 0.653-0.674.

The post-progression utility estimate within this submission is higher than that of stable disease. This is likely caused due to confounding from subsequent lines of therapy which has not been accounted for in the utility regression equation. However, this post-progression utility estimate is applied to all treatments in the model and so the incremental QALYs are expected to be the same.

5.11 Interpretation and conclusions of economic evidence

5.11.1 Interpretation

Based on the list price for ixazomib (N.B. a separate PAS template has been completed corresponding to a simple discounted PAS price which has been submitted to PASLU), the base case ICER for a 2nd line positioning for IXA+LEN+DEX vs. BORT+DEX is estimated to be [redacted] per QALY gained, and for a 3rd line positioning vs. LEN+DEX the ICER is estimated to be [redacted] per QALY gained. Sensitivity and scenario analysis has demonstrated that the results are sensitive to key parameters, in particular estimates of relative survival which impact on QALY outcomes, and the absolute and relative duration of treatment estimates, which primarily impacts on relative costs. IXA is the first oral PI treatment and as such offers patient and service benefits. The cost and utility advantage associated with this has been captured in the economic model. However, there are wider service benefits from having a new oral treatment available for the management of RRMM which release hospital resources for other uses.

There is estimated to be a significant QALY gain for IXA+LEN+DEX versus BORT+DEX of 3.49 life years gained and 2.34 QALYs. This is built on an estimated benefit in pre-progression survival of 0.22 life years gained and 0.20 QALYs, although the majority of the benefit is estimated to be in post progression survival and QALY gain (3.27 life years gained and 2.14 QALYs). These estimates were based on assuming a constant hazard for OS after 5 months, prior to 5 months the Kaplan-Meier data observed from the TMM1 clinical trial were used, assuming a gamma distribution for the PFS and assuming a Weibull distribution for ToT (Section 5.3). A limitation of this analysis is that it is not based on direct comparative evidence, but is estimated using data obtained from an NMA for BORT+DEX vs LEN+DEX, and from the TMM1 trial for IXA+LEN+DEX vs. LEN+DEX. The NMA had limitations in that there was no direct data available for a one prior therapy population for BORT+DEX (or any other potential comparator) to form a network. Hence, data were proxied by a 1+ prior therapy population for the comparator which, although a proxy, had the advantage of a larger evidence base and could be considered representative of the outcomes for a 1 prior therapy population.

A 3rd line positioning for IXA +LEN+DEX is seen by clinical experts as the most plausible clinical positioning in the RRMM treatment pathway in the UK (see section 3.3). Within the economic argument of this submission the data from the 2-3 prior therapies populations obtained from the TMM1 clinical trial proxies the outcomes associated with a 3rd line positioning. These data are thought to be representative of a patient population whom have had 2 prior therapies as the majority (74%) of the 2+ prior therapies population in the TMM1 clinical trial had only received two prior therapies, the rest having received 3 prior therapies (no patients received more than 3 therapies). The life years and QALY gain for IXA+LEN+DEX vs LEN+DEX for a 3rd line positioning estimated by the model is 1.38 and 0.97 respectively. The main strength of this comparison is that it is based on direct comparative evidence from a well designed RCT (TMM1) and so there is robust evidence on PFS, the primary endpoint in the trial. A limitation of the evidence base is that the survival data is immature based on current trial datacuts. Clinicians commented that long-term inferences could not be drawn from the OS data from IA1 due to the immaturity of the data. Consequently, most of the life years and QALY gain is estimated to be attained pre-progression with estimates of incremental LYG and QALY gains of 1.02 and 0.73, with post progression LYG and QALY gains estimated at 0.36 and 0.24 respectively (i.e. 74% pre-progression LYG).

These relatively low post progression benefits are associated with survival modelling that extrapolates from an immature OS data set with median survival benefit not reached, this means high uncertainty is incorporated in the analysis. Results could be made more robust with further follow-up and more mature OS data (further follow-ups for OS are planned for Q2 2017, and final OS analysis in Q3 2019). This expectation is supported by the analysis of Felix et al. (2013) [188] who show a relationship between pre-progression and OS outcomes in MM treatments, with a finding that for every one month increase in median PFS an increase of 2.45 months in OS could be expected (see Section 5.3.5). Based on inference from published studies it could be expected that the initial increase in PFS should prove to show an increase in OS, estimated as up to 3 months for the 1 prior population and up to 22 months for the 2+ prior therapiues population. We recognise that these are speculative findings; however, these are supported by the ratios of OS to PFS demonstrated by other RRMM studies.

Clinically effective and relatively safe treatments often cause patients to continue treatments for longer. Therefore, treatment costs can outweigh the additional QALY gain. This is reflected in the TMM1 clinical trial, where patients are remaining progression-free for longer and thus staying on treatment longer. This leads to the IXA+LEN+DEX arm accruing additional costs from treatment, resource use whilst on treatment and TRAEs. This emphasises the importance of accurately modelling the ToT in line with UK clinical practice. Clinician feedback and the literature have indicated that the ToT in the TMM1 clinical trial has issues of generalisability to the UK setting; ToT is higher in the trial reducing the external validity of the ToT trial data in the UK. The ToT data is also immature, with a large proportion of patients still on treatment at the 1st and 2nd interim datacuts (42.18% and 34.75% still on treatment after 26 treatment cycles and 24.18% and 29.19% still on treatment after 34 treatment cycles with IXA+LEN+DEX,

respectively). There is therefore a large impact associated with the extrapolation of ToT, which leads to uncertainty in the ICER – with no extrapolation of duration of treatment data the ICER reduces to [redacted] gained and [redacted] gained for 2nd line and 3rd line positioning respectively, which shows the degree to which extrapolation is adding to the cost and impact on the ICER. There is also a valid concern that the TMM1 trial data is overestimating time on treatment – real world evidence has shown that by 26 cycles 17.5% of RRMM patients are still on LEN+DEX [227] treatment, whereas 34.75% of patients remain on treatment with LEN+DEX in the TMM1 clinical trial, hence this seems overestimated and by inference the expectation is that the IXA+LEN+DEX ToT is also overestimated. Therefore, the uncertainty of extrapolation and potential for overestimation of treatment duration impacts on costs and drives our belief that the ICERs are potentially overestimated relative to actual clinical practice.

The combination of immature OS and ToT data means that the ICERs are based on uncertain incremental LYG and QALYs gained, and the ICERs could be expected to be better than in the current base case. There is a strong case for further OS and ToT data collection to reduce this uncertainty. A route for this whilst allowing access to ixazomib as an important new oral agent could be the funding of ixazomib via the CDF. CDF entry could be accompanied by a data collection plan consisting of further follow-up of the TMM1 trial to obtain more mature OS and ToT data, and a real world observational study to collect outcomes and treatment duration data for the IXA+LEN+DEX regimen that is relevant for actual UK clinical practice. The current ICERs (without a PAS) are not sufficient for IXA+LEN+DEX to be considered as a cost-effective use of NHS resources – however, the high uncertainty and the potential for improved cost-effectiveness makes ixazomib a suitable candidate for funding via the CDF alongside a data collection plan. This is described further in Section 1.4.

As a further interesting observation, [225] it is recognised that new technologies (e.g. ixazomib) that are administered in combination with existing high cost treatments (i.e. LEN+DEX) may struggle to demonstrate cost-effectiveness if those existing treatments (i.e. LEN+DEX) are themselves lying close to the WTP threshold. This was considered to be apparent in both the 1 prior line and 2+ prior line populations, and it was demonstrated that even when the cost of ixazomib was set to zero the ICERs were still significant (at [redacted] and [redacted] for the 1 prior and 2+ prior therapies populations, respectively).

Finally, within the 2+ prior therapies population, another scenario considered only costing the additional LEN+DEX in the IXA+LEN+DEX regimen, over and above what was received in the LEN+DEX regimen; this reduced the ICER from [redacted] to [redacted]. Whilst exploratory for the 2+ prior line population this ICER is potentially more representative of the cost-effectiveness of IXA+LEN+DEX compared to current UK standard of care, as without the introduction of IXA to the UK market LEN+DEX would still be administered. This is based on the premise that, the consequences of introducing IXA+LEN+DEX should only include the costs associated with IXA and the additional LEN+DEX for a fair assessmet of the cost-effectiveness of IXA+LEN+DEX vs LEN-DEX.

5.11.2 Conclusion

The cost-effectiveness of IXA+LEN+DEX has been evaluated vs BORT+DEX for 2nd line use in patients with RRMM, and vs. LEN+DEX for 3rd line use in patients with RRMM. Based on clinical feedback the highest need for a new effective oral agent that has shown benefits over LEN+DEX in a well-designed direct comparative RCT is after 2 prior therapies (typically a thalidomide based regimen followed by a bortezomib based regimen). The ICERs presented in this submission are well above the conventional thresholds of cost-effectiveness adopted by NICE, but are highly uncertain due to immaturity of OS and ToT data. There is reason to believe that the ICERs could be much more favourable for ixazomib, but the economic argument requires further trial follow-up and real world data collection to establish this.

The ICERs presented in this submission are based on the list price of ixazomib. A PAS has been submitted to PASLU consisting of a simple price discount. The results with PAS are presented in the separate PAS template, but improve the ICERs relative to those in this submission for both the 1 prior line and two prior lines assessments.

6. Assessment of factors relevant to the NHS and other parties

6.1 Budget impact assessment

An assessment has been made of the budget impact associated with IXA+LEN+DEX for the two patient populations considered in the cost-effectiveness argument:

- Patients with RRMM who have had one prior therapy
- Patients with RRMM who have had two prior therapies

6.1.1 1 prior line populations (2nd line)

Prevalence, incidence and market share

In 2014 there were 4,921 newly diagnosed cases of MM in England and Wales, this is the most recent data available from the Office of National Statistics and Cancer Research UK.[228,229] Based on a population of 45.6 million in 2015 for England and Wales (≥ 18-year-old) [228,229] this equated to an incidence rate of 0.01% per annum. It was assumed that the proportion of newly diagnosed cases of MM would not vary substantially year on year. Based on the UK projected population increase of 15.02% over the next 25 years [230] it was estimated that there were 4,921 new cases in year one, increasing to 5,047 new cases by year five.

The number of eligible patients for second-line treatment was 2,858 in year one increasing to 2,925 by year five. This was based on the number of newly diagnosed patients each year and the proportion of patients progressing from first-line treatment to second-line. The proportion of patients progressing through the lines of treatment was obtained from Willenbacher et al. (2016), an Austrian study considering RWE for MM patients and Yong et al. (2016). [93,231] The latter is a recent Real World Evidence study conducted across Europe, led by a UK based principal investigator, which analysed the typical multiple myeloma treatment pathway based on patient records including those of UK patients (Yong et al, 2016). The study found that in the real world setting, 61% of multiple-myeloma patients who are treated (95% of total MM patients) will receive second-line therapy. This calculates to approximately the same number of new second line patients annually as the Willenbacher et al (2016) study.

Market share data was sourced from the Multiple Myeloma Therapy Tracker,[232] this details the market share for each treatment regimen at second-line based on October/November 2016 data. Market share and uptake for IXA+LEN+DEX was based on Takeda expert clinical opinion, IXA+LEN+DEX achieved a [redacted] market share in year one increasing to [redacted] in year five. It is considered that IXA+LEN+DEX would displace BORT+DEX at second line, as such the budget impact considers IXA+LEN+DEX displacing the market share of BORT+DEX increasingly through years 1 to 5. The estimated market share with IXA+LEN+DEX is shown in Table 114. Table 115 depicts the estimated number of patients eligible for treatment after one prior therapy.

Table 114: Estimated market share with ixazomib – 1 prior line

Drug regimen	Year 1	Year 2	Year 3	Year 4	Year 5
Lenalidomide + dexamethasone	12.93%	12.93%	12.93%	12.93%	12.93%
Ixazomib + lenalidomide + dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib monotherapy (first treatment)	0.00%	0.00%	0.00%	0.00%	0.00%
Bortezomib monotherapy (retreatment)	3.21%	3.21%	3.21%	3.21%	3.21%

Bortezomib + dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Panobinostat + bortezomib + dexamethasone	1.60%	1.60%	1.60%	1.60%	1.60%
Lenalidomide monotherapy (previously treated with bortezomib)	1.60%	1.60%	1.60%	1.60%	1.60%
Carfilzomib + lenalidomide + dexamethasone	0.00%	0.00%	0.00%	0.00%	0.00%
Carfilzomib + dexamethasone	0.00%	0.00%	0.00%	0.00%	0.00%
Pomalidomide + dexamethasone	0.00%	0.00%	0.00%	0.00%	0.00%
Other bortezomib regimens	41.98%	41.98%	41.98%	41.98%	41.98%
Other lenalidomide regimens	4.81%	4.81%	4.81%	4.81%	4.81%
Other thalidomide regimens	11.22%	11.22%	11.22%	11.22%	11.22%
Other regimens	1.60%	1.60%	1.60%	1.60%	1.60%

Table 115: Patients in England and Wales eligible for treatment – 1 prior line

Patients eligible for treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients for treatment after 1 prior therapy	2,852	2,870	2,889	2,907	2,925
Number of patients treated with BORT+DEX without introduction of IXA+LEN+DEX	600	604	608	612	615
Uptake of IXA %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients expected to be treated with IXA+LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients expected to be treated with BORT +DEX each year with the introduction of IXA+LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: BORT, bortezomib; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide					

Costs and resource use

All costs used within the budget impact analysis were identical to the cost-effectiveness model described in Section 5. Costs were not discounted for the budget impact analysis.

Budget impact

The overall budget impact results are presented in **Table 116** for IXA+LEN+DEX compared to BORT+DEX based upon the market shares for each treatment. **Table 116** demonstrates the following results for the one prior line population:

- The estimated total cost for IXA+LEN+DEX [redacted] in year one, increasing to [redacted] in year 5. The total costs over 5-years for IXA+LEN+DEX is estimated to be [redacted].
- The estimated net budget impact after displacement is [redacted] in year one, increasing to [redacted] by year five as increasingly more patients receive treatment with IXA+LEN+DEX. The estimated total budget impact over 5-years after displacement of BORT+DEX [redacted].

Table 116: Patients in England and Wales eligible for treatment with IXA+LEN+DEX – 1 prior line

Gross Drug Budget Impact	Year 1	Year 2	Year 3	Year 4	Year 5
Total cost of pathway without IXA+LEN+DEX	£16,916,045	£18,596,173	£19,508,312	£20,177,498	£20,690,590
Total cost of pathway with IXA+LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost of IXA+LEN+DEX pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative cost of pathway without IXA+LEN+DEX	£16,916,045	£35,512,218	£55,020,529	£75,198,028	£95,888,618
Cumulative cost of pathway with IXA+LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cumulative cost of IXA+LEN+DEX pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: IXA, ixazomib; LEN, lenalidomide; DEX, dexamethasone					

6.1.2 2 prior lines population (3rd line)

Prevalence, incidence and market share

In 2014 there were -4,921 newly diagnosed cases of MM in England and Wales, this is the most recent data available from the Office of National Statistics and Cancer Research UK. [228,229] Based on a population of 45.6 million in 2015 for England and Wales (≥ 18-year-old) [233] this equated to an incidence rate of 0.01% per annum. It was assumed that the proportion of newly diagnosed cases of MM would not vary substantially year on year. Based on the UK projected population increase of 15.02% over the next 25 years [230] it was estimated that there were 4,921 new cases in year one, increasing to 5,047 new cases by year five.

The number of eligible patients for third-line treatment was 1,776 in year one increasing to 1,822 by year five. This was based on the number of newly diagnosed patients each year and the proportion of patients progressing from first-line treatment to third-line. The proportion of patients progressing through the lines of treatment was obtained from Willenbacher et al. (2016), an Austrian study considering RWE for MM patients. [231] As in one prior line to therapy, the number of eligible patients for 3rd line treatment is further supported by the Yong et al. (2016) RWE study based on patient charts across Europe, including UK based patients.

Market share data was sourced from the Multiple Myeloma Therapy Tracker, [232] this details the market share for each treatment regimen group (bortezomib, lenalidomide, pomalidomide, thalidomide, other) at third-line based on October/November 2016 data. The detailed market share figures for each individual treatment regimen at second-line were used to estimate the proportion of patients receiving each treatment regimen within the overall groups specified in the third-line data. This assumption was required due to the lack of data available for specific regimens including LEN+DEX at third line. Market share and uptake for IXA+LEN+DEX was based on Takeda expert clinical opinion; [132] IXA+LEN+DEX achieved a [redacted] market share in year one increasing to [redacted] in year five. It is considered that IXA+LEN+DEX would displace LEN+DEX at third line, as such the budget impact considers IXA+LEN+DEX displacing the market share of LEN+DEX increasingly through years 1 to 5. The estimated market

share with IXA+LEN+DEX is shown in Table 117. Table 118 depicts the estimated number of patients eligible for treatment after one prior therapy.

Table 117: Estimated market share with ixazomib – 2 prior lines

Drug regimen	Year 1	Year 2	Year 3	Year 4	Year 5
Lenalidomide + dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixazomib + lenalidomide + dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib monotherapy (first treatment)	0.56%	0.56%	0.56%	0.56%	0.56%
Bortezomib monotherapy (retreatment)	0.00%	0.00%	0.00%	0.00%	0.00%
Bortezomib + dexamethasone	3.67%	3.67%	3.67%	3.67%	3.67%
Panobinostat + bortezomib + dexamethasone	1.58%	1.58%	1.58%	1.58%	1.58%
Lenalidomide monotherapy (prep treated with BOR)	5.65%	5.65%	5.65%	5.65%	5.65%
Carfilzomib + lenalidomide + dexamethasone	0.00%	0.00%	0.00%	0.00%	0.00%
Carfilzomib + dexamethasone	0.00%	0.00%	0.00%	0.00%	0.00%
Pomalidomide + dexamethasone	4.94%	4.94%	4.94%	4.94%	4.94%
Other bort regimens	4.94%	4.94%	4.94%	4.94%	4.94%
Other Len regimens	8.88%	8.88%	8.88%	8.88%	8.88%
Other thal regimens	7.33%	7.33%	7.33%	7.33%	7.33%
Other regimens	16.94%	16.94%	16.94%	16.94%	16.94%

Table 118: Patients in England and Wales eligible for treatment – 2 prior lines

Patients eligible for treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients for treatment after 1 prior therapy	1,776	1,788	1,799	1,811	1,822
Number of patients treated with LEN+DEX without introduction of IXA+LEN+DEX	809	814	819	824	829
Uptake of IXA %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients expected to be treated with IXA+LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients expected to be treated with LEN+DEX each year with the introduction of IXA+LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide					

Costs and resource use

All costs used within the budget impact analysis were identical to the cost-effectiveness model described in Section 5. Costs were not discounted for the budget impact analysis.

Budget impact

The overall budget impact results are presented in Table 16 for IXA+LEN+DEX compared to LEN+DEX based upon the market shares for each treatment. Table 16 demonstrates the following results for the two prior lines population:

- The estimated total cost for IXA+LEN+DEX is [redacted] in year one, increasing to [redacted] in year 5. The total costs over 5-years for IXA+LEN+DEX is estimated to be [redacted].
- The estimated net budget impact after displacement is [redacted] in year one, increasing to [redacted] by year five as increasingly more patients receive treatment with IXA+LEN+DEX. The estimated total budget impact over 5-years after displacement of LEN+DEX is [redacted].

Table 119: Patients in England and Wales eligible for treatment with IXA+LEN+DEX – 2 prior lines

Gross Drug Budget Impact	Year 1	Year 2	Year 3	Year 4	Year 5
Total cost of pathway without IXA+LEN+DEX	£42,693,605	£64,497,229	£67,207,464	£69,217,776	£70,720,350
Total cost of pathway with IXA+LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost of IXA+LEN+DEX pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative cost of pathway without IXA+LEN+DEX	£42,693,605	£107,190,834	£174,398,298	£243,616,075	£314,336,424
Cumulative cost of pathway with IXA+LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cumulative cost of IXA+LEN+DEX pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: IXA, ixazomib; LEN, lenalidomide; DEX, dexamethasone					

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Single technology appraisal

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

Dear Eugene,

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on 14 December 2016 from Takeda. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **2 February 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Sophie Cooper, Technical Lead (Sophie.Cooper@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Encl. checklist for confidential information

Below is the list of abbreviations that have been used in our clarification questions.
AE: adverse event
BoR: best-of response
BORT: bortezomib
DEX: dexamethasone
HR: hazard ratio
IXA: ixazomib
KM: Kaplan-Meier
LEN: lenalidomide
MP: melphalan-prednisone
NMA: network meta-analysis
ORR: overall-response rate
OS: overall survival
PD: progressive diease
PFS: progression-free survival
PR: partial response
RRMM: relapsed refractory multiple myeloma
SD: stable disease
THAL: thalidomide
ToT: time on treatment
TTP: time-to-progression
VGPR: very good partial response

Section A: Clarification on clinical effectiveness data

Decision problem

A1. **PRIORITY QUESTION.** A number of people with multiple myeloma receive a BORT-based treatment regimen as first-line therapy (TA311 and TA228). The NICE scope lists 2 comparators for this population, which the company excluded from its submission: BORT re-treatment (with or without DEX) and LEN-DEX. This leaves no comparator for IXA-LEN-DEX in people with relapsed/refractory disease who have received 1 prior line of treatment with BORT, and therefore committee will be unlikely to be able to make a recommendation in this group. NICE acknowledge that BORT retreatment is no longer funded by the NHS for this indication. However, NICE's negative recommendation for second-line LEN-DEX is only preliminary guidance and a final recommendation has not been issued. Clinical advisors to the ERG have indicated that LEN-DEX is used in current practice within the NHS, in particular among patients who have received BORT at first line and who had an inadequate response or experienced toxicity. According to IMS data on market share trends provided by the

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company, LEN-DEX represents 26% of therapy used in the UK second line (table 62 company submission).

a. Please provide clinical and cost-effectiveness results for IXA-LEN-DEX compared with LEN-DEX for people with 1 prior therapy. If the company considers that neither LEN-DEX nor BORT retreatment are established practice for people at first relapse after receiving BORT, please clarify what the relevant comparator to IXA-LEN-DEX could be in this situation.

b. If you do not intend to submit a comparison for IXA-LEN-DEX in this group (people with relapsed/refractory disease who have received 1 prior line of treatment with BORT), please explain your rationale and acknowledge that the committee will be unable to make a recommendation for people with relapsed/refractory disease who have received 1 prior line of treatment with BORT. NICE recognise that the scope lists no alternative comparators to BORT retreatment and LEN-DEX in this group, and is investigating this with clinical experts.

c. Table 37 states that 69% of patients in TMM-1 had previously received BORT. Is it possible to split this into the number of patients that received BORT as a first line treatment (compared with later lines of therapy)? Please clarify whether this includes patients who received BORT as an induction to stem cell transplant.

A2. **PRIORITY QUESTION.** The company's analysis of IXA-LEN-DEX in the 2 prior therapies subgroup uses TMM-1 trial data from people who had received 2 or 3 previous treatments. The company states in section 5.2.2 of its submission (page 163) that randomisation in TMM-1 was stratified according to 1 prior therapy versus 2 or 3 prior therapies. That is, using data from the 2 prior therapies only subgroup would be a post hoc analysis and carry several limitations. However, the ERG consider that it would be valuable to show the results of a sensitivity analysis using the data from the subgroup of TMM-1 patients with 2 prior regimens only. Please provide these analyses.

Systematic review:

A3. Figure 9: Please provide a list of the 16 publications excluded after review of full-text articles, and the reasons for exclusion.

Direct treatment comparison:

A4. Table 40: please provide the 95% CI for all the variables that have been compared.

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A5. Please confirm that, in both the clinical sections and the economic sections of the submission:

a. All OS analyses use the 2nd interim analysis data cut of TMM-1
b. All PFS analyses use the 1st interim analysis data cut of TMM-1
c. All ToT analyses use the 1st interim analysis data cut of TMM-1

When responding to the following questions, please report the results using the data cuts specified above, except where the question specifies a different data cut.

A6. TMM-1 (C16010) clinical study report figure 11v. (Forest Plots of Time to Progression and Overall Response Rate in Subgroups): Please clarify how "Prior Therapies (1, 2 or 3)" and "Prior Therapies Derived (1, 2 or 3)" were derived and should be interpreted. Please replicate figure 19 of the submission using OS data.

A7. Table 37 (TMM-1 study baseline patient characteristics): Please complete the table below (ie please split the baseline characteristics of TMM-1 by arm for the 1 prior therapy and the 2+ prior therapy subgroups).

	1 prior		2+ prior	
	IXA-LEN-DEX	LEN-DEX	IXA-LEN-DEX	LEN-DEX
% Female	???	???	???	???
Mean age	???	???	???	???
Age % ≤65	???	???	???	???
Age % 65-75	???	???	???	???
Age % >75	???	???	???	???
Cytogenetics High Risk	???	???	???	???
ISS = Stage III	???	???	???	???
Age > 65 years	???	???	???	???
Light chain myeloma	???	???	???	???
Relapsed	???	???	???	???
Refractory	???	???	???	???
Relapsed and refractory	???	???	???	???
Proteasome inhibitor	???	???	???	???
Immunomodulation agent	???	???	???	???
ECOG performance score	???	???	???	???
ASCT undertaken	???	???	???	???
History of bone lesions	???	???	???	???
Renal dysfunction	???	???	???	???
Asian	???	???	???	???

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A8. TMM-1 (C16010) clinical study report table 12.a (Extent of Exposure – Safety population): Please replicate this table for the second interim analysis, and present the separate results for the 1 prior therapy subgroup, the 2+ prior therapies subgroup and, if possible, the 2 prior therapies subgroup.

Indirect and mixed treatment comparisons:

A9. In order to improve the clarity of the NMA, please add study names and/or reference numbers to the network diagrams, specifically for the links between interventions that come from a direct comparison.

A10. **PRIORITY QUESTION**: Within the NMA for PFS, we understand that the company linked BORT-DEX to LEN-DEX using the Montefusco trial. However, this trial compares BORT-DEX-CYCLOPHOSPHAMIDE to LEN-DEX-CYCLOPHOSPHAMIDE, which may give a very different relative effectiveness than a study comparing BORT-DEX with LEN-DEX.

a. Please explain the likely effects of cyclophosphamide on the relative effectiveness of BORT-DEX compared with LEN-DEX in this context.

b. Please provide a new NMA for PFS which excludes the Montefusco trial (this trial is considered inappropriate because the treatment regimens include cyclophosphamide). It appears that the company chose to use the Montefusco study because it reports both PFS and TTP, whereas other trials linking BORT-DEX to LEN-DEX (eg APEX, MM-009 and MM-010) report TTP only. Based on the definition of these outcomes, TTP can be considered a good proxy for PFS. In the revised NMA, use TTP as a proxy for PFS (for studies which do not report PFS). Please include the new NMA results in your model, and present the results as a sensitivity analysis.

A11. **PRIORITY QUESTION**: Please provide the following details for all NMAs:

a. all inputs (annotated with primary study sources)
b. all codes in R used to perform the NMAs
c. all the outputs from the NMA analyses (indicating whether HRs were adjusted or unadjusted).

A12. Please provide the rankograms for each NMA performed.

A13. In section 5.3.3.3 (table 65), the company presents the hazard ratios for OS and PFS for BORT-DEX compared with LEN-DEX, stating that these results are from an NMA. The results of this NMA were not reported in the relevant section of the clinical

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effectiveness in the company submission. Please provide the full results of the NMA on OS, PFS, ORR, BOR and discontinuation due to AEs, including all the drugs considered in the network.

A14. In section 4.10.6.2, the company indicated there were insufficient studies and data in the one prior therapy population to develop a network between IXA-LEN-DEX and BORT-DEX. However, no summary tables of results of primary studies for this were included. Please provide tables with these results.

Section B: Clarification on cost-effectiveness data

B1. Table 62 presents IMS multiple myeloma therapy tracker market share data, by line of treatment. Please provide information on the methods used to generate these data. Were these estimates collected only within the NHS or do they include private care?

B2. Please split the market share data in table 62 into monotherapies, doublets and triplets; ie some of the BORT data will be restricted to BORT monotherapy, some of the LEN data will be for other regimens, but a proportion of both will make up the BORT+LEN doublet.

Survival analysis:

B3. **PRIORITY QUESTION.** For the IXA-LEN-DEX arm of the model, Kaplan-Meier hazards observed from the TMM-1 clinical trial were applied for 5 months followed by the hazard of the fitted delayed exponential for IXA-LEN-DEX.

a. Please explain why a different approach was taken in the BORT-DEX arm of the model; it appears that the (hazard ratio conditioned) delayed exponential LEN-DEX hazard was applied *throughout*.

b. Please explore the impact on the ICER if, in the BORT-DEX arm, the (hazard ratio conditioned) LEN-DEX Kaplan-Meier hazards are applied for 5 months followed by the (hazard ratio conditioned) delayed exponential LEN-DEX hazard?

c. Page 177 of the submission (section 5.3.3.3) states that "*a hazard ratio was estimated for IXA+LEN+DEX compared with LEN+DEX [HR: 0.89, 95% CI: 0.5 – 1.60] and applied to the fitted exponential from 5 months*." The model contains a hazard ratio of 0.896 for the 1 prior therapy population. It appears that, for the IXA-LEN-DEX arm, the model applies the Kaplan-Meier data for the first 5 months and then the hazard of the fitted delayed exponential: 0.00262. The corresponding delayed exponential hazard for LEN+DEX is

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0.00234, the ratio between the two being 0.892. Please confirm if the hazard ratio of 0.89 on page 177 refers to the 0.892 ratio between the delayed exponential hazards.

i. If it is, is this hazard ratio in favour of IXA+LEN+DEX or in favour of LEN+DEX? Does this reflect the base case OS estimates for the 1 prior therapy population, which appear to suggest an OS gain for IXA-LEN-DEX?
ii. If it is not, please provide more detail of what the 0.89 hazard ratio on page 177 relates to and how it has been calculated.

B4. It appears that 1 month is defined differently in the graphs in the clinical effectiveness section (28 days) than in the graphs in the cost effectiveness section (one twelfth of year ie 30.4 days). Please clarify and also define the days in 1 month in APPENDIX 11 graphs.

B5. Please clarify why a generalised Gamma model was selected in preference to a Weibull model for PFS modelling in the 1 prior therapy population. The Weibull model has superior scores on information criteria (Appendix 11 Table 8).

B6. Figures 37 (PFS) and 39 (OS): please clarify why the LEN-DEX arm of TMM-1 has been omitted. Please add the Kaplan-Meier data and predicted curves for LEN-DEX into these 2 figures.

B7. Executable model:

a. Lifetable (OS) worksheet: please list all events that qualify as 'Deaths' and all events that qualify as 'Censored'.
b. Lifetable (PFS) worksheet: please list all events that qualify as 'Progressed' and all events that qualify as 'Censored'.
c. Lifetable (ToT) worksheet: please list all events that qualify as 'Disc Treatment' and all events that qualify as 'Censored'.

B8. **PRIORITY QUESTION**: Please clarify if the Kaplan-Meier data in the economic model is raw trial data or if it has been adjusted in any way. Please confirm the data cut (1st or 2nd interim analysis) for the Kaplan-Meier data in the following worksheets: Lifetable (OS), Lifetable (PFS) and Lifetable (ToT). Please provide the equivalent of the data in:

a. worksheet Lifetable(PFS) cells C160:F311, W160:Z311, C314:F464 and W314:Z464 for the 2nd interim analysis.
b. worksheet Lifetable(ToT) cells C160:F311, W160:Z311, C314:F464 and W314:Z464 for the 2nd interim analysis if this is not already the case.

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B9. **PRIORITY QUESTION:** If they are available or can be constructed in the time available please provide the equivalent of:

a. the parameterised curves for PFS in worksheets Survival(PFS - MV) and Survival(PFS - UV) for the second interim analysis
b. the Survival(ToT – MV) and Survival(ToT – UV) for the second interim analysis, together with their AICs and BICs. What is the sensitivity of the ICERs to these curves?

B10. **PRIORITY QUESTION**: Please provide the equivalent of the data in:

a. worksheet Lifetable(OS) cells W314:Z464
b. worksheet Lifetable(PFS) cells W314:Z464
c. worksheet Lifetable(ToT) cells W314:Z464
d. worksheet BoR cells E16:I17
e. worksheet Lifetable(OS) cells C314:F464
f. worksheet Lifetable(PFS) cells C314:F464
g. worksheet Lifetable(ToT) cells C314:F464
h. worksheet BoR cells E17:I17

for the 2-prior therapy patients in the IXA-LEN-DEX arm (n=97) for the worksheets listed in bullet points a-d, and for the 2-prior therapy patients in the placebo arm (n=111) for the worksheets listed in bullet points e-h.

If this is difficult within the time available please concentrate on the OS data.

B11. **PRIORITY QUESTION**: Please confirm that appendix 11 is specific to the final adjusted models.

a. Please provide a list of the covariates that were considered for the:

    i. 1 prior therapy analyses and recursively worked through to arrive at the final 1 prior therapy models.
    ii. 2+ prior therapies analyses and recursively worked through to arrive at the final 2+ prior therapies models.

b. What significance levels were used in the recursive analyses for the elimination of variables?

c. Please supply the equivalent of appendix 11 for the unadjusted models.

d. If time allows, please explore the impact on the base case ICERs of applying the unadjusted OS, PFS and ToT curves.

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B12. **PRIORITY QUESTION**: The *Cap_ToT_to_PFS curve* option in the *Main_Settings* worksheet appears to have been hard coded through data validation rules to be set to "*Off*".

a. Does this imply that treatment is not capped by PFS but is capped by OS, or something else?
b. What is the rationale behind the default "*Off*" value?
c. What is the impact of removing the data validation rules for cell E26 in the *Main_Settings* worksheet setting this cell equal to "*On*"?
d. What is the sensitivity of the base case ICERs to this variable?

B13. The *Comp* worksheet columns AZ and BA suggests that the OSModel=4 corresponds to the LogNormal, while OSModel=5 corresponds to the LogLogistic. But the treatment coefficient of AV9 suggests the reverse, and appears to be incorrect. Please clarify.

B14. Page 184 refers to Gelber et al. (1993) when describing OS extrapolation beyond 5 months for the 1 prior therapy population. Please explain in detail how this was undertaken.

B15. Figure 37: Please clarify how the red curve for BORT-DEX was derived. It appears that a hazard ratio of 1.06 was applied; according to Table 65 this is for the comparison BORT-DEX versus LEN-DEX. Please clarify what this hazard ratio was applied to and what the result represents.

B16. Appendix 11 Figure 20: Please explain the difference between the fitted OS curves and unadjusted Kaplan-Meier curves; this discrepancy appears too large to be explained by covariate imbalances and looks implausible.

B17. Page 90 (below figure 13) reports the availability of a non-inferential HR for PFS at a median follow-up of 23 months. Please provide the results of sensitivity analyses for both populations in the cost-effectiveness analyses (1 prior and 2+ prior therapies) using the HR for PFS from the second interim anlaysis.

B18. Figure 39: The BORT-DEX OS curve shown might be obtained by applying [a] the NMA HR for BORT-DEX compared with LEN-DEX (3.11, Table 65) to the OS model for LEN-DEX (not shown in Figure 39), or [b] by applying the NMA HR for BORT-DEX compared with IXA-LEN-DEX (1/0.31, Table 45 and section 1.3.5) to the model of OS for IXA-LEN-DEX shown in Figure 39.

Please confirm which method was used and provide a rationale for this method. Please provide the results from the alternative methods.

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B19. Executable model: in the survival worksheets (life tables OS and PFS), the total number of patients is not equal to the total number of events and censorings. Please clarify.

Using the data from these worksheets the ERG has not been able to reproduce the Kaplan-Meier and risk table plots shown in Appendix 11. Please confirm whether the plots in Appendix 11 have been derived using data shown in the model survival worksheets.

B20. In the NEJM paper for TMM-1 the methods state *; "Patients were randomly assigned, in a 1:1 ratio, to receive…. in 28-day cycles",* and "*Assessments of the response to the study regimen were performed every cycle until disease progression."* AND *"All patients were followed for survival after disease progression (every 12 weeks until death or termination of the study)".*

However in the model worksheets for survival (e.g. OS, PFS) the events and censorings occur at weekly intervals rather than monthly (28 day) intervals. Timing of data collection is unclear, and it appears data has been aggregated to weekly intervals for purposes of the economic model. Please clarify.

B21. Appendix 11: the horizontal axis of figures for "Log cumulative hazard plots" are labelled "ln(Time)". However, the the axis displays time, and this appears to be plotted on a logarithmic axis scale, which apperas to be log to the base 10 (rather than natural log base). Please clarify.

Health-related quality of life (HRQoL) analysis:

B22. **PRIORITY QUESTION**: Please clarify if people with an EQ-5D response who do not have PD, PR (not VGPR+) or SD are by definition in VGPR+. How was missing data handled in the HRQoL analysis, with particular reference to these variables? Please also clarify whether the response data relating to an EQ-5D response was measured at the same time as the EQ-5D, or within a 2 week window of it, or was the BoR.

B23. Please provide the following EQ-5D data separately for when patients are reporting VGPR+, PR but not VGPR+ and SD (3 data subsets): the number of patients, number of EQ-5D responses among those patients and mean (s.d.) EQ-5D values among those patients (see table below). Provide data separately for the 1 prior therapy group and the 2+ prior therapies group, and separately by TMM-1 arm (ie 4 tables for each of the 3 data subsets). A patient may move between data subsets over time; e.g. be in SD at baseline, PR but not VGPR+ at week 4 and VGPR+ at week 8.

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	VGPR+			
	N pat.	N EQ-5D	EQ-5D	ED-5D
Baseline	N=???	N=???	μ=???	s.d.=???
4 week	N=???	N=???	μ=???	s.d.=???
8 week	N=???	N=???	μ=???	s.d.=???
etc..	N=???	N=???	μ=???	s.d.=???

B24. Please provide the number of patients with progressive disease, number of EQ-5D responses among those patients and mean (s.d.) EQ-5D values among those patients (see table below). Provide data separately for the 1 prior group and the 2+ prior group, and separately by TMM-1 arm (ie 4 tables).

	PD			
	N pat.	N EQ-5D	EQ-5D	ED-5D
Baseline	N=???	N=???	μ=???	s.d.=???
1st PD EQ-5D	N=???	N=???	μ=???	s.d.=???
+ 12 week	N=???	N=???	μ=???	s.d.=???
+ 24 week	N=???	N=???	μ=???	s.d.=???
etc..	N=???	N=???	μ=???	s.d.=???

B25. **PRIORITY QUESTION**: Please provide the data in the table below from the EQ-5D data set, split by 1 prior and 2+ prior subgroups and by TMM-1 arm (4 tables).

Disease state	Number of responses, and responses with new prim. malig.	
	N EQ-5D responses	Of which resp. with new prim. malig.
VGPR+	n=???	n=???
PR	n=???	n=???
SD	n=???	n=???
PD	n=???	n=???

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B26. HRQoL was considered to be affected by a treatment-related adverse event (TRAE) only if the utility assessment occurred up to two weeks before or up to 2 weeks after the date of the adverse event.

a. Did the hospitalisation variable also have to be within a 4-week window of the EQ-5D measure?
b. Please confirm whether the hospitalisation variable in the quality of life regression includes hospitalisations for any reason or hospitalisation for any reason other than TRAE.
c. Please also clarify what windows the new primary malignancy had to be within.

B27. **PRIORITY QUESTION**: Please provide an updated HRQoL analysis which excludes hospitalisations and TRAEs. Please provide an updated HRQoL analysis which excludes hospitalisations, TRAEs and new primary malignancies. If time allows, please include the updated HRQoL analysis in the model and present the new ICERs as a sensitivity analysis.

Resource use:

B28. What resource use items were collected during TMM-1? Was this resource use data also collected after progression? Please provide the resource use data split by 1 prior therapy and 2+ prior therapies subgroups, by treatment arm, and by pre- and post-progression (to the extent that this is possible).

	Pre-progression				Post progression			
	IXA-LEN-DEX		LEN-DEX		IXA-LEN-DEX		LEN-DEX	
Res. Use.	1 prior	2+prior	1 prior	2+prior	1 prior	2+prior	1 prior	2+prior
Hospitalisations	N=???	N=???	N=???	N=???	N=???	N=???	N=???	N=???
Of which TRAE	N=???	N=???	N=???	N=???	N=???	N=???	N=???	N=???
Of which not TRAE	N=???	N=???	N=???	N=???	N=???	N=???	N=???	N=???
Inpatient days	N=???	N=???	N=???	N=???	N=???	N=???	N=???	N=???
Of which TRAE	N=???	N=???	N=???	N=???	N=???	N=???	N=???	N=???

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Of which not TRAE	N=???	N=???	N=???	N=???	N=???	N=???	N=???	N=???
Platelet transfusions	N=???	N=???	N=???	N=???	N=???	N=???	N=???	N=???
Etc…	N=???	N=???	N=???	N=???	N=???	N=???	N=???	N=???

Section C: Textual clarifications and additional points

C1. Please clarify why the Kaplan--Meier plots in Figures 33, 34, 35, 37, 39, 41 of the company submission are different to the corresponding Figures 5, 15, 27, 1, 11 and 23 presented in Appendix 11.

C2. In the text above figure 22, it is stated "*x studies contributing to a comparison*". Please clarify this.

C3. Please list the comparators included in the earlier Takeda Global NMA as alluded to in section 4.10.3.1 of the submission, and provide the report of this NMA.

C4. Please provide a copy of the report underlying the TMM-1 EQ-5D analysis that informed table 71 of the company submission.

C5. Please provide a copy of the report(s) of the recursive analyses that result in the final covariate adjusted parameterised curves presented in the executable model.

C6. TMM-1 baseline characteristics: table 37 of the company submission states that 441 people in the trial had received 1 prior treatment, whereas section 4.8.1 states 425. There is a corresponding discrepancy for the number of people who had received 2-3 prior treatments. Which statement is correct? Are the response rates in table 41 based on the correct subgroup data?

C7. For the cost-effectiveness analysis in the 1 prior therapy group, the model assumes 8 cycles of subcutaneous BORT on days 1, 4, 8 and 11. Was the stopping rule in NICE technology appraisal 129 included in the model (ie BORT is continued beyond cycle 4 only in people who have a complete or partial response)?

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

Submitted by Takeda UK Ltd.

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

Submitted 02nd February 2017

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List of Abbreviations

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

1. Overview

This document contains the response to the clarification questions from the evidence review group (ERG) sent to Takeda on 19th January 2017. We have attempted to address all questions as fully as possible within the timeframe permitted (deadline of 2nd February 2017). However, it has not been possible to provide a full response to all the questions, in particular some that are asking for additional analyses, such as A2, A10b and some of the questions relating to HRQoL. The focus of our attention has been on the priority questions and those specifically relating to the 2+ prior therapies population (3rd line positioning for the ixazomib regimen), where there is a clear clinical practice rationale for the use of IXA+LEN+DEX as an alternative to LEN+DEX alone in all relapsed and/or refractory (RRMM) patients after 2 prior therapies.

2. Response to clarification questions

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

Section A: Clarification on clinical effectiveness data

Decision problem

A1. PRIORITY QUESTION. A number of people with multiple myeloma receive a BORT-based treatment regimen as first-line therapy (TA311 and TA228). The NICE scope lists 2 comparators for this population, which the company excluded from its submission: BORT re-treatment (with or without DEX) and LEN-DEX. This leaves no comparator for IXA-LEN-DEX in people with relapsed/refractory disease who have received 1 prior line of treatment with BORT, and therefore committee will be unlikely to be able to make a recommendation in this group. NICE acknowledge that BORT retreatment is no longer funded by the NHS for this indication. However, NICE's negative recommendation for second-line LEN-DEX is only preliminary guidance and a final recommendation has not been issued. Clinical advisors to the ERG have indicated that LEN-DEX is used in current practice within the NHS, in particular among patients who have received BORT at first line and who had an inadequate response or experienced toxicity. According to IMS data on market share trends provided by the company, LEN-DEX represents 26% of therapy used in the UK second line (table 62 company submission).

Response:

Taken as a whole, Question A1 question highlights the significant lack of reimbursed and effective therapies available to relapsed and/or refractory multiple myeloma (RRMM) patients who have been treated upfront with a BORT-based regimen, which has been further antagonised by the loss of the Cancer Drugs Fund (CDF) cohort reimbursement for lenalidomide (LEN; Revlimid) plus dexamethasone (DEX; the Rd regimen) in second-line.

a. ***Please provide clinical and cost-effectiveness results for IXA-LEN-DEX compared with LEN-DEX for people with 1 prior therapy. If the company considers that neither LEN-DEX nor BORT retreatment are established practice for people at first relapse after receiving BORT, please clarify what the relevant comparator to IXA-LEN-DEX could be in this situation.***

Response:

The company is unable to provide clinical and cost-effectiveness results for IXA+LEN+DEX compared with LEN+DEX for people with 1 prior therapy.

Upon a detailed review of the latest NICE Pathway on multiple myeloma (MM), we have concluded that LEN+DEX (Rd) is not an eligible comparator for patients with one prior therapy as it is currently not funded by NHS England in this line; LEN+DEX recently had a draft negative Appraisal Consultation Document (ACD) response from NICE and there is no published timeline for the final NICE decision. Furthermore, the current NICE Pathway on the management of multiple myeloma lists BORT+DEX (Velcade+dexamethasone; Vd) as the only treatment currently recommended by NICE at second-line.

In relation to the question of what is the relevant comparator for IXA+LEN+DEX at second-line after frontline BORT, we provide the following response:

Upfront BORT treatment will be preferentially used in newly diagnosed MM patients with high-risk cytogenetics and renal impairment. Following relapse, second-line comparators used after frontline BORT in clinical practice (if available to prescribe on the NHS) currently consist of therapies that are either unlicensed or not recommended by NICE and which offer minimal duration of remission for patients (3-12 months) in comparison to a median 20.6 month PFS with IXA+LEN+DEX triplet therapy. Practice will vary according to networks but treatment selection will depend on a number of patient- and treatment-related factors:

1) **Bortezomib retreatment:**

BORT retreatment will be preferred in patients who have a durable prior remission with BORT therapy. Proteasome inhibitor therapy with BORT has demonstrated improved efficacy versus THAL or LEN-based therapies in patients with high-risk cytogenetics.

2) **Lenalidomide plus dexamethasone (Rd):**

LEN+DEX will be favoured in patients with prior neuropathy unlike BORT and THAL which are both neurotoxic. Only a small number of centres are able to access this due to strict controls following the loss of national CDF funding. The UK-based IMS market research data will likely inflate the second-line share of LEN+DEX due to the inclusion of Scotland and Wales (both of which have second-line funding of LEN+DEX) and an artefact of historical English patients who were prescribed the LEN+DEX combination when this was previously available on the CDF.

3) **Thalidomide-based combinations, such as cyclophosphamide, thalidomide, dexamethasone (CTd):**

Convenience of an all-oral regimen and can be used in patients with a suboptimal response to prior BORT. However, it has limited activity and no licence or reimbursement in RRMM so is effectively used as a short bridge to 3rd line therapy with LEN+DEX.

4) **Cytotoxic chemotherapy (e.g. melphalan)**

5) **Autologous stem cell transplant (for a small number of patients fit enough for intensive treatment)**

Note: of the above, only BORT retreatment and LEN+DEX were included in NICE's final scope for the ixazomib appraisal.

In terms of selecting a relevant comparator, BORT retreatment has been excluded in recent HTA submissions (e.g. see the lenalidomide second-line submission) where the committee concluded, in October 2016, that BORT retreatment was no longer a comparator as it is not commissioned by NHS England. Based on this logic, we have also excluded second-line LEN+DEX as a valid comparator because it is currently not recommended by NICE (or commissioned by NHS England) with a draft negative ACD response and no published timeline for the final NICE decision. THAL-based combinations were not in the NICE scope for ixazomib, and are neither licenced nor reimbursed at second-line, and so should be excluded. Similarly, cytotoxic chemotherapy and ASCT were not in the NICE scope for ixazomib and thus should also be excluded. Therefore, by applying the same logic on BORT retreatment, all potential systemic therapies that are be used in clinical practice at second-line after frontline BORT become excluded as valid (i.e. available and within scope) comparators. The failing of this logic is that this does not reflect routine practice. Furthermore, this means that it is not currently possible to assess the cost-effectiveness of any novel agent in this setting.

Due to the lack of available comparators after front-line BORT, we have used BORT+DEX as the second-line comparator as this is unequivocally the most commonly used regimen in this line of therapy and BORT is also the only treatment currently recommended by NICE at second-line. Unless LEN+DEX is approved at 1st relapse or NICE/NHS England reconsider their position on BORT-retreatment, we will be unable to determine the cost-effectiveness of

IXA+LEN+DEX in this subgroup and therefore IXA+LEN+DEX should only be considered for patients who have received front-line THAL-based therapy. We would propose that this situation should be discussed further at the appraisal committee meeting so that there is clarification from NICE on relevant comparators post-BORT treatment. If LEN+DEX is subsequently approved by NICE for 2nd line treatment after BORT therapy, discussions should include whether there are any clinically relevant subgroups, such as high-risk cytogenetics patients, that can be considered in the cost-effective modelling for IXA+LEN+DEX versus LEN+DEX.

b. ***If you do not intend to submit a comparison for IXA-LEN-DEX in this group (people with relapsed/refractory disease who have received 1 prior line of treatment with BORT), please explain your rationale and acknowledge that the committee will be unable to make a recommendation for people with relapsed/refractory disease who have received 1 prior line of treatment with BORT. NICE recognise that the scope lists no alternative comparators to BORT retreatment and LEN-DEX in this group, and is investigating this with clinical experts.***

Response:

Following on from the above, we acknowledge the suggestion that, in the absence of a second-line comparator for IXA+LEN+DEX (IRd) after frontline BORT, the committee may be unable to make a recommendation for this sub-group of patients who have received 1 prior line of treatment with BORT. We are clear that BORT+DEX (Vd) is the dominant treatment at second-line and that it is certainly the appropriate comparator for patients who were treated with a THAL-based regimen upfront. We note that this was confirmed recently in the ongoing NICE appraisal of carfilzomib (CARF) where the comparator for CARF+DEX (Kd) at second-line was accepted as BORT+DEX (Vd) in patients who had THAL in the frontline.

c. ***Table 37 states that 69% of patients in TMM-1 had previously received BORT. Is it possible to split this into the number of patients that received BORT as a first line treatment (compared with later lines of therapy)? Please clarify whether this includes patients who received BORT as an induction to stem cell transplant***.

Response:

Due to the methods of data collection, it is not be possible to split BORT use accurately by line of therapy. Due to how lines of therapy were defined, one treatment line could potentially include all initial treatments before a relapse (i.e. the induction, consolidation and maintenance) but could also be defined as one therapy only it would not be possible to determine how BORT was used within a particular line. As there is variability in the data collection limiting the accuracy of the analysis, we are not able to provide this additional detail.

A2. PRIORITY QUESTION. The company's analysis of IXA-LEN-DEX in the 2 prior therapies subgroup uses TMM-1 trial data from people who had received 2 or 3 previous treatments. The company states in section 5.2.2 of its submission (page 163) that randomisation in TMM-1 was stratified according to 1 prior therapy versus 2 or 3 prior therapies. That is, using data from the 2 prior therapies only subgroup would be a post hoc analysis and carry several limitations. However, the ERG consider that it would be valuable to show the results of a sensitivity analysis using the data from the subgroup of TMM-1 patients with 2 prior regimens only. Please provide these analyses.

Response:

Unfortunately, given the time constraints, we are unable to provide the results of a sensitivity analysis using the data from the subgroup of TMM1 patients with 2 prior regimens only. However, we have provided the response rate, progression free survival (PFS), time to progression (TTP) and overall survival (OS) results for the 2-prior line population for IA1 (30th October 2014) and IA2 (12th July 2015) in the corresponding tables below.

Table 1: Subgroup response data associated with the 2-prior line population, ITT data (IA1 data cut)

	ORR		VGPR or Better		CR or Better	
	LenDex N=362 n/N_1^* (%)	Ixazomib + LenDex N=360 n/N_1^* (%)	LenDex N=362 n/N_1^* (%)	Ixazomib + LenDex N=360 n/N_1^* (%)	LenDex N=362 n/N_1^* (%)	Ixazomib + LenDex N=360 n/N_1^* (%)
All Patients	259 (72)	282 (78)	141 (39)	173 (48)	24 (7)	42 (12)
Prior Lines of Therapy per Stratification						
2 or 3	100/149 (67)	119/148 (80)	48/149 (32)	78/148 (53)	7/149 (5)	23/148 (16)
Prior Lines of Therapy per Takeda review						
2	78/111 (70)	77/97 (79)	42/111 (38)	49/97 (51)	6/111 (5)	16/97 (16)
3	21/34 (62)	32/39 (82)	7/34 (21)	20/39 (51)	1/34 (3)	4/39 (10)

* N_1 is number of patients in each sub-group within each treatment arm which is used as denominator for percentage calculation. Key: CR, complete response; ITT, intention to treat; LenDex, lenalidomide and dexamethasone; n, number; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response

Table 2: Subgroup response data associated with the 2-prior line population, ITT data (IA2 data cut)

	ORR		VGPR or Better		CR or Better	
	LenDex N=362 n/N_1^* (%)	Ixazomib + LenDex N=360 n/N_1^* (%)	LenDex N=362 n/N_1^* (%)	Ixazomib + LenDex N=360 n/N_1^* (%)	LenDex N=362 n/N_1^* (%)	Ixazomib + LenDex N=360 n/N_1^* (%)
All Patients	265 (73)	283 (79)	159 (44)	185 (51)	37 (10)	53 (15)
Prior Lines of Therapy per Stratification						
2 or 3	99/149 (66)	119/148 (80)	54/149 (36)	80/148 (54)	10/149 (7)	27/148 (18)
Prior Lines of Therapy per Takeda review						
2	77/111 (69)	76/97 (78)	46/111 (41)	50/97 (52)	9/111 (8)	18/97 (19)
3	21/34 (62)	33/39 (85)	8/34 (24)	20/39 (51)	1/34 (3)	4/39 (10)

* N_1 is number of patients in each sub-group within each treatment arm which is used as denominator for percentage calculation.

Key: CR, complete response; ITT, intention to treat; LenDex, lenalidomide and dexamethasone; n, number; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response

Table 3: Subgroup PFS, TTP and OS data associated with the 2-prior line population, ITT data (IA1 data cut)

	Median[a] PFS (months)			Median[a] TTP (months)			Median[a] OS (months)		
	LenDex N=362	Ixazomib + LenDex N=360	HR[b]	LenDex N=362	Ixazomib + LenDex N=360	HR[b]	LenDex N=362	Ixazomib + LenDex N=360	HR[b]
All Patients	14.7(157/362)	20.6(129/360)	0.742	15.7	21.4	0.712	NE(56/362)	NE(51/360)	0.900
Prior Lines of Therapy per Stratification									
2 or 3	12.9(69/149)	NE(49/148)	0.580	13.0	NE	0.550	NE(30/149)	NE(20/148)	0.618
Prior Lines of Therapy per Takeda review									
2	14.1(47/111)	17.5(36/97)	0.723	14.9	18.7	0.668	NE(18/111)	NE(14/97)	0.720
3	10.2(19/34)	NE(10/39)	0.361	12.9	NE	0.385	NE(11/34)	NE(4/39)	0.315

NE = Not Estimable. P= placebo, LD=Len+dex; I+XD = Ixa + Len+Dex

a. Based on Kaplan-Meier product limit estimates.

b. Hazard ratios are based on a stratified Cox's proportional hazard regression model with stratification factors prior lines of therapy (1, 2 or 3), prior proteasome inhibitor (Exposed, Naïve), and ISS stage at Study Entry (I or II, III).

Key: HR, hazard ratio; ITT, intention to treat; LenDex, lenalidomide and dexamethasone; n, number; NE, not evaluable; OS, overall survival; PFS, progression free survival; TTP, time to progression

Table 4: Subgroup PFS, TTP and OS data associated with the 2-prior line population, ITT data (IA2 data cut)

	Median[a] PFS (months)			Median[a] TTP (months)			Median[a] OS (months)		
	P+Ld N=362	I+Ld N=360	HR[b]	P+Ld N=362	I+Ld N=360	HR[b]	P+Ld N=362	I+Ld N=360	HR[b]
All Patients	15.9(195/362)	20.0(177/360)	0.818	17.6	22.4	0.792	NE(90/362)	NE(81/360)	0.868
Prior Lines of Therapy per Stratification									
2 or 3	13.0(83/149)	22.0(68/148)	0.617	14.1	28.8	0.584	NE(45/149)	NE(33/148)	0.645
Prior Lines of Therapy per Takeda review									
2	15.6(58/111)	19.3(47/97)	0.749	17.9	20.5	0.694	NE(31/111)	NE(23/97)	0.695
3	10.2(21/34)	23.0(17/39)	0.487	13.6	29.4	0.524	NE(13/34)	NE(7/39)	0.441

NE = Not Estimable.

a. Based on Kaplan-Meier product limit estimates.

b. Hazard ratios are based on a stratified Cox's proportional hazard regression model with stratification factors prior lines of therapy (1, 2 or 3), prior proteasome inhibitor (Exposed, Naïve), and ISS stage at Study Entry (I or II, III).

Key: HR, hazard ratio; ITT, intention to treat; LenDex, lenalidomide and dexamethasone; n, number; NE, not evaluable; OS, overall survival; PFS, progression free survival; TTP, time to progression

Systematic review

A3. Figure 9: Please provide a list of the 16 publications excluded after review of full-text articles, and the reasons for exclusion

Response:

There were 20 publications that were excluded after review of the full-text articles (see Table 5). We apologise for this discrepancy. One study (Reference ID 33; San Miguel et al., 2015c) had been omitted from Table 43 in the submission: 'Data sources of all identified RCTs and observational studies for IXA+LEN+DEX and other treatments for the treatment of RRMM (Primary and Scenario Doses)' which has now been corrected (see Table 5 below for studies identified from the search but excluded from NMA with reason). Following this, we have updated Figure 9 from the submission this is the PRISMA diagram to account for the 21 publications from 14 studies that were included in the NMA (Figure 1), and the 20 studies that were excluded after review of the full-text articles (see Table 6). The highlighted green information refers to the study that was omitted.

Table 5: Studies identified from the systematic search, but excluded from the NMA

List of excluded studies (n=20)

Author	Title	Citation	Reason for exclusion
Bortezomib studies			
Bruno et al., 2006	Bortezomib with or without dexamethasone in relapsed multiple myeloma following allogeneic hematopoietic cell transplantation	Haematologica 2006;91:837-839	Insufficient outcomes of interest data
Hellmann et al., 2011	Effect of cytochrome P450 3A4 inducers on the pharmacokinetic, pharmacodynamic and safety profiles of bortezomib in patients with multiple myeloma or non-Hodgkin's lymphoma	Clinical pharmacokinetics 50, 781-791	Insufficient outcomes of interest data
Lee et al., 2008	Bortezomib is associated with better health-related quality of life than high-dose dexamethasone in patients with relapsed multiple myeloma: results from the APEX study	British journal of haematology 143, 511-519	Insufficient outcomes of interest data
Reyal et al.,	Real world experience of bortezomib re-treatment for patients with multiple myeloma at first relapse	Br J Haematol. doi:10.1111/bjh.14086	Insufficient outcomes of interest data
Richardson et al., 2007b	Safety and efficacy of bortezomib in high-risk and elderly patients with relapsed multiple myeloma. British journal of haematology	British journal of haematology 137, 429-435	Subgroup analysis not of interest
Carfilzomib studies			
Ashaye et al., 2015a	Estimating eortc-8d health state utility values from eortc QLQ-C30 scores in relapsed multiple myeloma	Value in Health 18 (7): A468	Insufficient outcomes of interest data
Ashaye et al., 2015b	Mapping utility scores from European organization for treatment of cancer core-30 questionnaire scores (EORTC QLQ-C30) in relapsed multiple myeloma	Value in Health 18 (3): A208	Insufficient outcomes of interest data

Author	Title	Citation	Reason for exclusion
Dimopoulos et al., 2015a	Effect of carfilzomib, lenalidomide, and dexamethasone (KRd) vs. lenalidomide and dexamethasone (Rd) in patients with relapsed multiple myeloma (RMM) by line of therapy: Secondary analysis from an interim analysis of the phase III study ASPIRE (NCT01080391)	Journal of Clinical Oncology. Conference 33(15 SUPPL. 1)	Identical abstract to Dimopoulos et al., 2015b. Effect of carfilzomib, lenalidomide, and dexamethasone vs. lenalidomide and dexamethasone in patients with relapsed multiple myeloma by line of therapy: Interim results from the phase 3 aspire study. Haematologica 100: 151-152
Dimopoulos et al., 2015c	Carfilzomib and dexamethasone (Kd) vs bortezomib and dexamethasone (Vd) in patients (pts.) with relapsed multiple myeloma (RMM): Results from the phase III study ENDEAVOR	Journal of Clinical Oncology. Conference 33(15 SUPPL. 1). Abstract 8509	Abstract from the full publication of Dimopoulos et al., 2016. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncology 17(1): 27-38)
Dimopoulos et al., 2015d	Carfilzomib and dexamethasone improves progression free survival and response rates vs. bortezomib and dexamethasone in patients (PTS) with relapsed multiple myeloma (RMM): The phase 3 study endeavor.	Haematologica 100: 336	Identical abstract to Dimopoulos et al., 2015b. Effect of carfilzomib, lenalidomide, and dexamethasone vs. lenalidomide and dexamethasone in patients with relapsed multiple myeloma by line of therapy: Interim results from the phase 3 aspire study. Haematologica 100: 151-152
Moreau et al., 2016	Impact of prior treatment on patients with relapsed multiple myeloma treated with carfilzomib and dexamethasone vs bortezomib and dexamethasone in the phase 3 ENDEAVOR study	Leukemia 2016; 1-8	Abstract from the full publication of Moreau et al., 2015. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncology 17(1): 27-38
Stewart et al., 2015b	Superior health-related quality of life with carfilzomib, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone in patients with relapsed multiple myeloma (MM): Results from the aspire trial	Clinical Lymphoma, Myeloma and Leukemia 15: e76	Insufficient outcomes of interest data
Stewart et al., 2015c	Interim results from ASPIRE, a randomized, open-label, multicentre phase 3 study evaluating carfilzomib, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone in patients with relapsed multiple myeloma	British Journal of Haematology 169: 20	Abstract from the full publication of Stewart et al., 2015a. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. New England Journal of Medicine 372(2): 142-152
Panobinostat studies			
Einsele et al., 2015	Subgroup analysis by prior treatment among patients with relapsed or relapsed and refractory multiple myeloma in the panorama 1 study of panobinostat or placebo plus bortezomib and dexamethasone	Haematologica 100: 1	Subgroup analysis not of interest
Hungria et al., 2015	Analysis of outcomes based on response for patients with relapsed or relapsed and refractory multiple myeloma in the phase 3 PANORAMA 1 study	Journal of Clinical Oncology. Conference 33(15 SUPPL. 1)	Subgroup analysis not of interest
Majer et al., 2015	Estimating utilities for panobinostat in combination with bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed and/or	Blood 126 (23): 4504	Insufficient outcomes of interest data

Author	Title	Citation	Reason for exclusion
	refractory multiple myeloma; evidence from the panorama-1 trial		
Moreau et al., 2015	Analysis of outcomes by response for patients with relapsed or relapsed and refractory multiple myeloma in the phase 3 panorama 1 study of panobinostat or placebo plus bortezomib and dexamethasone	Haematologica 100: 80-81	Subgroup analysis not of interest
Richardson et al., 2015	Subgroup analysis by prior treatment of the efficacy and safety of panobinostat plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma in the panorama 1 study	Clinical Lymphoma, Myeloma and Leukaemia 15: e78	Subgroup analysis not of interest
San-Miguel et al.,2015a	Analysis of outcomes based on response in patients with relapsed or relapsed and refractory multiple myeloma treated with panobinostat or placebo in combination with bortezomib and dexamethasone in the panorama 1 trial: Updated analysis based on prior treatment	Blood 126 (23): 4230	Subgroup analysis not of interest
San-Miguel et al.,2015b	Panobinostat plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma who received prior bortezomib and IMiDs: A predefined subgroup analysis of PANORAMA 1	J Clin Oncol 33 (suppl; abstr 8526)	Subgroup analysis not of interest

Figure 1 **Figure 9: PRISMA flow diagram of the study selection process for relapsed or refractory multiple myeloma patients (June 2015 original review, April and October 2016 updates)**

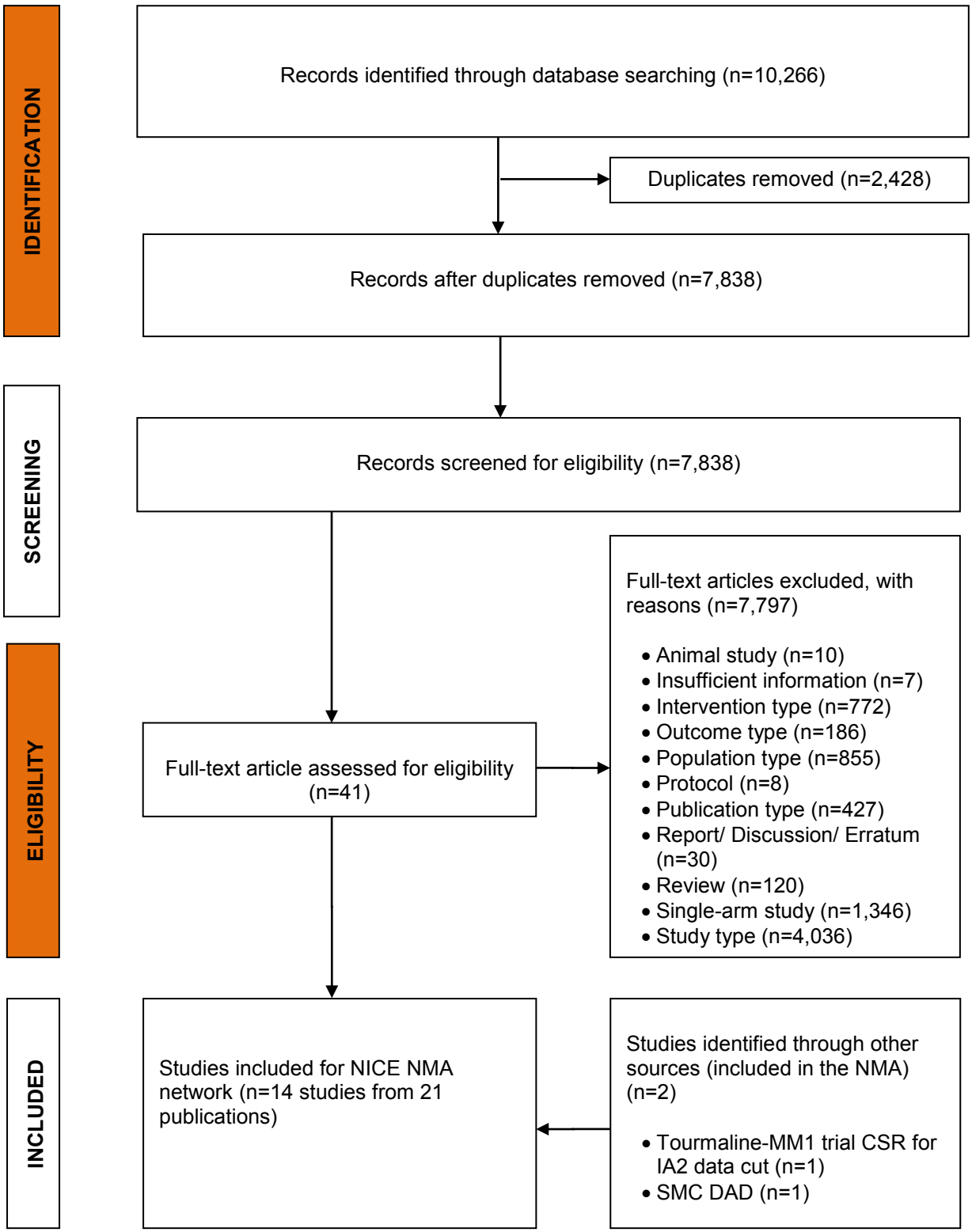


Table 6: **Data sources of all identified RCTs and observational studies for ixazomib plus lenalidomide – dexamethasone and other treatments for the treatment of RRMM (Primary and Scenario Doses) (update of Table 43 in the submission)**

Reference ID†	Study ID	Study type (RCT or Observational)	Primary data source	Location	Comparator 1	Comparator 2
1a	Tourmaline-MM1*	RCT	Data cut IA1 (30th October 2014) [5]Publication: Moreau et al., 2016a[12]	International, including UK	Ixazomib + LenDex	Placebo + LenDex
1b	Tourmaline-MM1	RCT	Data cut IA2 (12th July 2015)[6] CSR ixazomib 2015	International, including UK	Ixazomib + LenDex	Placebo + LenDex
1c	Tourmaline-MM1	RCT	Hou et al., 2016 (Data cut 12th July 2015)[13]	China	Ixazomib + LenDex	Placebo + LenDex
3	Matched-pairs of patients from 3 clinical trials: MMY-2045, APEX, and DOXIL-MMY-3001	Observational (retrospective analysis)	Dimopoulos et al., 2015 [14]	North America, Canada, and Europe (including the UK)	Bortezomib + Dex	Bortezomib
4	eVOBS	Observational	Dimopoulos et al., 2010 [15]	Belgium, France, Greece, Spain, Sweden, Turkey, and Brazil	Bortezomib + Dex	Bortezomib
7	Phase III	RCT	Montefusco et al., [16]	Italy	Bortezomib + Dex + cyclophosphamide	Len + Dex + cyclophosphamide
8	APEX	RCT	Richardson et al., 2005 [17]	North America, Canada, and Europe (including the UK)	Bortezomib	Dexamethasone
9	APEX	RCT	Richardson et al., 2007a [18]	North America, Canada, and Europe (including the UK)	Bortezomib	Dexamethasone
13	ENDEAVOR*	RCT	Dimopoulos et al., 2016 [19]	North and South America, Canada, Europe (including the UK), and the Asia-Pacific region	Carfilzomib + Dex	Bort + Dex
18c	ENDEAVOR	RCT	Moreau et al., 2015c [16]	North and South America, Canada, Europe (including the UK), and the Asia-Pacific region	Carfilzomib + Dex	Bort + Dex

Reference ID†	Study ID	Study type (RCT or Observational)	Primary data source	Location	Comparator 1	Comparator 2
19	ASPIRE	RCT	Stewart et al., 2015a [20]	North America, Canada, and Europe (including the UK)	Carfilzomib + Len + Dex	Len + Dex
15	ASPIRE	RCT	Dimopoulos et al., 2015b [14]	North America, Canada, and Europe (including the UK)	Carfilzomib + Len + Dex	Len + Dex
22	MM-010	RCT	Dimopoulos et al., 2007 [21]	Europe (including the UK), and Asia-Pacific region	Len + Dex	Placebo + Dex
23	MM-009	RCT	Weber et al., 2007 [22]	North America and Canada	Len + Dex	Placebo + Dex
39	–	Observational (retrospective analysis)	Zagouri et al., 2016 [23]	–	Len + intermediate dose Dex	Len + low dose Dex
40a 40b	Match-adjusted indirect analysis of patients from 3 clinical trials: PANORAMA-1, MM009/010, MM-003	Systematic review	Majer et al., 2016 [24]	–	Pano + Bort + Dex Pano + Bort+ Dex	Len + Dex Pom + Dex
28	PANORAMA-1	RCT	Richardson et al., 2016 [25]	North and South America, Canada, Europe (including the UK), and the Asia-Pacific region	Pano + Bort + Dex	Bort + Dex
30	PANORAMA-1*	RCT	San-Miguel et al., 2014 [26]	North and South America, Canada, Europe (including the UK), and the Asia-Pacific region	Pano + Bort + Dex	Bort + Dex
33	PANORAMA-1	RCT	San-Miguel et al., 2015c	North and South America, Canada, Europe (including the UK), and the Asia-Pacific region	Pano + Bort + Dex	Bort + Dex
37	PANORAMA-1	SMC DAD	SMC No. (1122/16), 2016 [2]			
34	MM-002	RCT	Richardson et al., 2014 [27]	North America and Canada	Pom + Dex	Pom
35	MM-003	RCT	San-Miguel et al., 2013 [28]	North America, Canada, Europe (including the UK), and the Asia-Pacific region	Pom + Dex	High dose Dex

Reference ID†	Study ID	Study type (RCT or Observational)	Primary data source	Location	Comparator 1	Comparator 2
36	MM-003	RCT	San-Miguel et al., 2015d [26]	North America, Canada, Europe (including the UK), and the Asia-Pacific region	Pom + Dex	High dose Dex

Abbreviations: CSR = clinical study report; LenDex = lenalidomide + dexamethasone; Bort = bortezomib; Dex = dexamethasone; Len = lenalidomide; Cyclo = cyclophosphamide; Pano = panobinostat; Pom = pomalidomide; SMC DAD = Scottish Medicines Consortium Detailed Advice Document

† The reference ID is used in the NMA results section and the Appendices for the identification of studies used in each network

* Studies in bold font indicate the primary publication

Direct treatment comparison

A4. Table 40: please provide the 95% CI for all the variables that have been compared.

Response:

The 95% CIs for the variables that have been compared have been added to Table 40 from the original submission dossier (highlighted in yellow in Table 7).

Table 7: Best confirmed treatment responses (blinded IRC assessment) and TTP in the ITT population (23-month analysis)

Variable	IRd (N=360)	Rd (N=362)	Statistical comparison
Overall response rate, n (%)	283 (78.6) (74.0, 82.7)	265 (73.2) (68.3, 77.7)	OR: 1.35 (0.96, 1.91)
≥VGPR, n (%)	185 (51.4) (46.1, 56.7)	159 (43.9) (38.7, 49.2)	OR: 1.35 (1.01, 1.81)
Best response			
CR, n (%)	53 (14.7) (11.2, 18.8)	37 (10.2) (7.3, 13.8)	OR: 1.52 (0.97, 2.38)
sCR[a], n (%)	12 (3.3) (1.7, 5.8)	4 (1.1) (0.3, 2.8)	
PR, n (%)	230 (63.9) (58.7, 68.9)	228 (63.0) (57.8, 68.0)	
VGPR[a], n (%)	132 (36.7) (31.7, 41.9)	122 (33.7) (28.8, 38.8)	
SD, n (%)	37 (10.3) (7.3, 13.9)	53 (14.6) (11.2, 18.7)	
Median time to response, months[b]	1.1 (1.05, 1.74)	1.9 (1.84, 1.94)	HR: 1.23 (1.04, 1.46)
Median duration of response (≥PR), months	26.0 (22.5, NE)	21.7 (17.8, NE)	-
Median TTP, months	22.4 (18.7, 27.7)	17.6 (14.5, 20.3)	HR: 0.79 (0.64, 0.98)

Variable	IRd (N=360)	Rd (N=362)	Statistical comparison
Key: CI = confidence intervals; CR = complete response; HR = hazard ratio; IRd = ixazomib with lenalidomide and dexamethasone; ITT = intent to treat; Rd = placebo with lenalidomide and dexamethasone; PR = partial response; sCR = stringent complete response; SD = stable disease; TTP, time to progression; VGPR = very good partial response [a] Stringent complete response is a subset of complete response, and very good partial response is a subset of partial response. [b] Median time to response in responding patients was 1.0 months vs. 1.1 months in the ixazomib vs. placebo groups. Source: TOURMALINE-MM1 CSR [42]			

A5. Please confirm that, in both the clinical sections and the economic sections of the submission:

a. All OS analyses use the 2nd interim analysis data cut of TMM-1
b. All PFS analyses use the 1st interim analysis data cut of TMM-1
c. All ToT analyses use the 1st interim analysis data cut of TMM-1

When responding to the following questions, please report the results using the data cuts specified above, except where the question specifies a different data cut.

Response:

In the NICE dossier, the clinical sections present data from both the 1st and 2nd interim analysis. In the economic sections the base case analysis uses only data from the 1st interim analysis (IA1), this includes response, OS, PFS and time on treatment (ToT) data. A scenario analysis, presented in the original submission dossier, considers the impact on the incremental cost-effectiveness ratio (ICER) of using data from the 2nd interim analysis for all outcomes of interest.

When responding to questions within this document we have used the data cuts as specified by the relevant question.

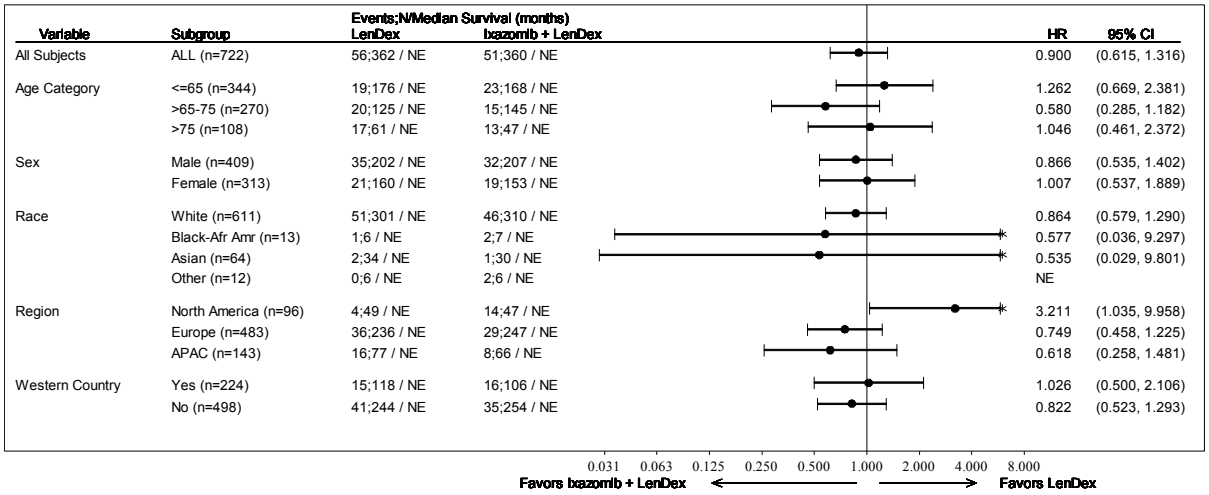
A6. TMM-1 (C16010) clinical study report figure 11v. (Forest Plots of Time to Progression and Overall Response Rate in Subgroups): Please clarify how "Prior Therapies (1, 2 or 3)" and "Prior Therapies Derived (1, 2 or 3)" were derived and should be interpreted. Please replicate figure 19 of the submission using OS data.

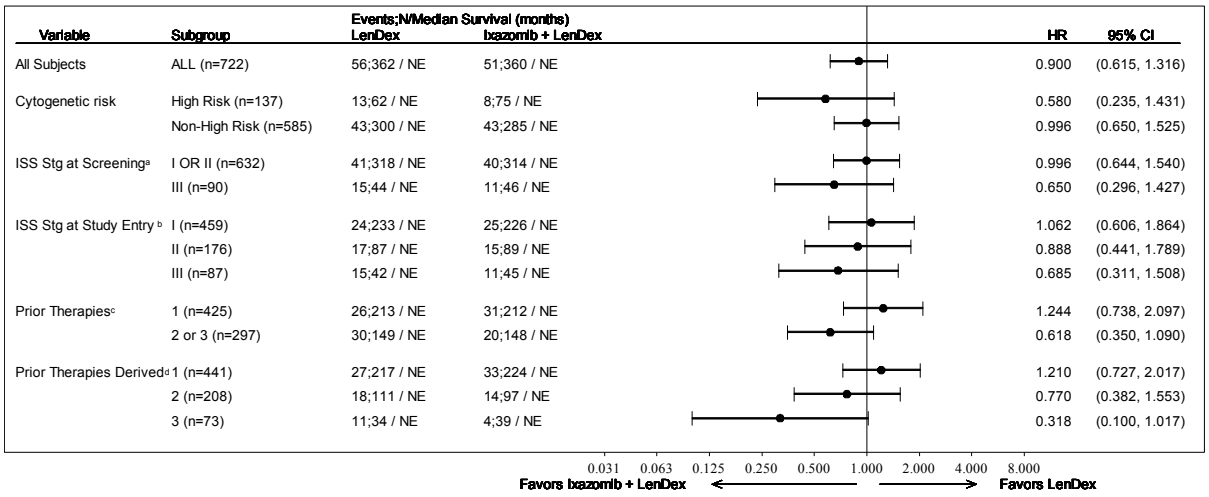
Response:

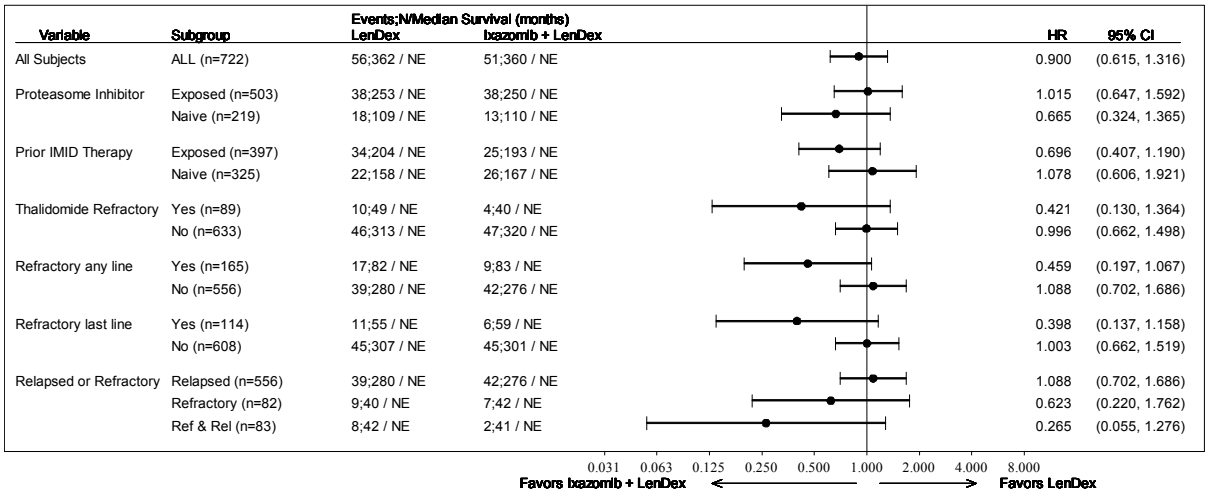
"Prior Therapies (1, 2 or 3)" is based on the stratification factor (with stratification by 1vs 2-3 prior therapies at enrolment). "Prior Therapies Derived (1, 2 or 3)" is based on the Takeda medical review, which was considered in a sensitivity analysis, as stratification does not break down 2-3 line by 2 and 3.

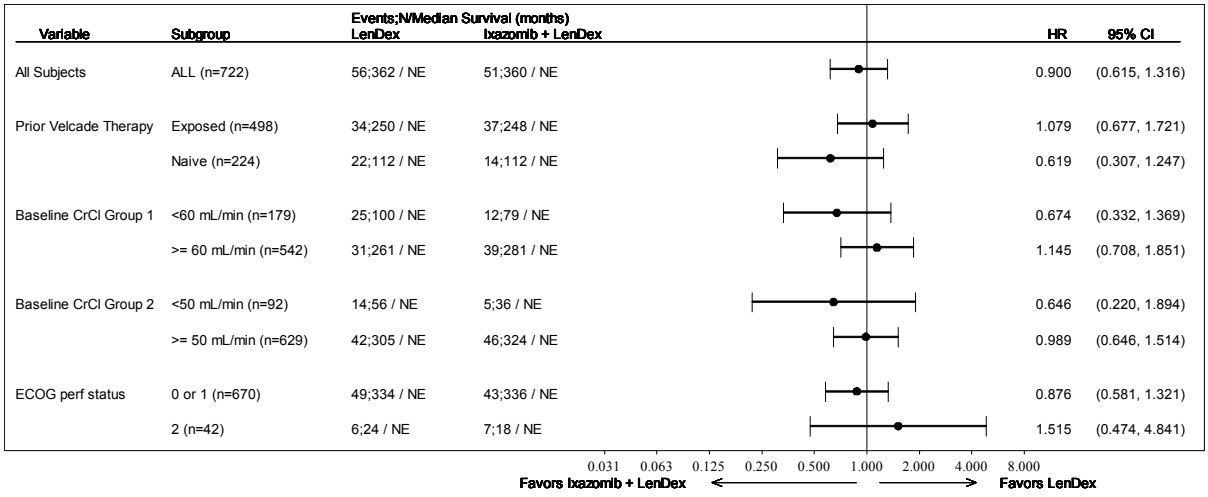
Figure 19 of the submission is replicated below using OS outcomes (Figure 2 for IA1 data cut and Figure 3 for IA2 data cut).

Figure 2: Subgroup Analysis: Forest Plot of Overall Survival ITT Population (IA1 data cut)









* indicates that upper confidence limit is truncated at 6 to fit on the graph.
CrCl= Creatinine Clearance. NE = Not Estimable

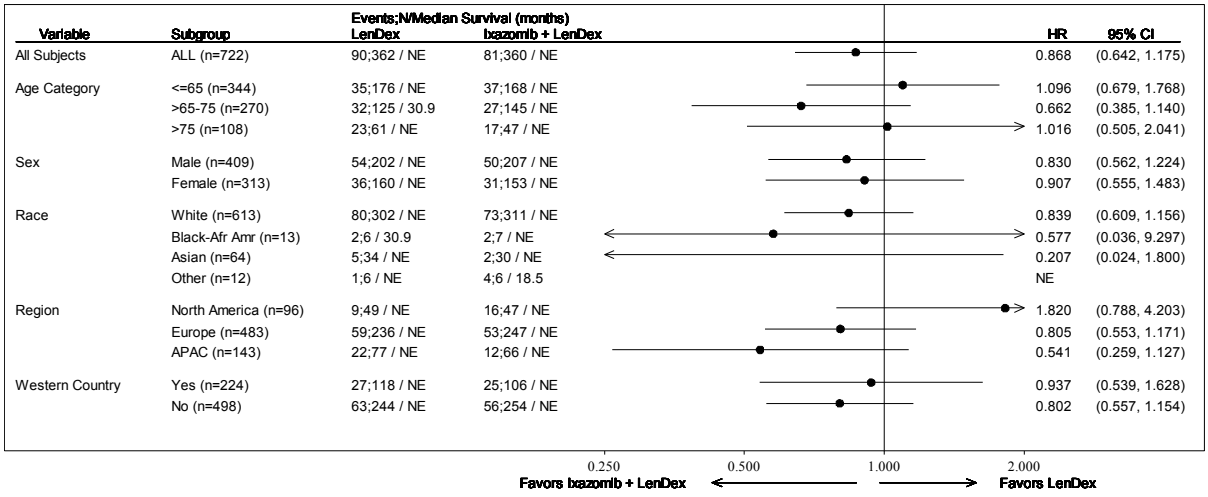
a ISS stage stratification per IVRS at enrollment.

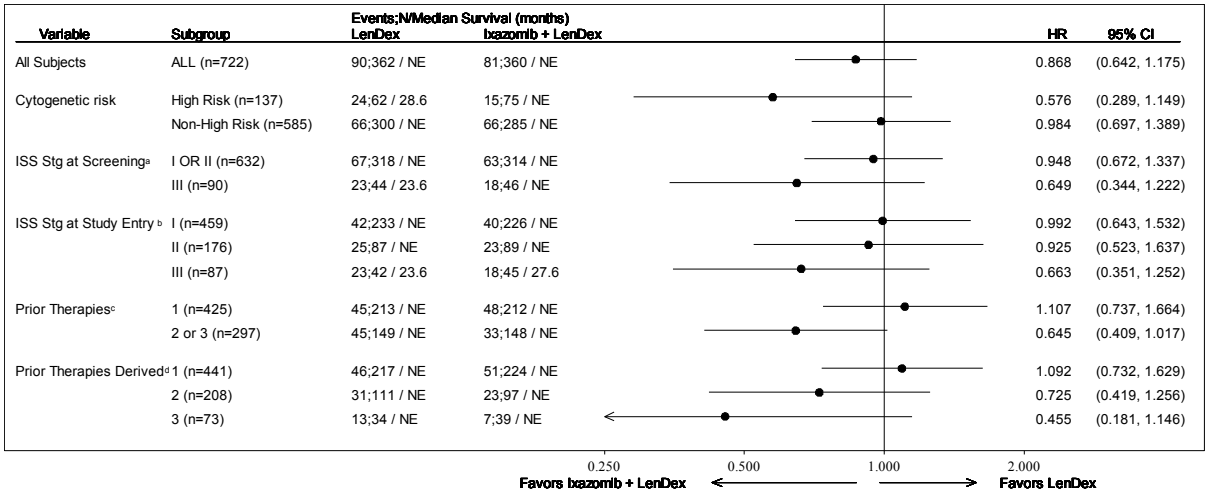
b ISS stage as collected on eCRF.

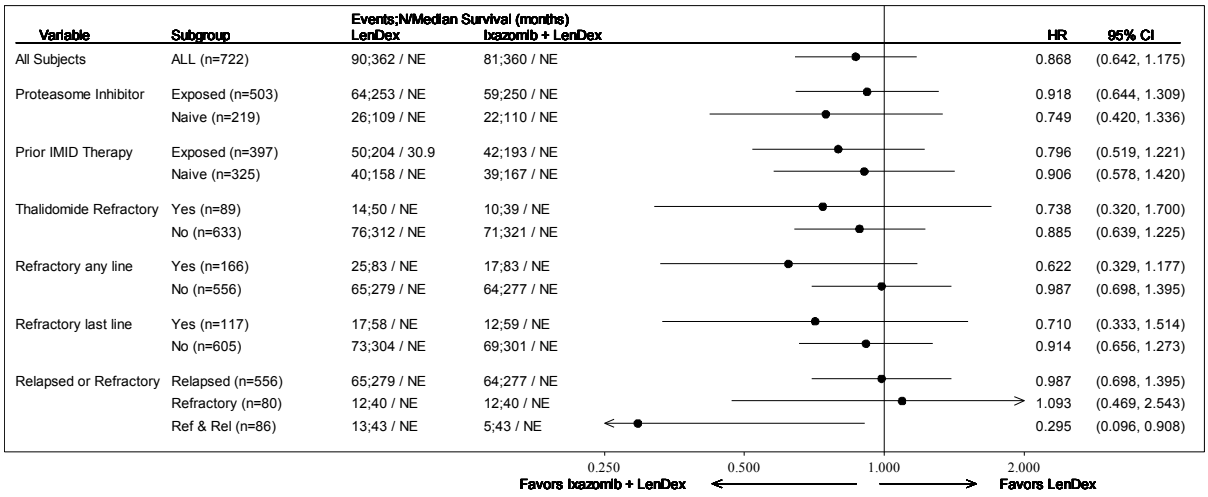
c Prior therapies stratification per IVRS at enrollment.

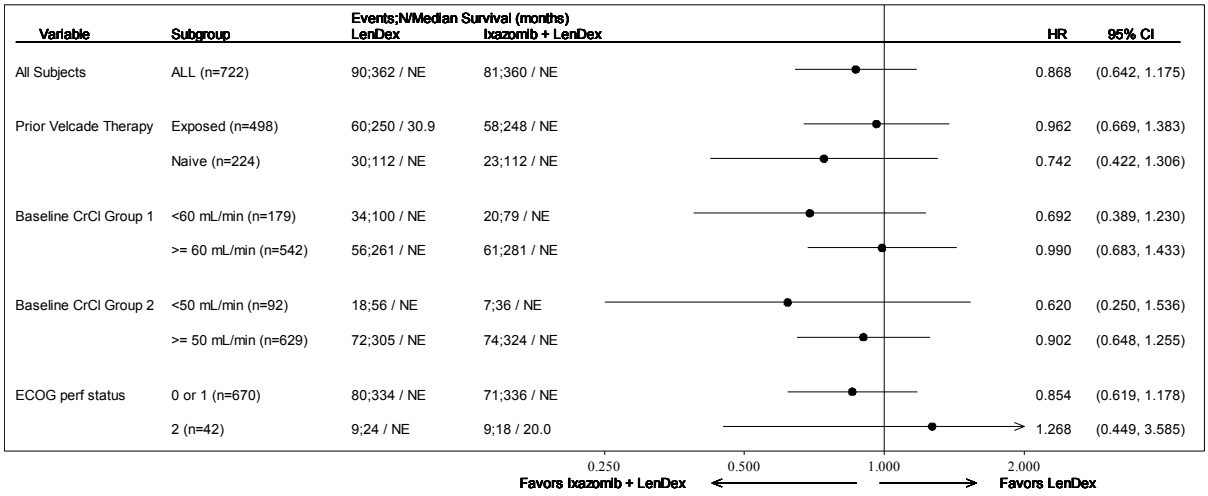
d Prior therapies as determined by Takeda medical review of prior therapy data.

Figure 3: Subgroup Analysis: Forest Plot of Overall Survival Intent to treat Population (IA2 data cut)









CrCl=Creatinine Clearance. NE=Not Estimable

a ISS stage stratification per IVRS at enrollment.

b ISS stage as collected on eCRF.

c Prior therapies stratification per IVRS at enrollment.

d Prior therapies as determined by Takeda medical review of prior therapy data.

A7. Table 37 (TMM-1 study baseline patient characteristics): Please complete the table below (ie please split the baseline characteristics of TMM-1 by arm for the 1 prior therapy and the 2+ prior therapy subgroups).

Response:

A table with baseline characteristics for 1 vs 2-3 prior therapies per stratification is detailed below (Table 8).

Table 8: Characteristics by Prior Lines of Therapy per Stratification ITT Population

	LenDex N=362		Ixazomib + LenDex N=360	
	1 N=213 n (%)	2 or 3 N=149 n (%)	1 N=212 n (%)	2 or 3 N=148 n (%)
Age				
<=65 yrs	104 (49)	72 (48)	100 (47)	68 (46)
>65 and <=75 yrs	76 (36)	49 (33)	87 (41)	58 (39)
>75 yrs	33 (15)	28 (19)	25 (12)	22 (15)
Mean age (std. dev)	65.6 (9.44)	66.1 (10.09)	65.3 (8.90)	65.9 (9.46)
Race				
White	181 (85)	120 (81)	185 (87)	125 (84)
Asian	14 (7)	20 (13)	16 (8)	14 (9)
Japanese	9 (4)	12 (8)	10 (5)	10 (7)
Black/AA	3 (1)	3 (2)	5 (2)	2 (1)
Other	4 (2)	2 (1)	1 (<1)	5 (3)
Not Reported	11 (5)	4 (3)	5 (2)	2 (1)
Sex				
Male	116 (54)	86 (58)	126 (59)	81 (55)
Female	97 (46)	63 (42)	86 (41)	67 (45)
Region				
Europe	145 (68)	91 (61)	148 (70)	99 (67)
APAC	30 (14)	47 (32)	28 (13)	38 (26)
NA	38 (18)	11 (7)	36 (17)	11 (7)
Cytogenetics Risk				
Non-high risk	179 (84)	121 (81)	167 (79)	118 (80)
High risk	34 (16)	28 (19)	45 (21)	30 (20)
High risk: del(17)	19 (9)	14 (9)	19 (9)	17 (11)
High risk: t(4:14)	13 (6)	12 (8)	24 (11)	12 (8)
High risk: t(14:16)	2 (<1)	2 (1)	2 (<1)	1 (<1)
ECOG				
0	112 (53)	58 (39)	121 (57)	59 (40)
1	90 (42)	74 (50)	79 (37)	77 (52)
2	9 (4)	15 (10)	8 (4)	10 (7)
Missing	2	2	4	2
Prior Lines of Therapy per Stratification				
1	213 (100)	0	212 (100)	0
2 or 3	0	149 (100)	0	148 (100)

	LenDex N=362		Ixazomib + LenDex N=360	
	1 N=213 n (%)	2 or 3 N=149 n (%)	1 N=212 n (%)	2 or 3 N=148 n (%)
Prior Lines of Therapy per Takeda review				
1	203 (95)	14 (9)	206 (97)	18 (12)
2	9 (4)	102 (68)	6 (3)	91 (61)
3	1 (<1)	33 (22)	0	39 (26)
Relapsed/Refractory Type				
Relapsed *	190 (89)	90 (60)	183 (86)	93 (63)
Refractory **	21 (10)	19 (13)	27 (13)	15 (10)
Relapsed and Refractory ***	2 (<1)	40 (27)	1 (<1)	40 (27)
Primary Refractory ****	12 (6)	10 (7)	13 (6)	11 (7)
Prior Proteasome Inhibitor				
Exposed	139 (65)	114 (77)	137 (65)	113 (76)
Naïve	74 (35)	35 (23)	75 (35)	35 (24)
Refractory	5 (2)	12 (8)	11 (5)	11 (7)
Vc-Refractory (Takeda)	3 (1)	5 (3)	3 (1)	3 (2)
CFZ-Refractory (Takeda)	0	0	1 (<1)	0
Prior IMiD				
Exposed	102 (48)	102 (68)	93 (44)	100 (68)
Naïve	111 (52)	47 (32)	119 (56)	48 (32)
Refractory	15 (7)	35 (23)	17 (8)	24 (16)
Thal-Refractory (Takeda)	14 (7)	35 (23)	16 (8)	24 (16)
Len-Refractory (Takeda)	1 (<1)	0	0	0
ISS stage per Stratification				
I or II	187 (88)	131 (88)	186 (88)	128 (86)
III	26 (12)	18 (12)	26 (12)	20 (14)
Creatinine Clearance at Baseline				
<30 ml/min	3 (1)	2 (1)	2 (<1)	3 (2)
30-50 ml/min	30 (14)	21 (14)	16 (8)	16 (11)
>50 ml/min	180 (85)	125 (84)	194 (92)	129 (87)
Missing	0	1	0	0
Type of Myeloma				
IgG	114 (54)	81 (54)	122 (58)	74 (50)
IgA	26 (12)	22 (15)	39 (18)	36 (24)
Other	18 (8)	14 (9)	15 (7)	6 (4)
Missing	55	32	36	32
Light chain multiple myeloma				
Free Kappa Light Chains (no Heavy Chain) n (%)	28 (13)	22 (15)	16 (8)	18 (12)
Free Lambda Light Chains (no Heavy Chain) n (%)	27 (13)	9 (6)	19 (9)	14 (9)
Evidence of lytic bone disease n (%)				
Present	143 (67)	106 (71)	143 (67)	111 (75)
Absent	61 (29)	34 (23)	59 (28)	34 (23)
Unknown	9 (4)	9 (6)	10 (5)	3 (2)
Prior ASCT n	118	81	126	86
Measurable Disease				
SPEP only	102 (48)	69 (46)	108 (51)	76 (51)

	LenDex N=362		Ixazomib + LenDex N=360	
	1 N=213 n (%)	2 or 3 N=149 n (%)	1 N=212 n (%)	2 or 3 N=148 n (%)
UPEP only	40 (19)	24 (16)	28 (13)	24 (16)
SPEP and UPEP	40 (19)	35 (23)	47 (22)	26 (18)
FLC only	31 (15)	13 (9)	25 (12)	18 (12)
Not Measurable	0	8 (5)	4 (2)	4 (3)
Median #cycles	13	12	13	13
Median Follow up (months)	15.0	14.0	15.2	14.3

*Relapsed (PD > 60 days after last dose of any previous treatment) but not refractory.
**Refractory (PD on or within 60 days after last dose of any previous treatment).
*** Relapsed from at least 1 previous treatment AND additionally refractory to at least 1 previous treatment.
****Refractory to all lines of previous therapy defined as best response to prior therapy SD or disease progression on all lines of therapy.

A8. TMM-1 (C16010) clinical study report table 12.a (Extent of Exposure – Safety population): Please replicate this table for the second interim analysis, and present the separate results for the 1 prior therapy subgroup, the 2+ prior therapies subgroup and, if possible, the 2 prior therapies subgroup.

Response:

The requested IA2 extent of exposure table for 1 prior therapy vs 2-3 prior therapies per stratification is provided below (Table 9). Please note Takeda do not have separate 2-prior therapies extent of exposure analysis currently available.

Table 9: Extent of Exposure by Prior Line by Stratification Safety Population

	LenDex N=359		Ixazomib + LenDex N=361	
	1 line n=211	2-3 lines n=148	1 line n=212	2-3 lines n=149
Number of Treated Cycles[a]				
n	211	148	212	149
Mean (std dev)	16.6 (8.60)	14.3 (9.17)	16.0 (9.39)	16.4 (9.03)
Median	17.0	14.0	16.0	18.0
Min, Max	1, 34	1, 34	1, 34	1, 34
Subjects with Number of Treated Cycles[a] n (%)				
>=1	211 (100)	148 (100)	212 (100)	149 (100)
>=2	208 (99)	140 (95)	201 (95)	144 (97)
>=3	201 (95)	132 (89)	197 (93)	140 (94)
>=4	197 (93)	126 (85)	193 (91)	136 (91)
>=5	190 (90)	119 (80)	184 (87)	128 (86)
>=6	184 (87)	113 (76)	175 (83)	122 (82)

	LenDex N=359		Ixazomib + LenDex N=361	
	1 line n=211	2-3 lines n=148	1 line n=212	2-3 lines n=149
>=7	177 (84)	106 (72)	168 (79)	115 (77)
>=8	172 (82)	103 (70)	162 (76)	113 (76)
>=9	166 (79)	99 (67)	155 (73)	111 (74)
>=10	159 (75)	94 (64)	143 (67)	107 (72)
>=11	151 (72)	91 (61)	138 (65)	104 (70)
>=12	142 (67)	85 (57)	132 (62)	101 (68)
>=13	136 (64)	79 (53)	125 (59)	97 (65)
>=14	127 (60)	75 (51)	118 (56)	92 (62)
>=15	122 (58)	70 (47)	113 (53)	89 (60)
>=16	113 (54)	66 (45)	108 (51)	82 (55)
>=17	106 (50)	61 (41)	101 (48)	82 (55)
>=18	100 (47)	56 (38)	96 (45)	78 (52)
>=19	97 (46)	52 (35)	93 (44)	72 (48)
>=20	90 (43)	46 (31)	88 (42)	66 (44)
>=21	86 (41)	42 (28)	84 (40)	59 (40)
>=22	74 (35)	37 (25)	73 (34)	50 (34)
>=23	62 (29)	34 (23)	64 (30)	45 (30)
>=24	52 (25)	29 (20)	49 (23)	35 (23)
>=25	41 (19)	27 (18)	44 (21)	30 (20)
>=26	34 (16)	21 (14)	38 (18)	27 (18)
>=27	27 (13)	19 (13)	35 (17)	21 (14)
>=28	23 (11)	15 (10)	30 (14)	19 (13)
>=29	19 (9)	12 (8)	26 (12)	11 (7)
>=30	14 (7)	8 (5)	20 (9)	7 (5)
>=31	9 (4)	4 (3)	13 (6)	4 (3)
Subjects with Number of Treated Cycles[a] n (%)				
1-6	34 (16)	42 (28)	44 (21)	34 (23)
7-12	41 (19)	27 (18)	43 (20)	18 (12)
13-18	39 (18)	27 (18)	32 (15)	25 (17)
19-24	56 (27)	25 (17)	49 (23)	42 (28)
25-30	32 (15)	23 (16)	31 (15)	26 (17)
>=31	9 (4)	4 (3)	13 (6)	4 (3)
Extent of Exposure (days)[b]				
n	211	148	212	149
Mean (std dev)	465.0 (243.99)	403.5 (263.04)	453.5 (268.46)	465.1 (259.22)
Median	470.0	382.0	456.0	520.0
Min, Max	4, 950	2, 958	1, 968	7, 944

a treated cycle is defined as a cycle in which the subject received any amount of any study drug.

b Extent of exposure is calculated as (last dose date of study drug - first dose date of study drug + 1) for the specified period.

Indirect and mixed treatment comparisons

A9. In order to improve the clarity of the NMA, please add study names and/or reference numbers to the network diagrams, specifically for the links between interventions that come from a direct comparison.

Response:

Please see updated network diagrams with reference identifiers for the 8 base case NMAs included in the submission (Figure 4, to Figure 11).

Figure 4: Network for PFS in the 1+ prior therapies population – RCT and observational studies, combined doses, and primary publications (Fig 20 in the submission)

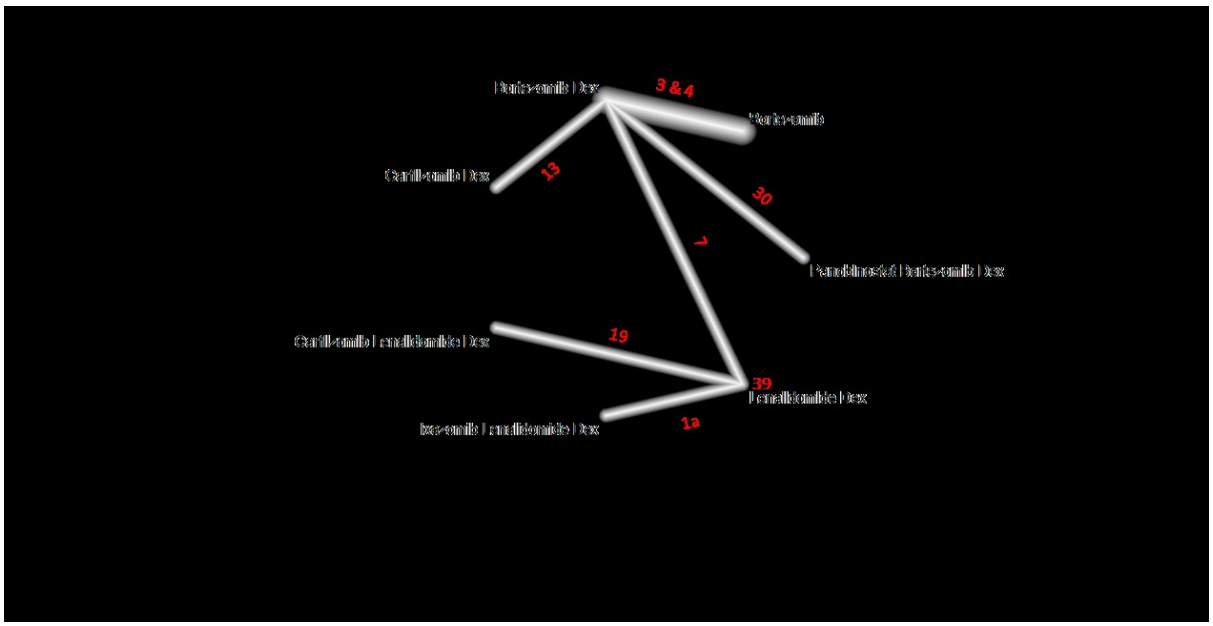


Figure 5: **Network for OS in the 1+ prior therapies population – RCT and observational studies, specific doses, and primary publications (Fig 21 in the submission)**

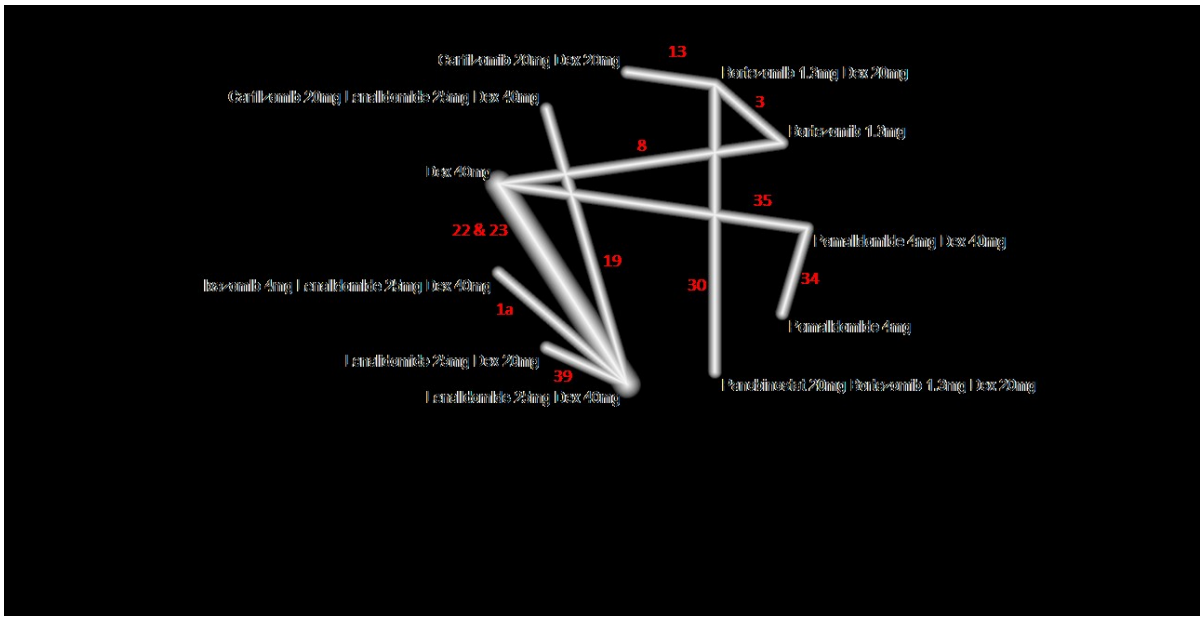


Figure 6: **Network for ORR in the 1+ prior therapies population – RCT and observational studies, specific doses, and primary publications (Fig 22 in the submission)**

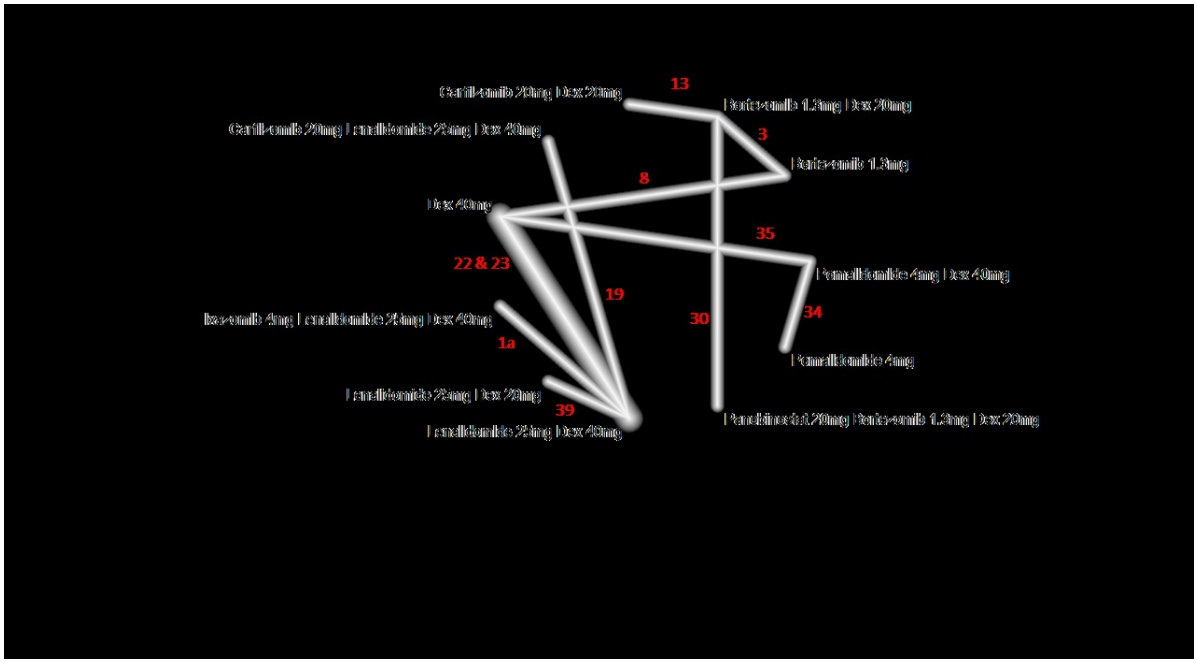


Figure 7: **Network for BoR in the 1+ prior therapies population – RCT studies, combined doses, and primary publications (Fig 26 in the submission)**

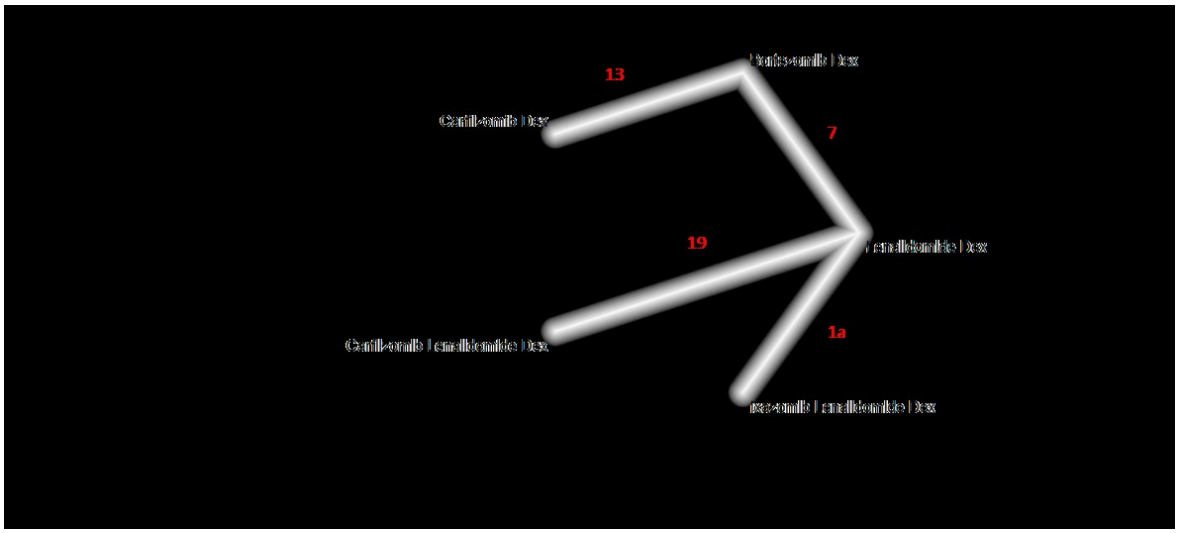


Figure 8: **Network for Treatment discontinuation due to AEs in the 1+ prior therapies population – RCT and observational studies, specific doses, and primary publications (Fig 27 in the submission)**

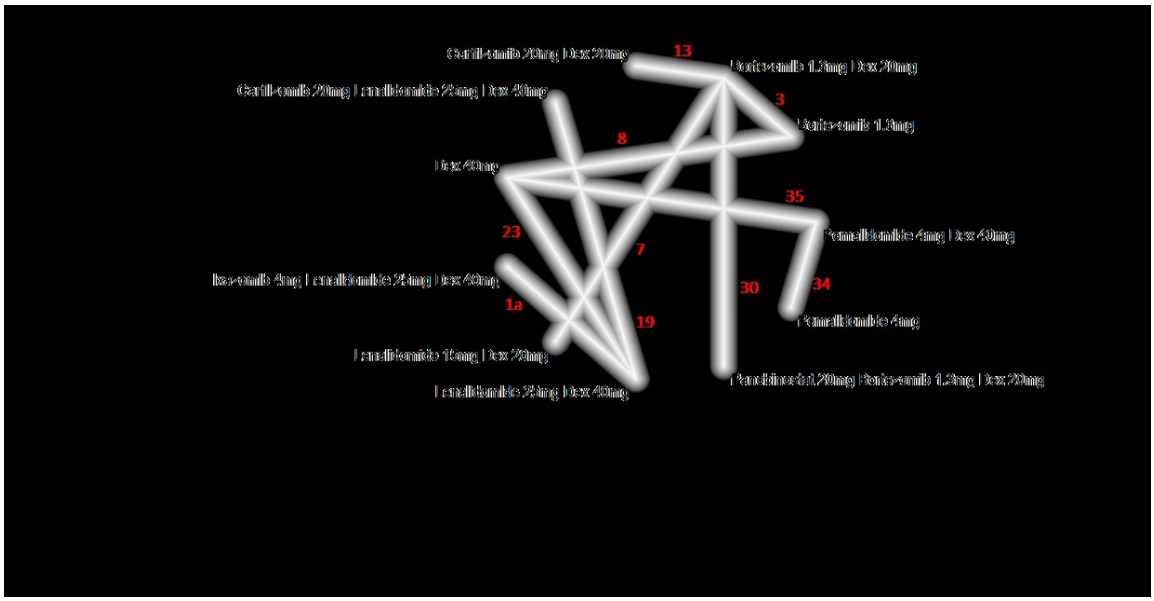


Figure 9: **Network for PFS in the 2+ prior therapies population – RCT only, dose specific, primary publications (Fig 28 in the submission)**

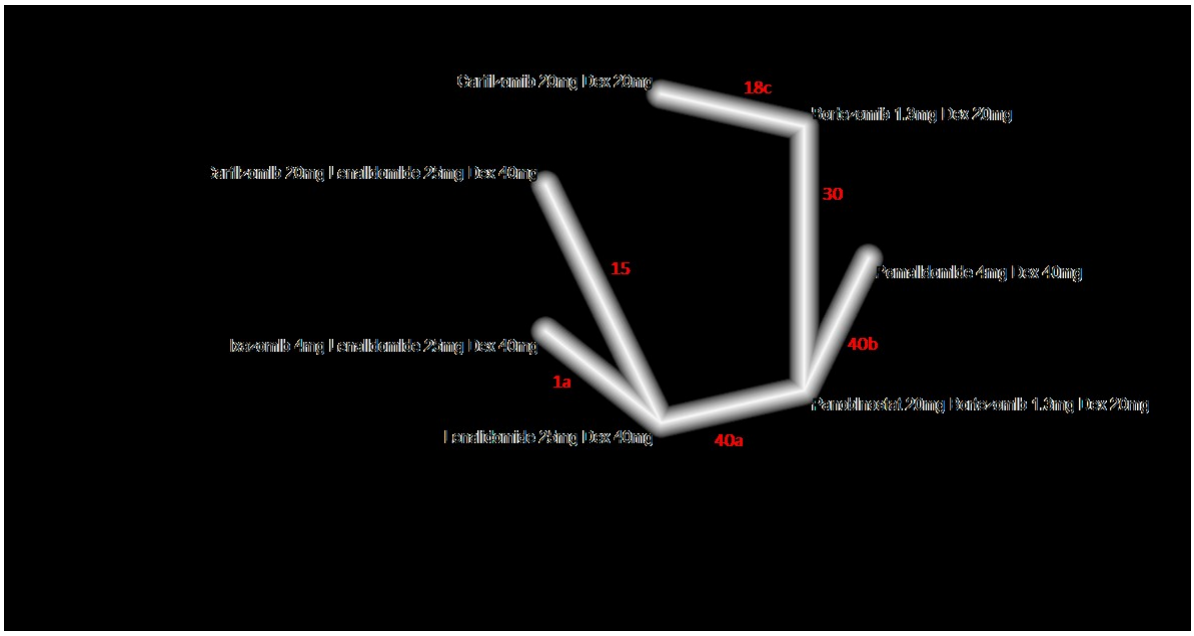


Figure 10: **Network for OS in the 2+ prior therapies population: RCT only, dose specific: primary publications (Fig 29 in the submission)**

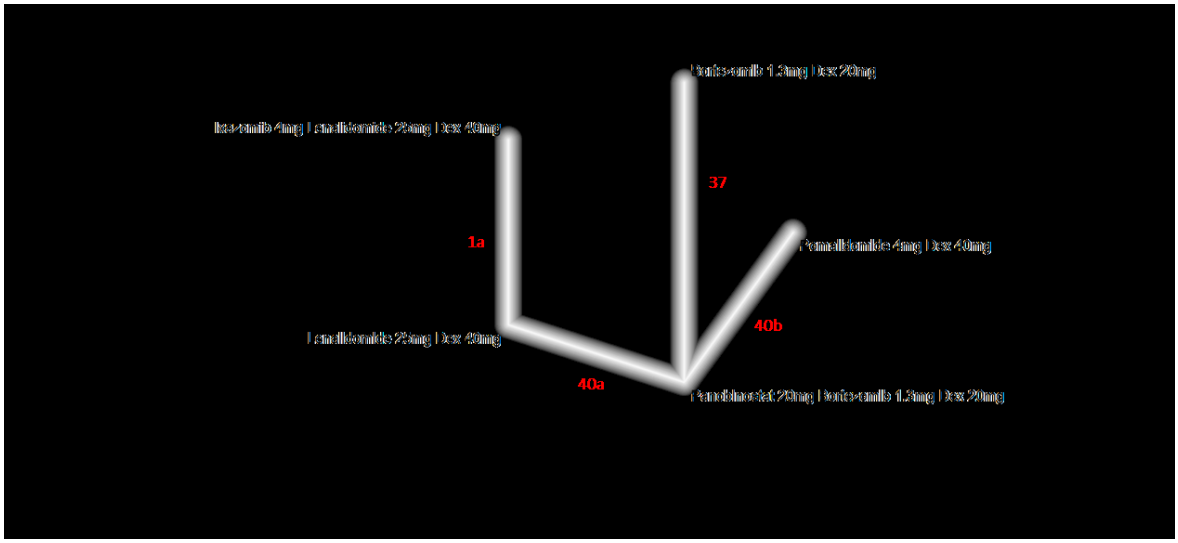
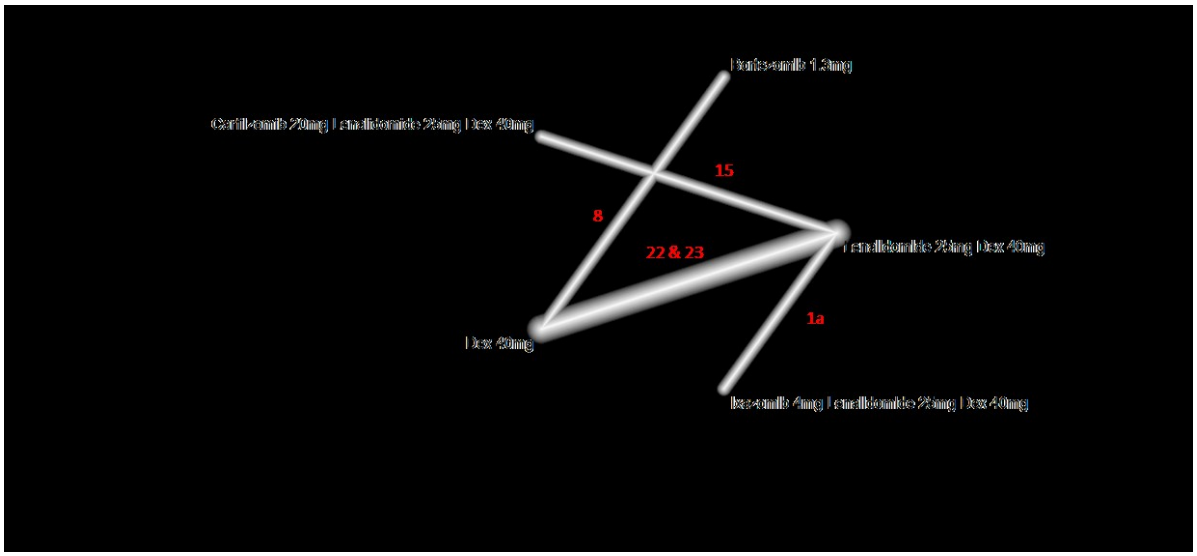


Figure 11: Network for ORR in the 2+ prior therapies population: RCT only, dose specific, and primary publications (Fig 30 in the submission)



A10. PRIORITY QUESTION: Within the NMA for PFS, we understand that the company linked BORT-DEX to LEN-DEX using the Montefusco trial. However, this trial compares BORT-DEX-CYCLOPHOSPHAMIDE to LEN-DEX-CYCLOPHOSPHAMIDE, which may give a very different relative effectiveness than a study comparing BORT-DEX with LEN-DEX.

a. Please explain the likely effects of cyclophosphamide on the relative effectiveness of BORT-DEX compared with LEN-DEX in this context.

Response:

The Montefusco trial was included in the network as without it a network could not be formed in order to compare IXA+LEN+DEX with BORT+DEX for the PFS outcome in the 1+ prior therapies population. Whilst we recognise the limitations of this trial in that it includes cyclophosphamide treatment in both the BORT+DEX and LEN+DEX arms, in order to include it to facilitate a PFS network we have assumed that the relative effectiveness of BORT+DEX vs LEN+DEX is not impacted by the addition of cyclophosphamide to each treatment arm. We cannot categorically prove this as the addition of cyclophosphamide was not a separate treatment arm in the Montefusco trial, but generally clinician feedback was that the reason for adding cyclophosphamide was to add an agent with a different mechanism of action to complement the proteasome inhibitor, IMiD or steroid and increase absolute efficacy in both treatment regimens. With no a priori reason why one of the named regimens would benefit from the addition more than the other, we have made the assumption that the addition of cyclophosphamide will increase the efficacy of both regimens by the same relative amount and therefore leave unaltered the relative efficacy comparison between them.

b. Please provide a new NMA for PFS which excludes the Montefusco trial (this trial is considered inappropriate because the treatment regimens

include cyclophosphamide). It appears that the company chose to use the Montefusco study because it reports both PFS and TTP, whereas other trials linking BORT-DEX to LEN-DEX (eg APEX, MM-009 and MM-010) report TTP only. Based on the definition of these outcomes, TTP can be considered a good proxy for PFS. In the revised NMA, use TTP as a proxy for PFS (for studies which do not report PFS). Please include the new NMA results in your model, and present the results as a sensitivity analysis.

Response:

As stated above excluding Montefusco means that a network cannot be formed to enable a PFS comparison of IXA+LEN+DEX with BORT+DEX, as this provides an essential link to LEN+DEX (with cyclophosphamide in this trial assumed to not impact relative efficacy as explained above). The ERG has asked for an analysis excluding this study but including studies that report TTP as a proxy for PFS. Whilst this represents a logical extension of the NMA to perform as a scenario analysis, on investigation by Takeda it was not felt possible to perform in time for the 2nd February deadline. This is because TTP was not included in the protocol as an outcome for the NMA, and so this would require adding it and revisiting the systematic search in order to identify relevant studies to include in the requested PFS+TTP network. This would also require data extraction, quality checking (e.g. for the definition of TTP to see if it matches sufficiently that for PFS and can be considered a proxy in each identified study) and running of the NMA.

It is uncertain if this will impact on the relative effectiveness results compared to the current NMA, and/or how robust this analysis will be. It would not be anticipated to have a large impact (as can be seen with the various scenario analyses that have been performed for PFS outcomes in the 1+ prior therapy population) and in the economic model variation in relative PFS is not the main driver of the cost-effectiveness results (compared to OS), please see the one-way sensitivity analysis presented in the original submission dossier.

A11. PRIORITY QUESTION: Please provide the following details for all NMAs:

- ***a. all inputs (annotated with primary study sources)***
- ***b. all codes in R used to perform the NMAs***
- ***c. all the outputs from the NMA analyses (indicating whether HRs were adjusted or unadjusted).***

Response:

The information relating to this question are provided in the following attached zip files:

a. Please see folder ‘A11a all inputs (annotated with primary study sources)’
b. Please see folder: ‘A11b R codes’
c. All endpoints presented in the attached files (odds ratios, hazard ratios) are from the NMAs and clearly labelled as whether in logged or unlogged form. We are unsure what the terms “unadjusted” and “adjusted” represent in the question but hope that our response provides some clarity.

A12. Please provide the rankograms for each NMA performed.

Response:

The rankograms (Figure 12, to Figure 19) and corresponding SUCRA scores (Table 10 to Table 17) corresponding to the 8 base case NMAs included in the submission are provided below. Please note that these results are provided for all therapies included in the NMA, including those treatments not relevant according to the appraisal scope and decision problem table presented in Table 1 in the submission dossier document. In the submission, the rankograms and SUCRA scores for the relevant comparators of BORT+DEX for a second line positioning (i.e. after 1 prior therapy, proxied by 1+ prior therapy data and networks), and LEN+DEX for a third line positioning (represented by 2+ prior therapy data) are presented.

Figure 12: **Rankogram for PFS in the 1+ prior therapies population – RCT and observational studies, combined doses, and primary publications (relates to analysis for Fig 20 in the submission)**

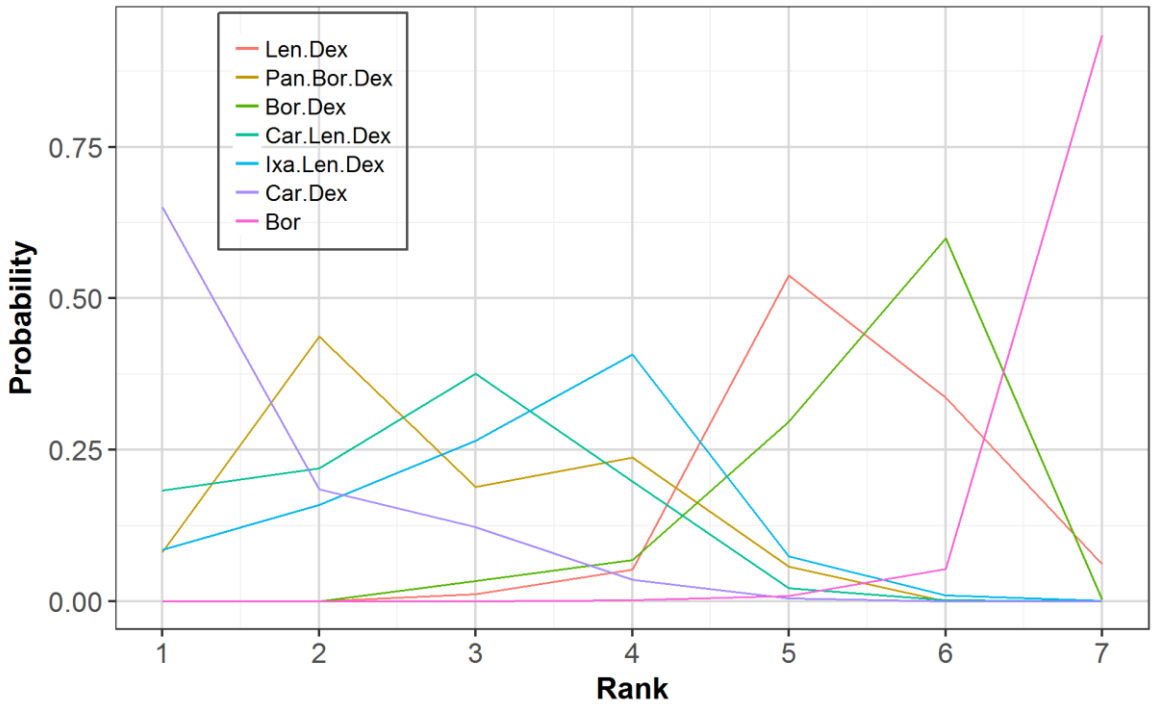


Table 10: **Surface Under the Cumulative Ranking Distribution (SUCRA): for PFS in the 1+ prior therapies population – RCT and observational studies, combined doses, and primary publications**

	SUCRA
Lenalidomide Dex	0.270
Panobinostat Bortezomib Dex	0.708
Bortezomib Dex	0.255
Carfilzomib Lenalidomide Dex	0.723
Ixazomib Lenalidomide Dex	0.624
Carfilzomib Dex	0.907
Bortezomib	0.013

Figure 13: **Rankogram for OS in the 1+ prior therapies population – RCT and observational studies, specific doses, and primary publications (relates to analysis for Fig 21 in the submission)**

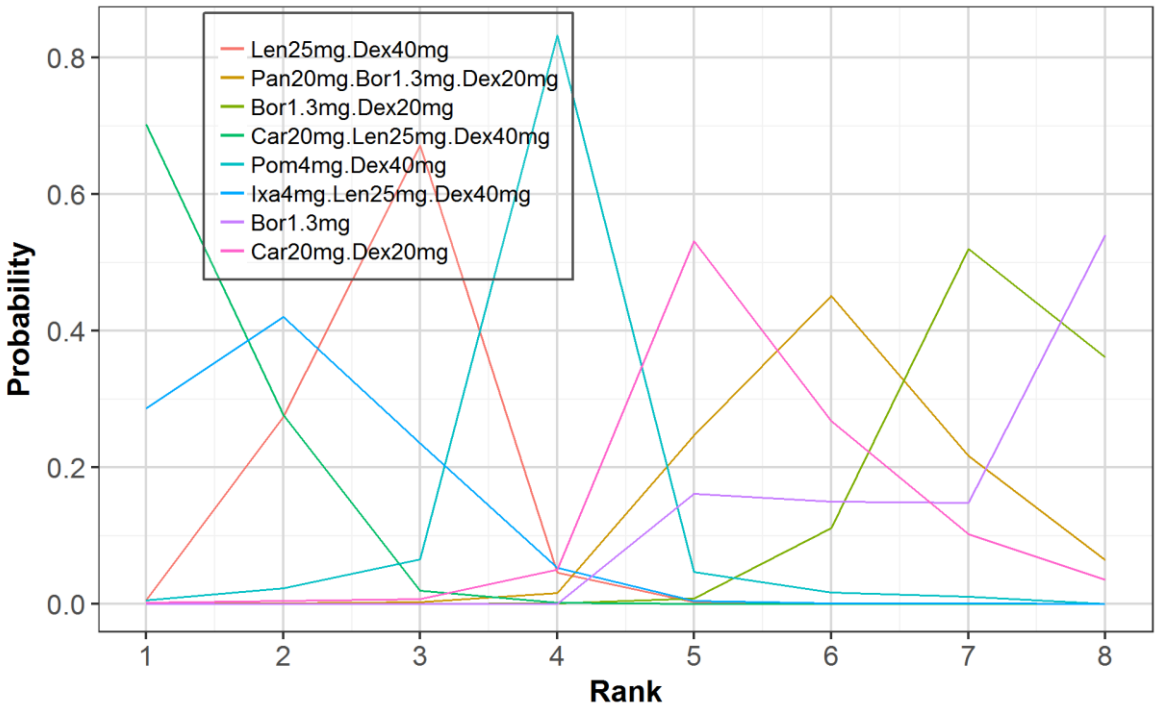


Table 11: **Surface Under the Cumulative Ranking Distribution (SUCRA): OS in the 1+ prior therapies population – RCT and observational studies, specific doses, and primary publications**

	SUCRA
Lenalidomide 25mg Dex 40mg	0.747
Panobinostat 20mg Bortezomib 1.3mg Dex 20mg	0.279
Bortezomib 1.3mg Dex 20mg	0.110
Carfilzomib 20mg Lenalidomide 25mg Dex 40mg	0.954
Pomalidomide 4mg Dex 40mg	0.573
Ixazomib 4mg Lenalidomide 25mg Dex 40mg	0.846
Bortezomib 1.3mg	0.133
Carfilzomib 20mg Dex 20mg	0.358

Figure 14: **Rankogram for ORR in the 1+ prior therapies population – RCT and observational studies, specific doses, and primary publications (relates to analysis for Fig 22 in the submission)**

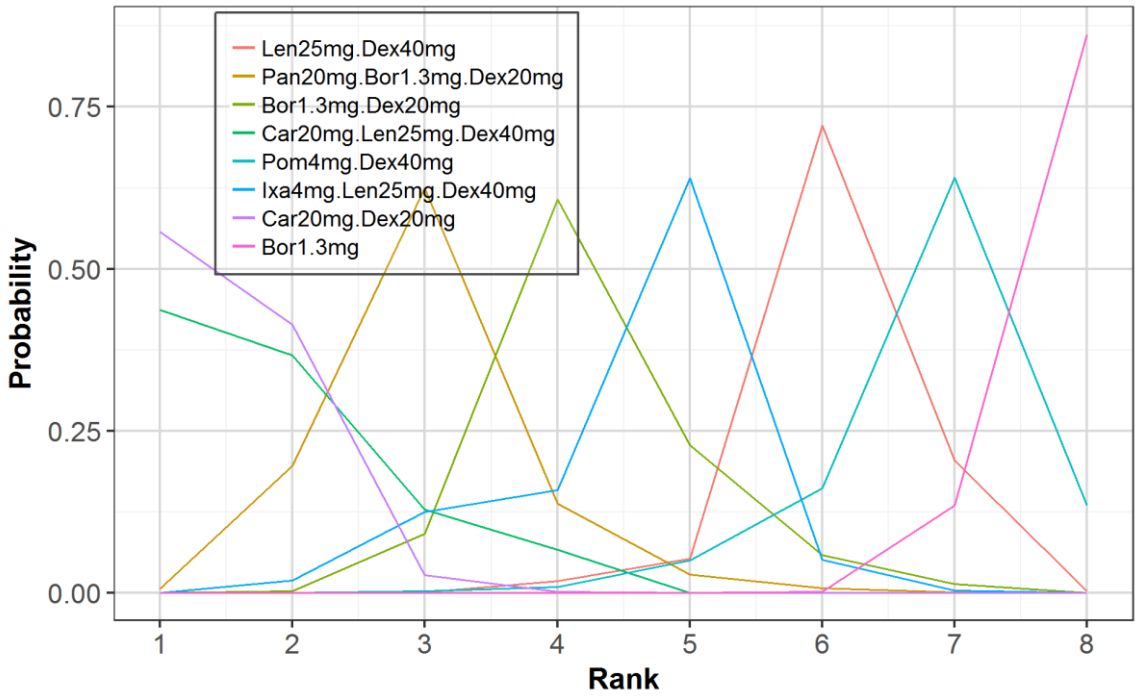


Table 12: **Surface Under the Cumulative Ranking Distribution (SUCRA): Overall Response Rate: 1+ Prior Therapies: RCT and Observational Studies: Dose Specific: Primary Publications Data**

	SUCRA
Lenalidomide 25mg Dex 40mg	0.269
Panobinostat 20mg Bortezomib 1.3mg Dex 20mg	0.713
Bortezomib 1.3mg Dex 20mg	0.530
Carfilzomib 20mg Lenalidomide 25mg Dex 40mg	0.882
Pomalidomide 4mg Dex 40mg	0.167
Ixazomib 4mg Lenalidomide 25mg Dex 40mg	0.487
Carfilzomib 20mg Dex 20mg	0.932
Bortezomib 1.3mg	0.020

Figure 15: **Rankogram for BoR in the 1+ prior therapies population – RCT studies, combined doses, and primary publications (relates to analysis for Fig 26 in the submission)**

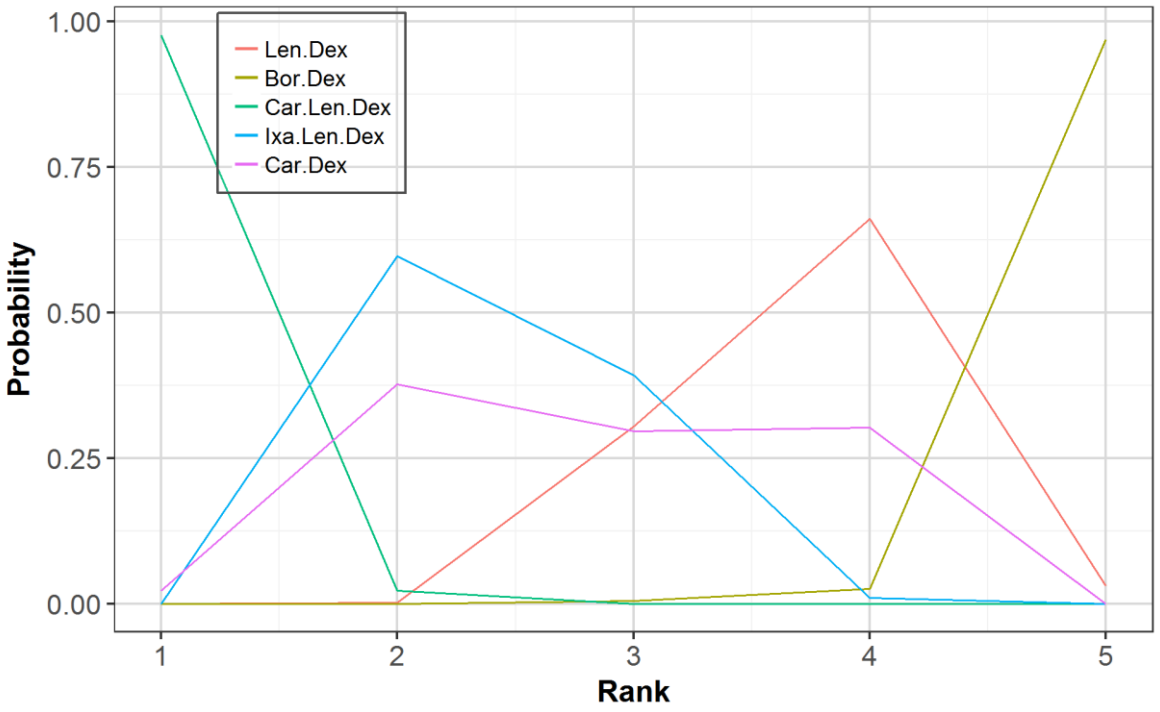


Table 13: **Surface Under the Cumulative Ranking Distribution (SUCRA): BoR in the 1+ prior therapies population – RCT studies, combined doses, and primary publications**

	SUCRA
Lenalidomide Dex	0.320
Bortezomib Dex	0.009
Carfilzomib Lenalidomide Dex	0.994
Ixazomib Lenalidomide Dex	0.647
Carfilzomib Dex	0.530

Figure 16: **Rankogram for Treatment discontinuation due to AEs in the 1+ prior therapies population – RCT and observational studies, specific doses, and primary publications (relates to analysis for Fig 27 in the submission)**

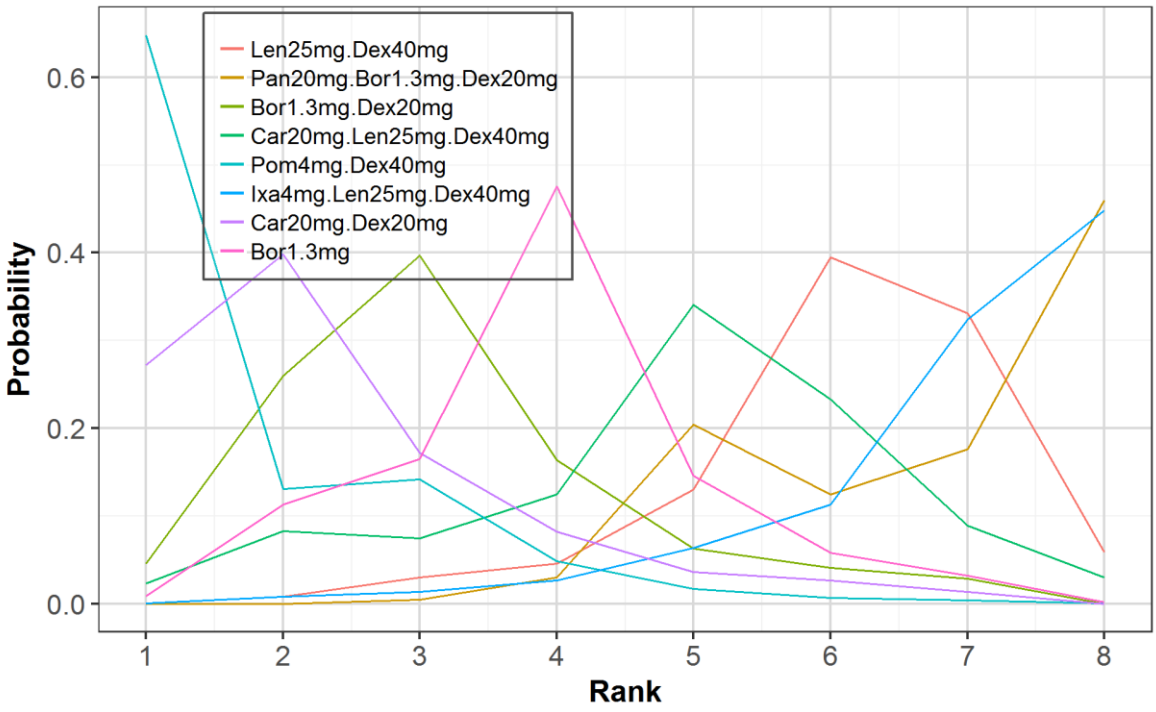


Table 14: **Surface Under the Cumulative Ranking Distribution (SUCRA): Treatment discontinuation due to AEs in the 1+ prior therapies population – RCT and observational studies, specific doses, and primary publications**

	SUCRA
Lenalidomide 25mg Dex 40mg	0.271
Panobinostat 20mg Bortezomib 1.3mg Dex 20mg	0.169
Bortezomib 1.3mg Dex 20mg	0.689
Carfilzomib 20mg Lenalidomide 25mg Dex 40mg	0.445
Pomalidomide 4mg Dex 40mg	0.900
Ixazomib 4mg Lenalidomide 25mg Dex 40mg	0.140
Carfilzomib 20mg Dex 20mg	0.807
Bortezomib 1.3mg	0.579

Figure 17: **Rankogram for PFS in the 2+ prior therapies population – RCT only, dose specific, primary publications (relates to analysis for Fig 28 in the submission)**

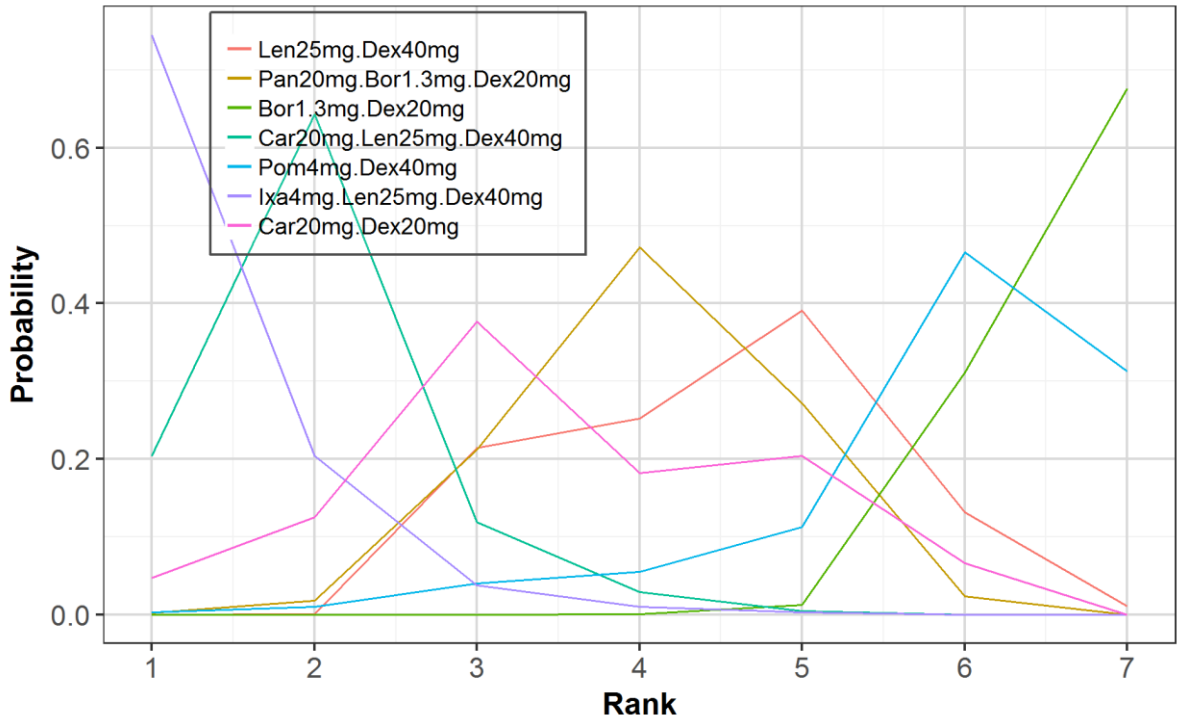


Table 15: **Surface Under the Cumulative Ranking Distribution (SUCRA): PFS in the 2+ prior therapies population – RCT only, dose specific, primary publications**

	SUCRA
Lenalidomide 25mg Dex 40mg	0.421
Panobinostat 20mg Bortezomib 1.3mg Dex 20mg	0.489
Bortezomib 1.3mg Dex 20mg	0.056
Carfilzomib 20mg Lenalidomide 25mg Dex 40mg	0.835
Pomalidomide 4mg Dex 40mg	0.180
Ixazomib 4mg Lenalidomide 25mg Dex 40mg	0.946
Carfilzomib 20mg Dex 20mg	0.572

Figure 18: **Rankogram for OS in the 2+ prior therapies population: RCT only, dose specific: primary publications (relates to analysis for Fig 29 in the submission)**

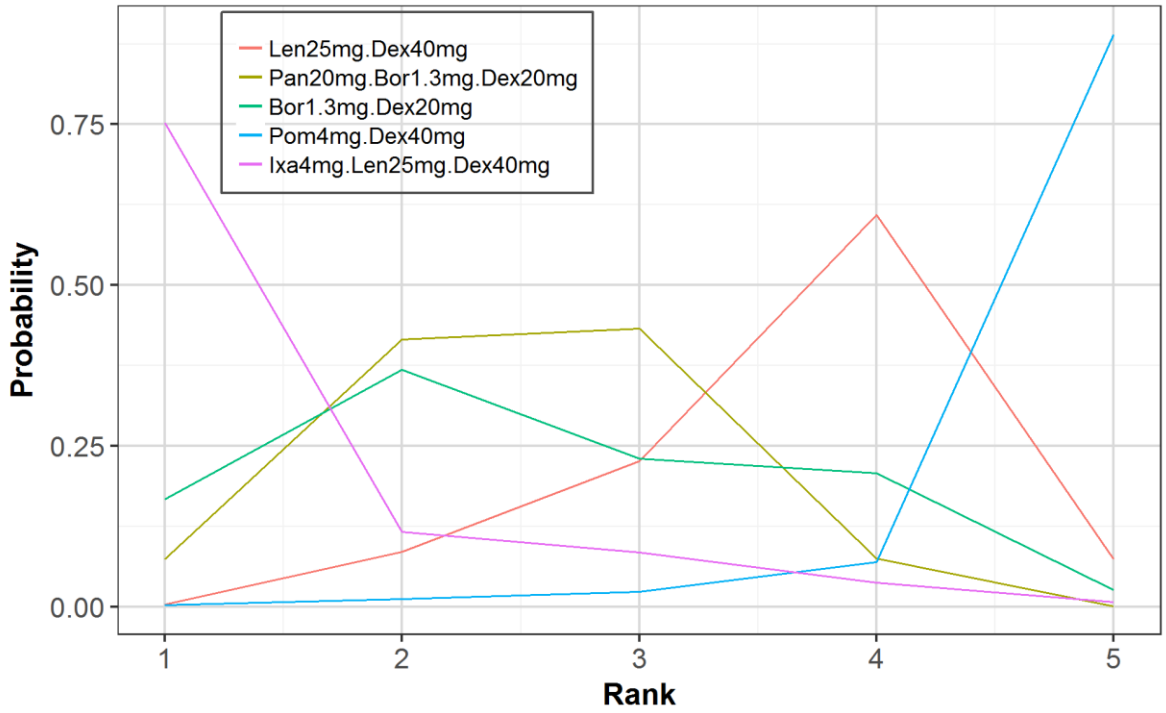


Table 16: **Surface Under the Cumulative Ranking Distribution (SUCRA): OS in the 2+ prior therapies population: RCT only, dose specific: primary publications**

	SUCRA
Lenalidomide 25mg Dex 40mg	0.334
Panobinostat 20mg Bortezomib 1.3mg Dex 20mg	0.622
Bortezomib 1.3mg Dex 20mg	0.610
Pomalidomide 4mg Dex 40mg	0.042
Ixazomib 4mg Lenalidomide 25mg Dex 40mg	0.892

Figure 19: **Rankogram for ORR in the 2+ prior therapies population: RCT only, dose specific, and primary publications (relates to analysis for Fig 30 in the submission)**

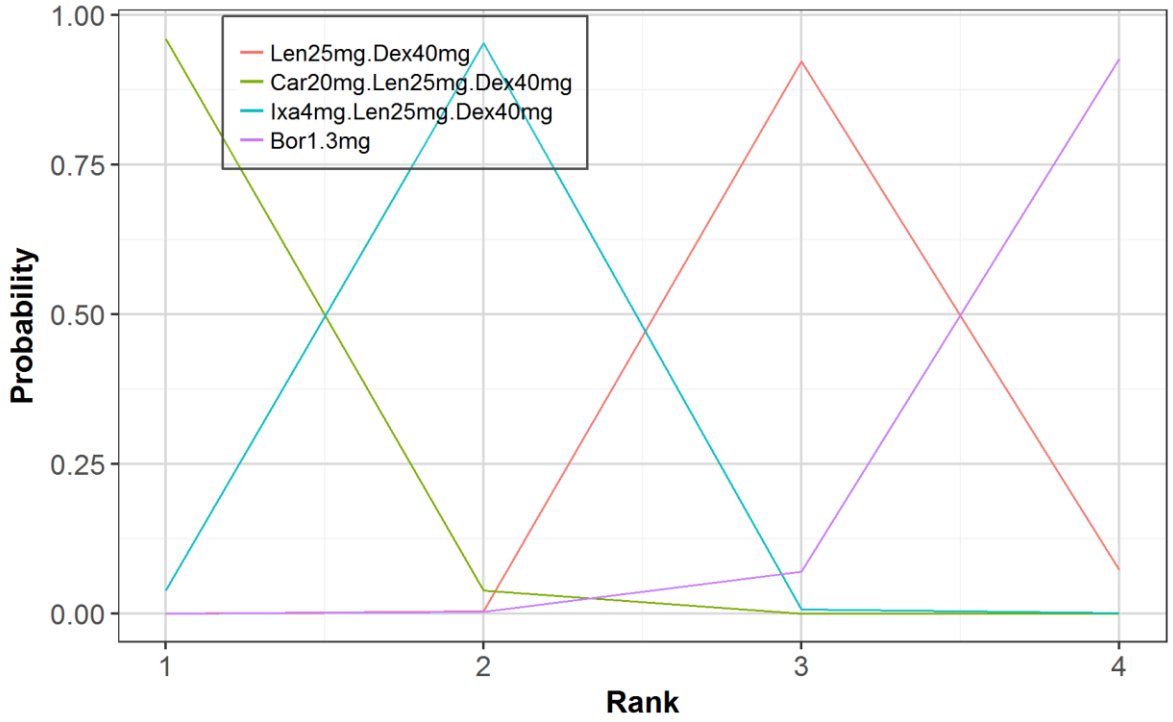


Table 17: **Surface Under the Cumulative Ranking Distribution (SUCRA): ORR in the 2+ prior therapies population: RCT only, dose specific, and primary publications**

	SUCRA
Lenalidomide 25mg Dex 40mg	0.310
Carfilzomib 20mg Lenalidomide 25mg Dex 40mg	0.987
Ixazomib 4mg Lenalidomide 25mg Dex 40mg	0.677
Bortezomib 1.3mg	0.026

A13. In section 5.3.3.3 (table 65), the company presents the hazard ratios for OS and PFS for BORT-DEX compared with LEN-DEX, stating that these results are from an NMA. The results of this NMA were not reported in the relevant section of the clinical effectiveness in the company submission. Please provide the full results of the NMA on OS, PFS, ORR, BOR and discontinuation due to AEs, including all the drugs considered in the network.

Response:

The full methodology and network plots for each of the relevant outcomes (OS, PFS, ORR and BoR) and for each population of interest are presented in Section 4.10 of the original submission dossier. These are presented for all comparators included in the NMAs.

The results of the NMAs are provided for LEN+DEX and BORT+DEX relative to IXA+LEN+DEX, as IXA+LEN+DEX is the reference treatment in this submission. However, the model utilises relative efficacy estimates for BORT+DEX compared with LEN+DEX to enable a comparison of BORT+DEX and IXA+LEN+DEX in the 1 prior line population. Therefore, we have updated the results in Section 4.10.6 of the original submission to include results associated with BORT+DEX vs. LEN+DEX.

Please note, results are only provided for the therapies included in the NMA that are relevant to the appraisal scope and the decision problem table presented in the submission dossier (Table 1). The NMA included comparators which may be relevant to other UK HTA bodies at 2nd line, 3rd line or later; in line with the decision problem table these were not considered relevant for inclusion in the NICE submission dossier. Please refer to the response to A12 for associated rankograms.

Insufficient evidence was available to create a network for PFS, OS, ORR and BoR in the 1 prior line population. Therefore, estimates of treatment effect for BORT+DEX relative to LEN+DEX using data from a 1+ prior lines population were assumed as a proxy for the 1 prior line population. The results for BORT+DEX relative to LEN+DEX from the NMAs are presented in Table 18, Table 19 and Table 20 for PFS, OS and ORR outcomes, respectively.

Progression free survival

Figure 20 in the original submission provides the network for the NMA considering PFS in a 1+ prior lines population, when all RCTs, observational data, all doses and primary publications are considered. This is presented for all comparators included in the NMA. The results for the comparisons used within the model are presented in Table 18.

Table 18: Hazard ratios from the NMA for PFS comparisons in the 1+ prior therapies population, an update to Table 44 in the original submission dossier

PFS NMA – 1+ prior therapies population	Definition	IXA+LEN+DEX vs. LEN+DEX Hazard Ratio (95% CrI)	IXA+LEN+DEX vs. BORT+DEX Hazard Ratio (95% CrI)	BORT+DEX vs. LEN+DEX Hazard Ratio (95% CrI)
Base case PFS network	RCT and observational studies, combined doses, and primary publications (+ 10% pseudo drop out). *	0.74 (0.59, 0.94)	0.72 (0.41, 1.19)	1.06 (0.61, 1.85)
Scenario analysis 1:	**RCT studies only**, combined doses, and primary publications	0.74 (0.58, 0.94)	0.72 (0.41, 1.18)	1.06 (0.60, 1.84)

PFS NMA – 1+ prior therapies population	Definition	IXA+LEN+DEX vs. LEN+DEX Hazard Ratio (95% CrI)	IXA+LEN+DEX vs. BORT+DEX Hazard Ratio (95% CrI)	BORT+DEX vs. LEN+DEX Hazard Ratio (95% CrI)
Scenario analysis 2:	RCT and observational studies, combined doses and **secondary publications**	0.82 (0.67, 1.01)	0.80 (0.46, 1.29)	1.06 (0.61, 1.85)
Scenario analysis 3:	RCT and observational studies, combined doses and secondary publications **+ Hou et al. (2016)**	0.78 (0.65, 0.94)	0.76 (0.44, 1.22)	1.06 (0.61, 1.85)
Scenario analysis 4:	RCT and observational studies, combined doses, and primary publications **(+ 60% pseudo drop out).**	0.74 (0.59, 0.94)	0.74 (0.38, 1.29)	1.05 (0.51, 2.15)
Key: BORT, bortezomib; CrI, credible interval; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; OS, overall survival; N/A, not available; RCT, randomised controlled trial				

Overall survival

Figure 21 in the original submission provides the network for the NMA considering OS in a 1+ prior lines population, when all RCTs, observational data, doses specific to marketing authorisations and primary publications are considered. This is presented for all comparators included in the NMA. The results for the comparisons used within the model are presented in Table 19.

Table 19: Hazard rates from the NMA for OS comparisons in the 1+ prior therapies population, an update to Table 45 in the original submission dossier

OS NMA – 1+ prior therapies population	Definition	IXA+LEN+DEX vs. LEN+DEX Hazard Ratio (95% CrI)	IXA+LEN+DEX vs. BORT+DEX Hazard Ratio (95% CrI)	BORT+DEX vs. LEN+DEX Hazard Ratio (95% CrI)
Base case OS network	RCT and observational studies, specific doses, and primary publications	0.90 (0.61, 1.31)	0.31 (0.13, 0.65)	3.11 (1.52, 6.35)

OS NMA – 1+ prior therapies population	Definition	IXA+LEN+DEX vs. LEN+DEX Hazard Ratio (95% CrI)	IXA+LEN+DEX vs. BORT+DEX Hazard Ratio (95% CrI)	BORT+DEX vs. LEN+DEX Hazard Ratio (95% CrI)
Scenario analysis 1:	**RCT studies only**, specific doses, and primary publications	0.90 (0.61, 1.31)	N/A	N/A
Scenario analysis 2:	RCT and observational studies, **combined doses** and primary publications	0.89 (0.61, 1.31)	0.31 (0.15, 0.57)	3.05 (1.78, 5.22)
Scenario analysis 3:	RCT and observational studies, specific doses and **secondary publications**	0.87 (0.64, 1.18)	0.41 (0.18, 0.79)	2.30 (1.17, 4.51)
Key: BORT, bortezomib; CrI, credible interval; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; OS, overall survival; N/A, not available; RCT, randomised controlled trial				

Overall response rate

Figure 22 in the original submission provides the network for the NMA considering ORR in a 1+ prior lines population, when all RCTs, observational data, doses specific to marketing authorisations and primary publications are considered. This is presented for all comparators included in the NMA. The results for the comparisons used within the model are presented in Table 20.

Table 20: Odds ratios from the NMA for ORR comparisons in the 1+ prior therapies population, an update to Table 46 in the original submission dossier

ORR NMA – 1+ prior therapies population	Definition	IXA+LEN+DEX vs. LEN+DEX Odds Ratio (95% CrI)	IXA+LEN+DEX vs. BORT+DEX Odds Ratio (95% CrI)	BORT+DEX vs. LEN+DEX Odds Ratio (95% CrI)
Base case ORR network	RCT and observational studies, specific doses, and primary publications	1.44 (1.03, 2.03)	0.88 (0.35, 1.85)	2.28 (1.06, 4.93)
Scenario analysis 1:	**RCT studies only**, specific doses, and primary publications	1.44 (1.03, 2.03)	N/A	N/A

ORR NMA – 1+ prior therapies population	Definition	IXA+LEN+DEX vs. LEN+DEX Odds Ratio (95% CrI)	IXA+LEN+DEX vs. BORT+DEX Odds Ratio (95% CrI)	BORT+DEX vs. LEN+DEX Odds Ratio (95% CrI)
Key: BORT, bortezomib; CrI, credible interval; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; N/A, not available; NMA, network meta-analysis; ORR, overall response rate				

A14. In section 4.10.6.2, the company indicated there were insufficient studies and data in the one prior therapy population to develop a network between IXA-LEN-DEX and BORT-DEX. However, no summary tables of results of primary studies for this were included. Please provide tables with these results.

Response:

Below are the network diagrams for all results in the one prior therapy setting. These are PFS one only prior therapy all studies (all RCT also) Primary Dose Specific and ORR one only prior all studies (all RCTs) Primary Dose Specific. There were no results within the OS and BoR settings for one prior therapy..

For the one only prior therapy group, there were no results recorded for a BORT+DEX arm in any study for the efficacy endpoints: OS and BOR. For the efficacy endpoints PFS and ORR, there were such studies but could connect to IXA+LEN+DEX in the network.

Tables are presented below for what information has been gathered under each efficacy endpoint for this one only prior therapy group (based on the Excel input files supplied in part response to request A11).

The network plots presented for PFS and ORR show which studies/treatments did connect to IXA+LEN+DEX in the NMA network.

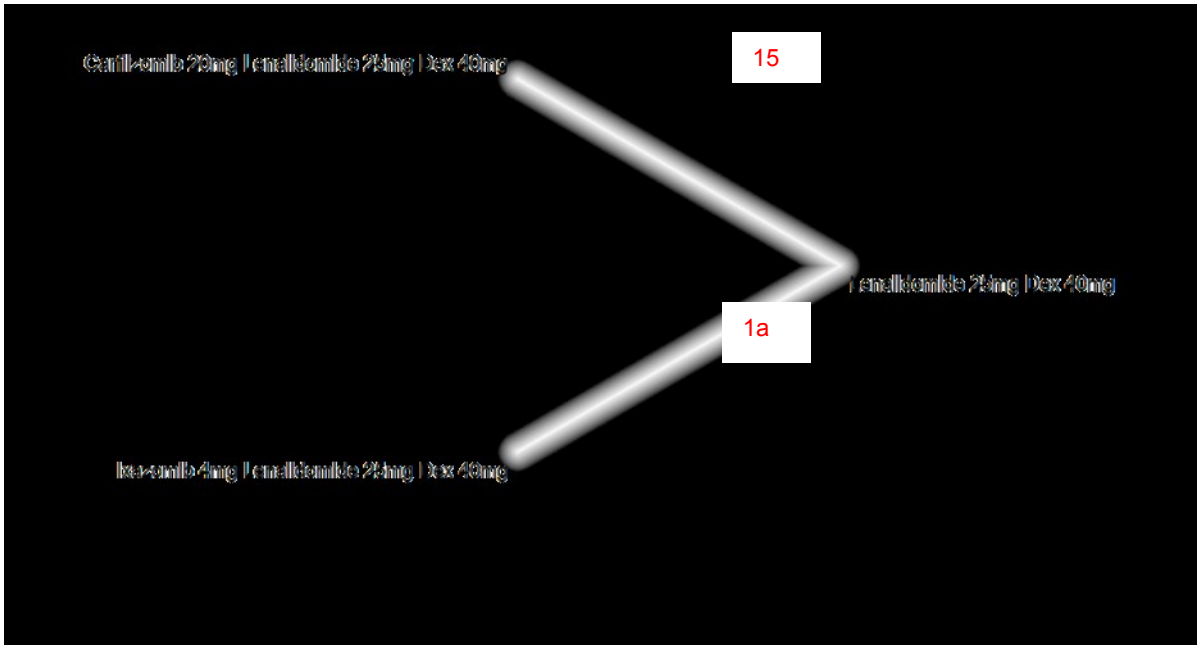
Progression Free Survival

Table 21: Studies with Data

Reference ID number	Treatment 1 (=Control)	Treatment 2	Study type (RCT or Observational)	Log (Hazard Ratio)	Std Error (Log Hazard Ratio)
1a	Lenalidomide 25mg Dex 40mg	Ixazomib 4mg Lenalidomide 25mg Dex 40mg	RCT	-0.13	0.16
1b	Lenalidomide 25mg Dex 40mg	Ixazomib 4mg Lenalidomide 25mg Dex 40mg	RCT	-0.01	0.13

15	Lenalidomide 25mg Dex 40mg	Carfilzomib 20mg Lenalidomide 25mg Dex 40mg	RCT	-0.37	0.14
18c	Bortezomib 1.3mg Dex 20mg	Carfilzomib 20mg Dex 20mg	RCT	-0.80	0.16
30	Bortezomib 1.3mg Dex 20mg	Panobinostat 20mg Bortezomib 1.3mg Dex 20mg	RCT	-0.42	0.14

Figure 20: PFS Connecting Treatments/Studies to IXA+LEN+DEX: Network Plot



Overall Response Rate

Table 22: Studies with Data

Reference ID number	Treatment 1	Treatment 2	Study type (RCT or Observational)	Base Treat 1	N event (%) Treat 1	Base Treat 2	N event (%) Treat 2

1a	Lenalidomide 25mg Dex 40mg	Ixazomib 4mg Lenalidomide 25mg Dex 40mg	RCT	213	159 (75%)	212	163 (77%)
1b	Lenalidomide 25mg Dex 40mg	Ixazomib 4mg Lenalidomide 25mg Dex 40mg	RCT	213	166 (78%)	212	164 (77%)
8	Bortezomib 1.3mg	Dex 40mg	RCT	132	59 (45%)	119	31 (26%)
15	Lenalidomide 25mg Dex 40mg	Carfilzomib 20mg Lenalidomide 25mg Dex 40mg	RCT	157	110 (70%)	184	160 (87%)
18c	Bortezomib 1.3mg Dex 20mg	Carfilzomib 20mg Dex 20mg	RCT	232	152 (66%)	232	190 (82%)
22	Dex 40mg	Lenalidomide 25mg Dex 40mg	RCT	57	17 (30%)	56	37 (66%)
23	Dex 40mg	Lenalidomide 25mg Dex 40mg	RCT	67	15 (22%)	68	44 (65%)

Figure 21: ORR Connecting Treatments/Studies to IXA+LEN+DEX: Network Plot

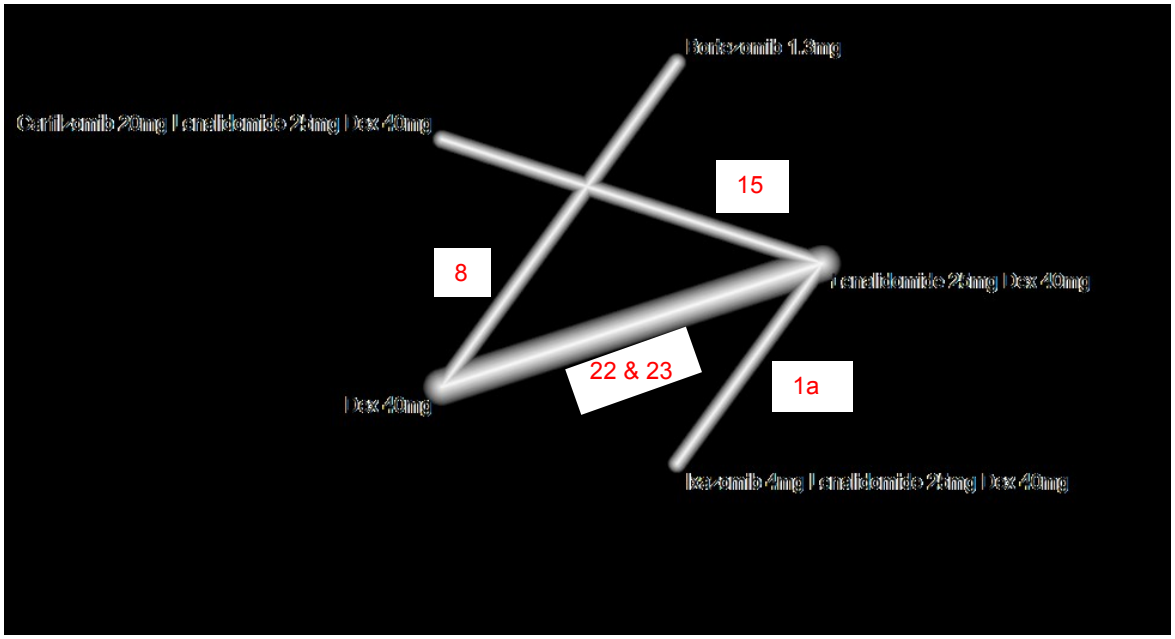


Table 23: Overall Survival - Studies with Data

Reference ID number	Treatment 1 (=Control)	Treatment 2	Study type (RCT or Observational)	Hazard Ratio	p value
1a	**Lenalidomide 25mg Dex 40mg**	**Ixazomib 4mg Lenalidomide 25mg Dex 40mg**	RCT	-0.13	0.41
1b	**Lenalidomide 25mg Dex 40mg**	**Ixazomib 4mg Lenalidomide 25mg Dex 40mg**	RCT	-0.01	0.62
8	**Bortezomib 1.3mg**	**Dex 40mg**	RCT	-0.37	0.01

Table 24: Best Overall Response - Studies with Data

Reference ID number	Treatment 1	Treatment 2	Study type (RCT or Observational)	Base Treat 1	N event (%) Treat 1	Base Treat2	N event (%) Treat 2
1a	Lenalidomide 25mg Dex 40mg	Ixazomib 4mg Lenalidomide 25mg Dex 40mg	RCT	213	93 (44%)	212 (45%)	95
1b	Lenalidomide 25mg Dex 40mg	Ixazomib 4mg Lenalidomide 25mg Dex 40mg	RCT	213	105 (49%)	212 (50%)	105

Section B: Clarification on cost-effectiveness data

B1. ***Table 62 presents IMS multiple myeloma therapy tracker market share data, by line of treatment. Please provide information on the methods used to generate these data. Were these estimates collected only within the NHS or do they include private care?***

Response:

The data presented in Table 62 in the original submission dossier was collected by IMS Quintiles for their syndicated Multiple Myeloma therapy tracker. The data is collected through a 35-minute web-based survey with Haematologists and Haem-Oncologists treating MM (see study design diagram below). The study is conducted periodically with the information found in Table 62 representing results from the October/November 2016 wave of research. This data cut included responses from 37 specialists across England, Northern Ireland, Wales and Scotland, representing 347 MM patient records across all lines of therapy.

All surveyed physicians practice in the NHS and therefore their patient records reflect NHS practice. A small proportion of the surveyed physicians may also have a secondary private practice, however as this affected a small proportion of those surveyed, the data on private patients and their time split between private and public practice is not collected.

Figure 22: Study Design

Study design

- **Haematologists and haem-oncologists treating Multiple Myeloma**
- **35-minute web survey**
- **Respondents screened based on number of years in practice and Multiple Myeloma patient workload**
- **Information provided on the last 8 patients treated during the month prior to the survey. Additional patient records relating to individuals being treated at 3rd line and 4th + line were collected in the Oct/Nov 2016 wave.**

B2. ***Please split the market share data in table 62 into monotherapies, doublets and triplets; i.e. some of the BORT data will be restricted to BORT monotherapy, some of the LEN data will be for other regimens, but a proportion of both will make up the BORT+LEN doublet.***

Response:

Upon consultation with IMS on splitting the Multiple Myeloma Therapy Tracker market shares by line into monotherapies, doublets and triplets, Takeda was informed that due to the relatively small number of physicians surveyed (n=37), conducting the further sub-group analysis required is not possible as it would introduce significant uncertainties.

However, IMS did provide the hierarchy used to assign a mutually exclusive treatment regimen for each patient, which we have included below for your reference. This information is tabulated in Table 25.

Table 25: Hierarchy for categorisation of mutually exclusive treatment regimens in the IMS Multiple Myeloma Therapy Tracker market data

Regimen	Description
Bortezomib regimen	All regimens containing bortezomib
Lenalidomide regimen	All regimens containing lenalidomide but not bortezomib

Pomalidomide regimen	All regimens containing pomalidomide but not bortezomib or lenalidomide
Thalidomide regimen	All regimens containing thalidomide but not bortezomib, lenalidomide or pomalidomide
Other regimen	All regimens not falling into any of the categories above

Survival analysis

B3. ***PRIORITY QUESTION. For the IXA-LEN-DEX arm of the model, Kaplan-Meier hazards observed from the TMM-1 clinical trial were applied for 5 months followed by the hazard of the fitted delayed exponential for IXA-LEN-DEX.***

a. Please explain why a different approach was taken in the BORT-DEX arm of the model; it appears that the (hazard ratio conditioned) delayed exponential LEN-DEX hazard was applied throughout.

Response:

This method should have been applied to both the reference treatment (IXA+LEN+DEX) and comparator treatment arm (BORT+DEX) when considering the 1 prior line population. We have addressed this issue in the model and note the impact on the results in Table 26 and Table 18 without a PAS and with the PAS applied, respectively. This amendment increases the ICER for IXA+LEN+DEX compared with BORT+DEX from £69,565 to £73,333 (with a PAS applied). Please note this amendment only impacts the results in the 1 prior line population.

Table 26: Base case results for 1 prior therapy sub-population including amendment for B3 - without PAS

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental cost/QALY (ICER)
IXA+LEN+DEX	[redacted]	3.93			
BORT+DEX	£40,612	1.74	[redacted]	2.19	[redacted]
Key: BORT, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; PAS, patient access scheme; QALY, quality adjusted life year					

Table 27: Base case results for 1 prior therapy sub-population including amendment for B3 - with PAS

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental cost/QALY (ICER)
IXA+LEN+DEX	£201,274	3.93			
BORT+DEX	£40,612	1.74	£160,662	2.19	£73,333
Key: BORT, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; PAS, patient access scheme; QALY, quality adjusted life year					

b. Please explore the impact on the ICER if, in the BORT-DEX arm, the (hazard ratio conditioned) LEN-DEX Kaplan-Meier hazards are applied for 5 months followed by the (hazard ratio conditioned) delayed exponential LEN-DEX hazard?

Response:

Please see response to B3a above, which addresses this question

c. ***Page 177 of the submission (section 5.3.3.3) states that "a hazard ratio was estimated for IXA+LEN+DEX compared with LEN+DEX [HR: 0.89, 95% CI: 0.5 – 1.60] and applied to the fitted exponential from 5 months." The model contains a hazard ratio of 0.896 for the 1 prior therapy population. It appears that, for the IXA-LEN-DEX arm, the model applies the Kaplan-Meier data for the first 5 months and then the hazard of the fitted delayed exponential: 0.00262. The corresponding delayed exponential hazard for LEN+DEX is 0.00234, the ratio between the two being 0.892. Please confirm if the hazard ratio of 0.89 on page 177 refers to the 0.892 ratio between the delayed exponential hazards***.

Response:

The hazard ratio of 0.89 on page 177 does refer to the 0.892 ratio between the delayed exponential hazards. This can also be seen on the "Survival(OS-MV)" sheet, where the hazard ratio associated with the treatment effect of IXA+LEN+DEX is stated to be 0.892 (1/1.121), it is this figure that is applied in the model.

i. If it is, is this hazard ratio in favour of IXA+LEN+DEX or in favour of LEN+DEX? Does this reflect the base case OS estimates for the 1 prior therapy population, which appear to suggest an OS gain for IXA-LEN-DEX?

Response:

This hazard ratio is in favour of LEN+DEX and can confirm this reflect the estimates in the model. This can be seen in the "Comp2" sheet, whereby the modelled OS for IXA+LEN+DEX is consistently lower than the observed OS from the LEN+DEX arm in the TMM1 clinical trial for the 1 prior line population

ii. If it is not, please provide more detail of what the 0.89 hazard ratio on page 177 relates to and how it has been calculated.

Response:

Please see response to i. above.

B4. ***It appears that 1 month is defined differently in the graphs in the clinical effectiveness section (28 days) than in the graphs in the cost effectiveness section (one twelfth of year i.e. 30.4 days). Please clarify and also define the days in 1 month in APPENDIX 11 graphs.***

Response:

Please would you be able to refer to the graphs in the clinical effectiveness section that refer to 28-days? IXA+LEN+DEX is administered over a 28-day treatment cycle, hence this is why this duration has been referred to within the submission within the clinical effectiveness section. However, the economic model calculates the cost per month of IXA+LEN+DEX (and other comparators) based on a month being 30.4 days. All graphs presented in the appendices consider 1 month to be 30.4 days.

B5. ***Please clarify why a generalised Gamma model was selected in preference to a Weibull model for PFS modelling in the 1 prior therapy population. The Weibull model has superior scores on information criteria (Appendix 11 Table 8).***

Response:

The AIC and BIC associated with the covariate-adjusted generalised gamma curve were only slightly higher than those associated with Weibull (1415.72 vs. 1414.99 and 1444.09 vs. 1439.30 for AIC and BIC, respectively). Given the small difference in AIC and BIC estimates the generalised gamma curve was selected in the base case in preference to a Weibull model for PFS modelling in the 1 prior therapy population to maintain consistency between the curve fits across the 1 prior and 2+ prior therapies populations

Furthermore, the visual fit of the modelled generalised gamma IXA+LEN+DEX curves with the observed IXA+LEN+DEX PFS data indicates that this method provides a good fit to the data.

We recognise that the Weibull curve is also a plausible fit to the data and the impact of different parametric curve fits was analysed in the scenario analyses presented in Section 5.8 of the submission.

B6. ***Figures 37 (PFS) and 39 (OS): please clarify why the LEN-DEX arm of TMM-1 has been omitted. Please add the Kaplan-Meier data and predicted curves for LEN-DEX into these 2 figures.***

Response:

The LEN+DEX arm was not included as it was not considered a relevant 2nd line comparator (see rationale in answer to question A1a and b). We will require further clarification from NICE on relevant 2nd line comparators and potential subgroups after front-line BORT-therapy before submitting further analyses.

B7. ***Executable model:***

a. ***Lifetable (OS) worksheet: please list all events that qualify as 'Deaths' and all events that qualify as 'Censored'.***

Response:

For OS, an event is defined as death these events are presented in column D of the "Lifetable(OS)" sheet. Censored events include:

- Patients lost to follow-up
- Patients still alive at date of last contact

These events are presented in column E of the "Lifetable(OS)" sheet.

b. ***Lifetable (PFS) worksheet: please list all events that qualify as 'Progressed' and all events that qualify as 'Censored'.***

Response:

For PFS, an event is defined as progression or death. Progressed events are presented in column D of the "Lifetable(PFS)" sheet. Censored events include:

- Patients receiving alternative therapies
- Patients dying or progressing after more than one missed visit
- Patients lost to follow up
- Patients with no baseline/no post-baseline
- Patients with no documented death or disease progression
- Patients who withdrew their consent

These events are presented in column E of the "Lifetable(PFS)" sheet

c. ***Lifetable (ToT) worksheet: please list all events that qualify as 'Disc Treatment' and all events that qualify as 'Censored'***.

Response:

For ToT, an event is defined as discontinuing treatment. Discontinuation of treatment may have been for any one of the following reasons: adverse everts, protocol violation, study terminated by sponsor, withdrawal by patient, lost to follow-up, progression or other.

B8. ***PRIORITY QUESTION: Please clarify if the Kaplan-Meier data in the economic model is raw trial data or if it has been adjusted in any way. Please confirm the data cut (1st or 2nd interim analysis) for the Kaplan-Meier data in the following worksheets: Lifetable (OS), Lifetable (PFS) and Lifetable (ToT). Please provide the equivalent of the data in:***

a. ***worksheet Lifetable(PFS) cells C160:F311, W160:Z311, C314:F464 and W314:Z464 for the 2nd interim analysis.***

Response:

The Kaplan-Meier data in the economic model are the raw unadjusted trial data from the 1st interim analysis, this includes to OS, PFS, ToT and response outcomes. Please see Table 28 which provides details of these data for the 2nd interim analysis of the TMM1 clinical trial for PFS (IA2 data cut of 12th July 2015).

Table 28: Kaplan-Meier data for number at risk for PFS in the 2nd interim analysis of the TMM1 clinical trial (IA2 data cut)

Weeks	1 prior line		2+ prior lines	
	Total patients LEN+DEX	Total patients IXA+LEN+DEX	Total patients LEN+DEX	Total patients IXA+LEN+DEX
0	213.000	212.000	149.000	148.000
1	213.000	212.000	149.000	148.000
2	211.000	208.000	144.000	143.000
3	211.000	208.000	142.000	143.000
4	211.000	206.000	141.000	143.000
5	208.000	206.000	141.000	143.000
6	199.000	202.000	138.000	141.000
7	199.000	201.000	136.000	139.000
8	199.000	199.000	133.000	138.000
9	198.000	197.000	133.000	137.000
10	196.000	192.000	127.000	135.000
11	195.000	192.000	126.000	133.000
12	194.000	192.000	123.000	132.000
13	192.000	190.000	123.000	130.000
14	188.000	184.000	119.000	128.000
15	187.000	183.000	116.000	126.000
16	185.000	182.000	116.000	125.000
17	184.000	180.000	115.000	125.000
18	180.000	175.000	108.000	122.000
19	179.000	174.000	107.000	120.000
20	179.000	174.000	106.000	119.000
21	178.000	173.000	104.000	118.000
22	175.000	168.000	101.000	115.000
23	174.000	167.000	101.000	115.000
24	172.000	166.000	98.000	114.000
25	171.000	166.000	98.000	112.000
26	169.000	165.000	94.000	110.000

27	168.000	162.000	94.000	110.000
28	167.000	159.000	93.000	110.000
29	166.000	157.000	92.000	109.000
30	160.000	153.000	91.000	106.000
31	156.000	150.000	91.000	106.000
32	156.000	147.000	90.000	106.000
33	154.000	147.000	89.000	105.000
34	149.000	143.000	87.000	104.000
35	146.000	140.000	87.000	104.000
36	146.000	140.000	86.000	104.000
37	146.000	137.000	84.000	103.000
38	143.000	134.000	84.000	103.000
39	142.000	133.000	83.000	103.000
40	142.000	133.000	83.000	103.000
41	140.000	133.000	80.000	101.000
42	136.000	129.000	76.000	100.000
43	134.000	128.000	76.000	100.000
44	133.000	128.000	73.000	100.000
45	133.000	126.000	72.000	98.000
46	129.000	126.000	69.000	95.000
47	128.000	125.000	69.000	95.000
48	127.000	123.000	69.000	94.000
49	125.000	122.000	69.000	92.000
50	122.000	122.000	69.000	89.000
51	121.000	120.000	68.000	88.000
52	121.000	119.000	67.000	87.000
53	121.000	118.000	65.000	86.000
54	119.000	115.000	63.000	86.000
55	116.000	114.000	63.000	85.000
56	115.000	113.000	62.000	85.000
57	115.000	112.000	60.000	85.000
58	113.000	108.000	57.000	85.000

59	111.000	107.000	57.000	83.000
60	111.000	105.000	56.000	83.000
61	109.000	105.000	54.000	80.000
62	107.000	105.000	53.000	79.000
63	107.000	104.000	50.000	79.000
64	106.000	104.000	49.000	79.000
65	103.000	103.000	49.000	79.000
66	101.000	99.000	48.000	79.000
67	99.000	99.000	48.000	79.000
68	99.000	98.000	48.000	79.000
69	98.000	98.000	47.000	77.000
70	94.000	96.000	46.000	76.000
71	92.000	95.000	44.000	75.000
72	91.000	94.000	44.000	74.000
73	88.000	94.000	44.000	74.000
74	88.000	93.000	44.000	73.000
75	88.000	89.000	43.000	71.000
76	88.000	89.000	42.000	71.000
77	88.000	89.000	40.000	70.000
78	85.000	87.000	40.000	69.000
79	84.000	87.000	39.000	69.000
80	84.000	86.000	39.000	69.000
81	82.000	85.000	36.000	67.000
82	80.000	82.000	35.000	65.000
83	75.000	79.000	32.000	62.000
84	74.000	77.000	32.000	61.000
85	72.000	75.000	30.000	58.000
86	69.000	71.000	30.000	55.000
87	67.000	68.000	29.000	51.000
88	65.000	64.000	29.000	50.000
89	61.000	62.000	28.000	46.000
90	58.000	59.000	25.000	43.000

91	54.000	56.000	24.000	38.000
92	52.000	55.000	24.000	37.000
93	48.000	53.000	24.000	36.000
94	47.000	48.000	23.000	35.000
95	44.000	48.000	22.000	35.000
96	44.000	47.000	22.000	35.000
97	44.000	47.000	22.000	34.000
98	43.000	47.000	18.000	34.000
99	40.000	45.000	16.000	32.000
100	39.000	44.000	16.000	31.000
101	39.000	43.000	16.000	28.000
102	34.000	41.000	16.000	26.000
103	33.000	40.000	15.000	26.000
104	32.000	39.000	15.000	25.000
105	30.000	38.000	14.000	25.000
106	29.000	35.000	14.000	25.000
107	27.000	34.000	14.000	25.000
108	27.000	32.000	12.000	23.000
109	27.000	31.000	11.000	21.000
110	24.000	31.000	11.000	18.000
111	22.000	30.000	9.000	16.000
112	21.000	28.000	8.000	16.000
113	20.000	28.000	8.000	16.000
114	16.000	24.000	6.000	13.000
115	15.000	23.000	6.000	13.000
116	15.000	21.000	6.000	10.000
117	15.000	21.000	5.000	10.000
118	13.000	17.000	3.000	9.000
119	13.000	15.000	2.000	9.000
120	13.000	15.000	2.000	9.000
121	11.000	15.000	2.000	9.000
122	10.000	12.000	2.000	9.000

123	10.000	11.000	2.000	9.000
124	9.000	10.000	2.000	9.000
125	6.000	9.000	2.000	9.000
126	5.000	9.000	1.000	8.000
127	5.000	8.000	1.000	6.000
128	5.000	8.000	1.000	5.000
129	2.000	7.000	1.000	4.000
130	2.000	5.000	1.000	3.000
131	1.000	5.000	1.000	2.000
132		5.000	1.000	2.000
133		5.000	1.000	2.000
134		4.000	1.000	1.000
135		4.000		
Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide				

b. worksheet Lifetable (ToT) cells C160:F311, W160:Z311, C314:F464 and W314:Z464 for the 2nd interim analysis if this is not already the case.

Response:

Please see Table 29 which details these data for the 2nd interim analysis of the TMM1 clinical trial for ToT (IA2 data cut).

Table 29: Kaplan-Meier data for number at risk for ToT in the 2nd interim analysis of the TMM1 clinical trial (IA2 data cut)

Weeks	1 prior therapy		2+ prior therapies	
	Total patients LEN+DEX	Total patients IXA+LEN+DEX	Total patients LEN+DEX	Total patients IXA+LEN+DEX
0	213.000	210.000	149.000	148.000
1	213.000	210.000	149.000	148.000
2	212.000	209.000	147.000	147.000
3	212.000	208.000	146.000	144.000
4	210.000	204.000	143.000	143.000
5	210.000	199.000	141.000	143.000
6	207.000	199.000	140.000	143.000
7	206.000	198.000	140.000	142.000
8	206.000	196.000	137.000	141.000
9	204.000	195.000	135.000	139.000
10	204.000	194.000	132.000	138.000
11	203.000	193.000	131.000	137.000
12	202.000	191.000	131.000	137.000
13	199.000	191.000	128.000	136.000
14	199.000	190.000	127.000	133.000
15	198.000	188.000	127.000	133.000
16	194.000	185.000	127.000	131.000
17	193.000	183.000	121.000	128.000
18	193.000	183.000	118.000	127.000
19	191.000	180.000	118.000	127.000
20	189.000	180.000	116.000	125.000
21	186.000	176.000	115.000	123.000
22	186.000	174.000	114.000	121.000
23	184.000	172.000	113.000	120.000
24	183.000	172.000	111.000	119.000
25	180.000	171.000	108.000	116.000
26	180.000	167.000	108.000	115.000
27	180.000	166.000	108.000	113.000

28	177.000	164.000	106.000	112.000
29	176.000	163.000	105.000	112.000
30	176.000	162.000	105.000	112.000
31	175.000	161.000	105.000	112.000
32	174.000	160.000	104.000	111.000
33	172.000	158.000	102.000	110.000
34	171.000	156.000	101.000	110.000
35	168.000	154.000	101.000	110.000
36	166.000	152.000	100.000	110.000
37	163.000	149.000	100.000	109.000
38	162.000	145.000	99.000	107.000
39	161.000	145.000	99.000	107.000
40	161.000	144.000	98.000	107.000
41	159.000	142.000	95.000	106.000
42	156.000	141.000	94.000	105.000
43	156.000	139.000	92.000	105.000
44	152.000	138.000	92.000	104.000
45	150.000	136.000	90.000	104.000
46	149.000	132.000	89.000	102.000
47	147.000	132.000	89.000	101.000
48	144.000	131.000	88.000	100.000
49	138.000	128.000	87.000	99.000
50	138.000	124.000	81.000	98.000
51	135.000	123.000	81.000	98.000
52	133.000	122.000	78.000	97.000
53	129.000	118.000	77.000	93.000
54	129.000	117.000	77.000	92.000
55	128.000	116.000	76.000	92.000
56	127.000	114.000	74.000	91.000
57	125.000	111.000	74.000	90.000
58	125.000	111.000	72.000	89.000
59	122.000	110.000	72.000	88.000

60	121.000	109.000	68.000	88.000
61	119.000	108.000	67.000	86.000
62	118.000	106.000	67.000	85.000
63	116.000	106.000	67.000	84.000
64	114.000	105.000	67.000	84.000
65	111.000	105.000	64.000	84.000
66	110.000	104.000	64.000	84.000
67	109.000	103.000	63.000	84.000
68	108.000	101.000	62.000	83.000
69	106.000	100.000	62.000	82.000
70	105.000	100.000	60.000	82.000
71	105.000	98.000	59.000	81.000
72	105.000	97.000	59.000	79.000
73	104.000	96.000	58.000	77.000
74	103.000	95.000	56.000	77.000
75	102.000	95.000	56.000	75.000
76	99.000	92.000	56.000	71.000
77	97.000	92.000	54.000	70.000
78	95.000	92.000	52.000	70.000
79	93.000	90.000	51.000	68.000
80	92.000	90.000	50.000	67.000
81	92.000	90.000	50.000	64.000
82	92.000	86.000	50.000	64.000
83	90.000	86.000	48.000	63.000
84	87.000	83.000	44.000	59.000
85	82.000	80.000	42.000	58.000
86	77.000	79.000	40.000	56.000
87	75.000	77.000	39.000	52.000
88	75.000	75.000	39.000	50.000
89	73.000	72.000	37.000	48.000
90	70.000	67.000	36.000	46.000
91	67.000	63.000	35.000	40.000

92	64.000	61.000	33.000	37.000
93	60.000	56.000	33.000	36.000
94	55.000	53.000	32.000	36.000
95	52.000	51.000	32.000	36.000
96	48.000	50.000	31.000	34.000
97	46.000	47.000	29.000	34.000
98	46.000	47.000	27.000	34.000
99	43.000	46.000	27.000	34.000
100	41.000	46.000	25.000	33.000
101	41.000	44.000	24.000	33.000
102	39.000	43.000	24.000	31.000
103	35.000	41.000	23.000	29.000
104	34.000	39.000	23.000	26.000
105	33.000	38.000	23.000	25.000
106	31.000	38.000	23.000	24.000
107	30.000	37.000	23.000	24.000
108	28.000	36.000	23.000	24.000
109	28.000	33.000	22.000	23.000
110	27.000	32.000	20.000	21.000
111	27.000	29.000	19.000	19.000
112	26.000	28.000	19.000	16.000
113	25.000	28.000	18.000	16.000
114	22.000	26.000	15.000	15.000
115	20.000	25.000	14.000	14.000
116	18.000	23.000	13.000	13.000
117	17.000	22.000	10.000	12.000
118	16.000	21.000	8.000	9.000
119	15.000	18.000	7.000	9.000
120	15.000	17.000	6.000	8.000
121	15.000	15.000	5.000	8.000
122	15.000	15.000	4.000	8.000
123	14.000	15.000	4.000	8.000

124	14.000	14.000	3.000	8.000
125	12.000	12.000	3.000	8.000
126	11.000	11.000	3.000	8.000
127	8.000	9.000	2.000	8.000
128	7.000	8.000	1.000	7.000
129	4.000	7.000	1.000	6.000
130	3.000	6.000	1.000	5.000
131	3.000	5.000	1.000	5.000
132	3.000	5.000	1.000	4.000
133	3.000	5.000	1.000	4.000
134	3.000	5.000	1.000	4.000
135	1.000	4.000	1.000	3.000
136		3.000	1.000	1.000
137		2.000		
138		1.000		
Key: DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide				

B9. ***PRIORITY QUESTION: If they are available or can be constructed in the time available please provide the equivalent of:***

a. the parameterised curves for PFS in worksheets Survival (PFS - MV) and Survival(PFS - UV) for the second interim analysis

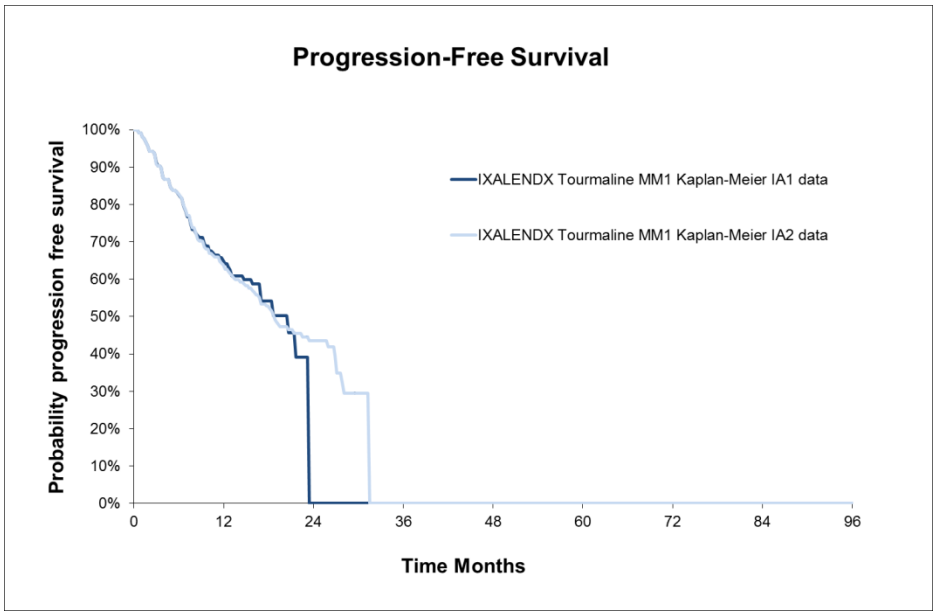
Response:

PFS (2nd interim analysis; IA2) – 1 prior line population

Figure 23 compares the ***unadjusted*** PFS Kaplan-Meier data for IXA+LEN+DEX from the 1st interim analysis (IA1) and the 2nd interim analysis (IA2) for the 1 prior line population.

Using the data from IA2 within the model increases the mean predicted PFS across the lifetime of a patient (26.02 months to 30.61 months, as estimated by the model) and median PFS estimates (17.94 months to 18.40 months, as estimated by the model). This highlights that the extrapolation of the IA1 data may be underestimating the true underlying PFS. The uncertainty associated with extrapolating the PFS data will reduce with the IA3 data cut, expected Summer 2017 (as the analysis is event driven the exact timing cannot be confirmed).

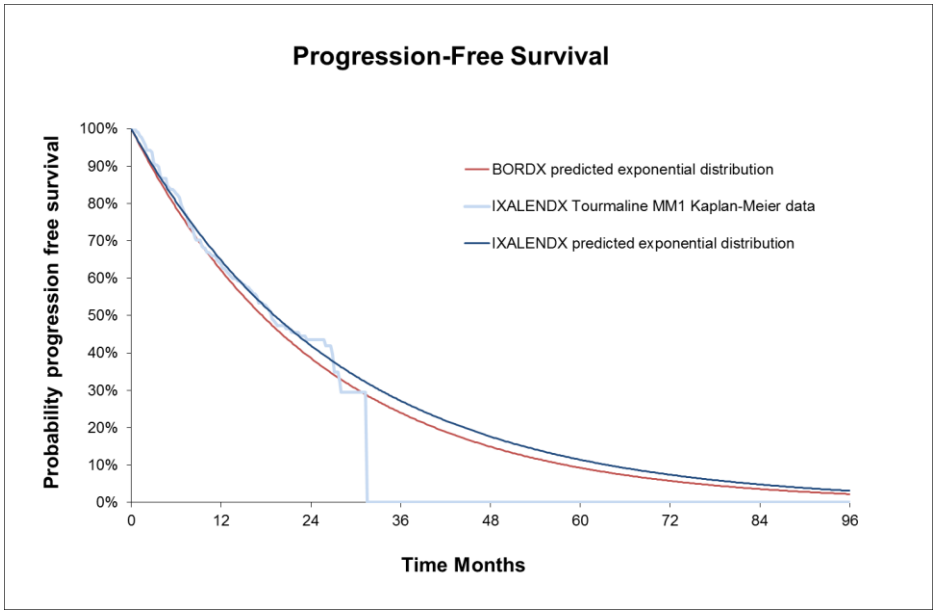
Figure 23: Comparison of unadjusted IXA+LEN+DEX PFS Kaplan-Meier data from the IA1 and IA2 data cuts, 1 prior line population



Key: IXALENDX, ixazomib + lenalidomide + dexamethasone; PFS, progression free survival

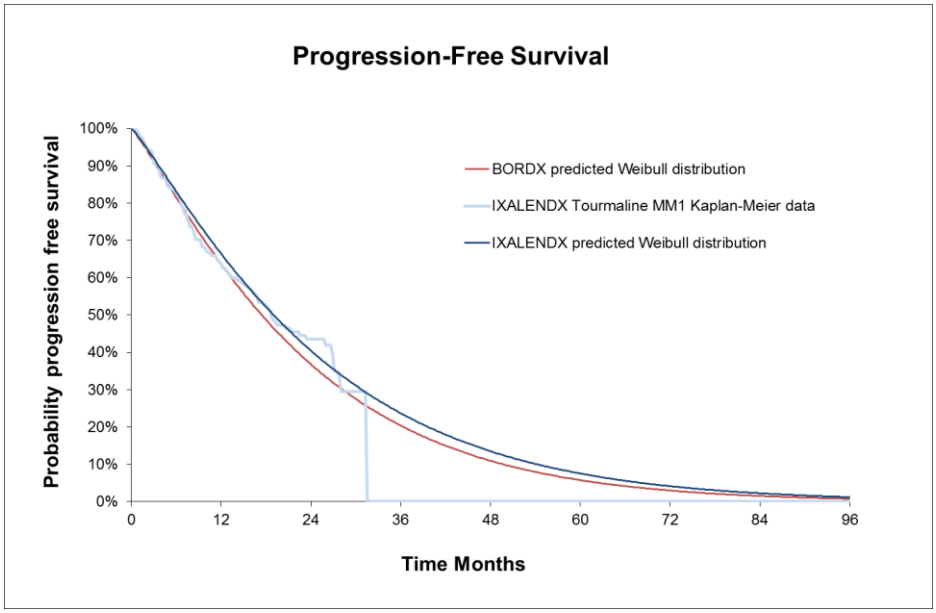
The covariate-adjusted parameterised curves for PFS, using the data for the 1 prior line population from the 2nd interim analysis (IA2 data cut) to enable the comparison with BORT+DEX, are presented in Figure 24 to Figure 29. Please note all Kaplan-Meier data presented are unadjusted and have been updated based on B13.

Figure 24: Covariate-adjusted exponential curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 1 prior line population



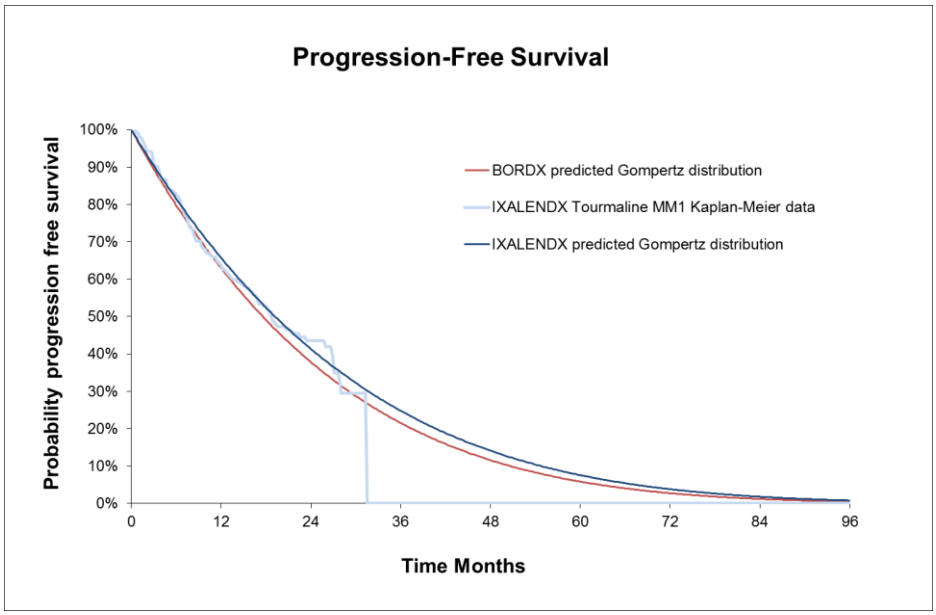
Key: BORDX, bortezomib and dexamethasone; IXALENDX, ixazomib, lenalidomide and dexamethasone; PFS, progression free survival

Figure 25: Covariate-adjusted weibull curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 1 prior line population



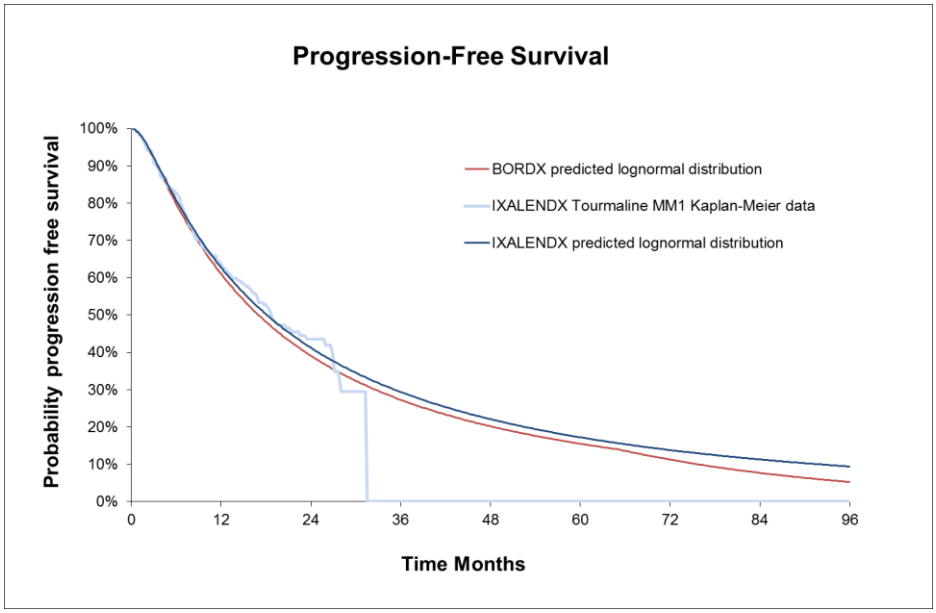
Key: BORDX, bortezomib and dexamethasone; IXALENDX, ixazomib, lenalidomide and dexamethasone; PFS, progression free survival

Figure 26: Covariate-adjusted gompertz curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 1 prior line population



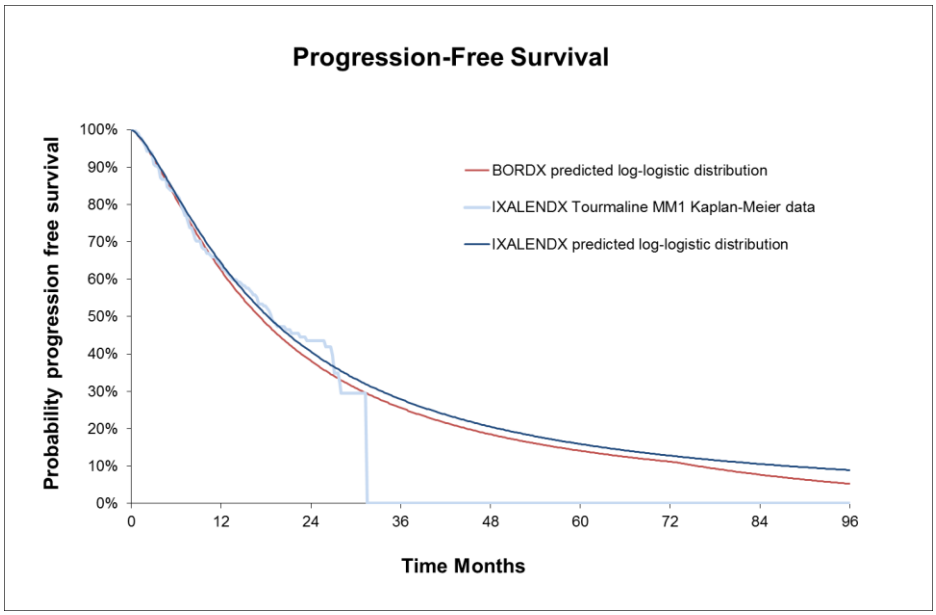
Key: BORDX, bortezomib and dexamethasone; IXALENDX, ixazomib, lenalidomide and dexamethasone; PFS, progression free survival

Figure 27: Covariate-adjusted log-normal curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 1 prior line population



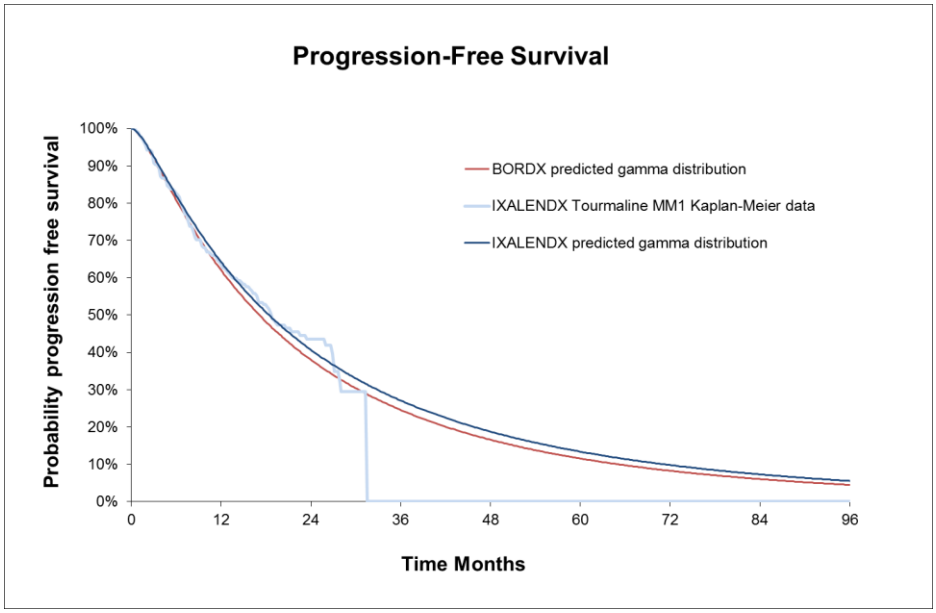
Key: BORDX, bortezomib and dexamethasone; IXALENDX, ixazomib, lenalidomide and dexamethasone; PFS, progression free survival

Figure 28: Covariate-adjusted log-logistic curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 1 prior line population



Key: BORDX, bortezomib and dexamethasone; IXALENDX, ixazomib, lenalidomide and dexamethasone; PFS, progression free survival

Figure 29: Covariate-adjusted generalised gamma curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 1 prior line population



Key: BORDX, bortezomib and dexamethasone; IXALENDX, ixazomib, lenalidomide and dexamethasone; PFS, progression free survival

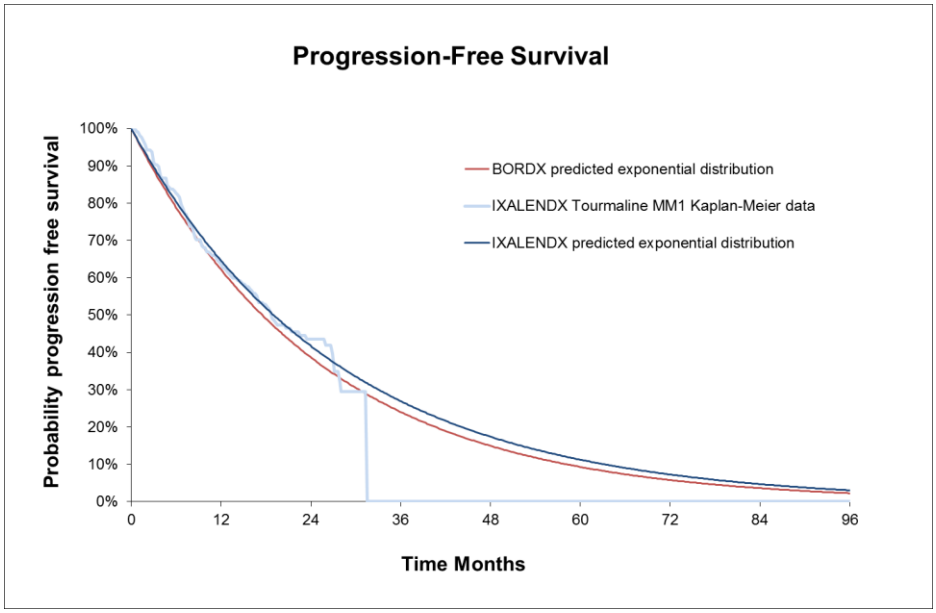
Table 30 provides the AIC and BIC estimates for the covariate-adjusted parametric curve fits, fit to the 1 prior therapy PFS data from the 2nd interim analysis of the TMM1 clinical trial.

Table 30: AIC and BIC estimates for covariate-adjusted parametric curves fit to the PFS data for 1 prior therapy from the 2nd interim analysis of the TMM1 data

Model	N	ll(null)	ll(model)	df	AIC	BIC
Exponential	425	-950.10	-941.81	5	1893.62	1913.88
Weibull	425	-948.25	-939.23	6	1890.46	1914.77
Gompertz	425	-950.00	-941.45	6	1894.90	1919.22
Log-normal	425	-943.73	-937.84	6	1887.68	1912.00
Log logistic	425	-945.17	-937.52	6	1887.04	1911.35
Gamma	425	-943.64	-936.75	7	1887.51	1915.87
Key: AIC, Aikaike Information Criterion; BIC, Bayes Information Criterion; df, degrees of freedom; N, number; PFS, progression free survival						

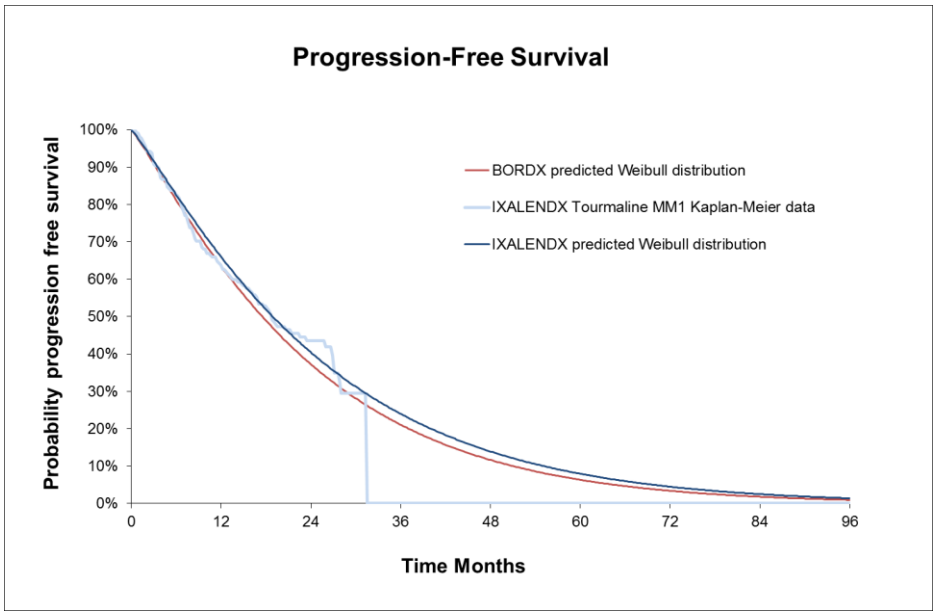
The unadjusted parameterised curves for PFS, using the data for the 1 prior line population from the 2nd interim analysis (IA2 data cut) to enable the comparison with BORT+DEX, are presented in Figure 30 to Figure 35. Please note all Kaplan-Meier data presented are unadjusted and haven updated based on B13.

Figure 30: Unadjusted exponential curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 1 prior line population



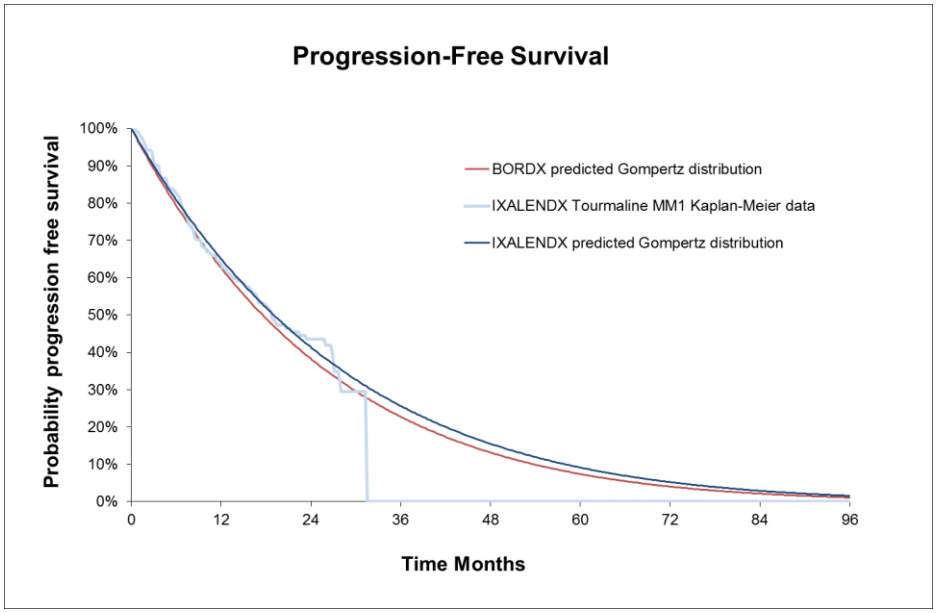
Key: BORDX, bortezomib and dexamethasone; IXALENDX, ixazomib, lenalidomide and dexamethasone; PFS, progression free survival

Figure 31: Unadjusted weibull curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 1 prior line population



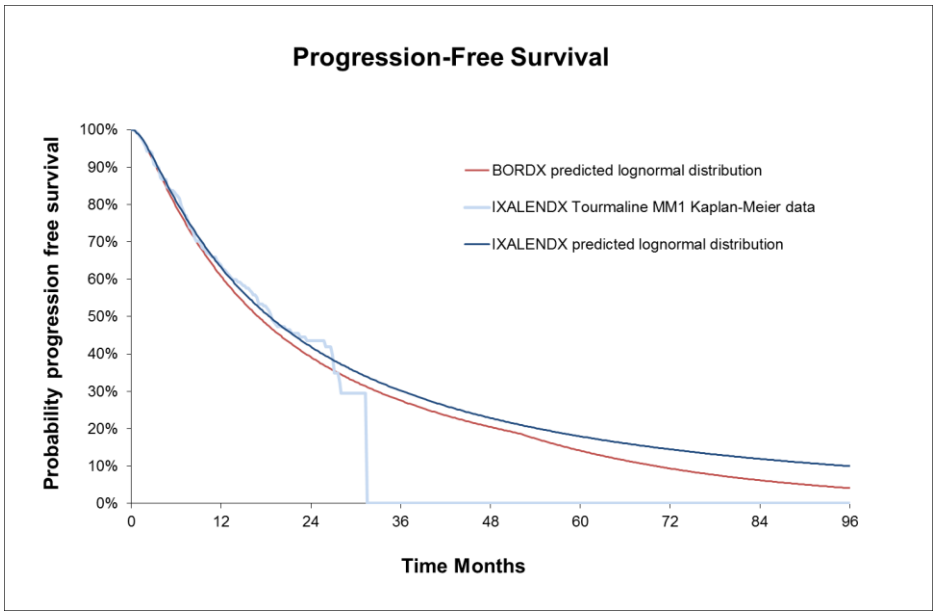
Key: BORDX, bortezomib and dexamethasone; IXALENDX, ixazomib, lenalidomide and dexamethasone; PFS, progression free survival

Figure 32: Unadjusted gompertz curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 1 prior line population



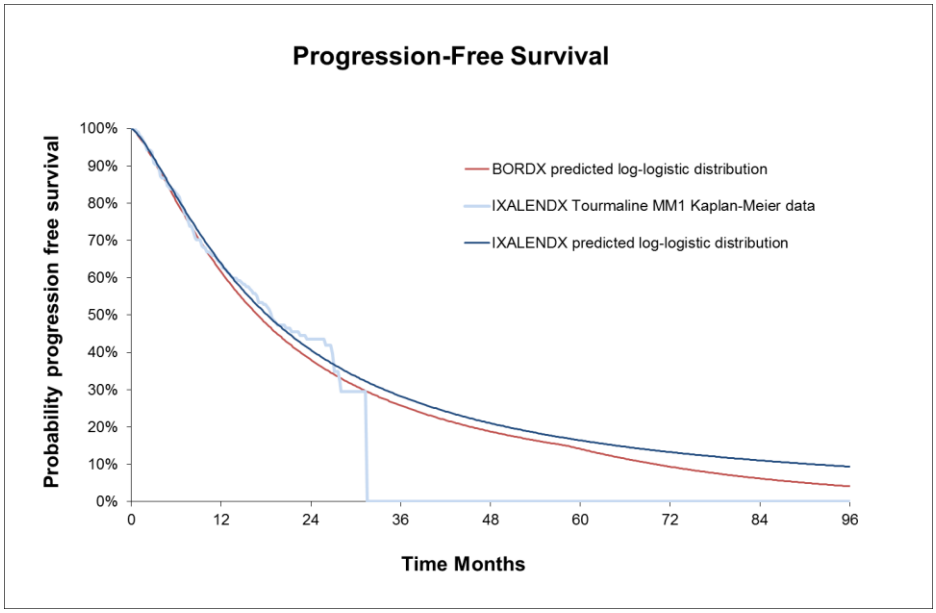
Key: BORDX, bortezomib and dexamethasone; IXALENDX, ixazomib, lenalidomide and dexamethasone; PFS, progression free survival

Figure 33: Unadjusted log-normal curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 1 prior line population



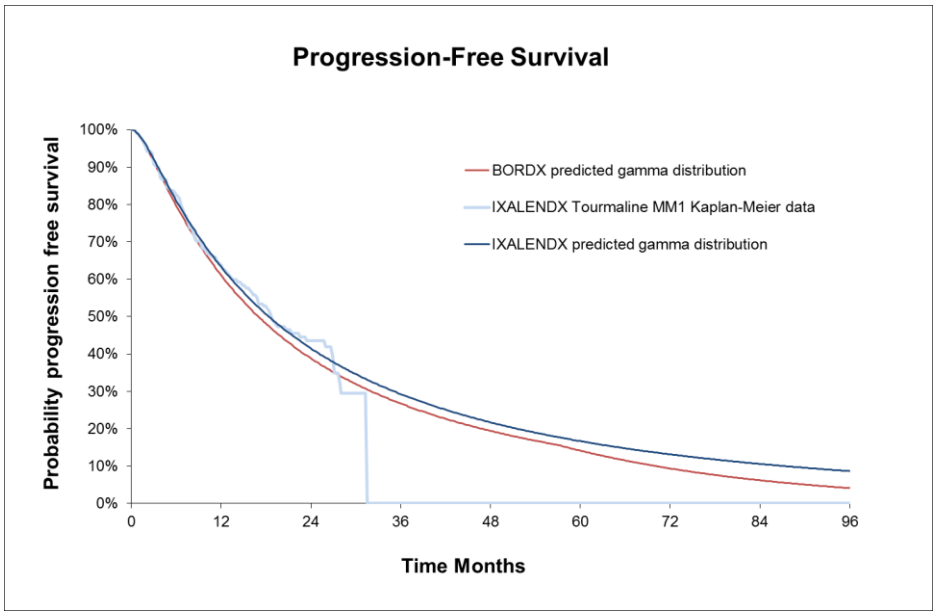
Key: BORDX, bortezomib and dexamethasone; IXALENDX, ixazomib, lenalidomide and dexamethasone; PFS, progression free survival

Figure 34: Unadjusted log-logistic curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 1 prior line population



Key: BORDX, bortezomib and dexamethasone; IXALENDX, ixazomib, lenalidomide and dexamethasone; PFS, progression free survival

Figure 35: Unadjusted generalised gamma curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 1 prior line population



Key: BORDX, bortezomib and dexamethasone; IXALENDX, ixazomib, lenalidomide and dexamethasone; PFS, progression free survival

Table 31 provides the AIC and BIC estimates for the unadjusted parametric curve fits, fit to the 1 prior therapy PFS data from the 2nd interim analysis of the TMM1 clinical trial.

Table 31: AIC and BIC estimates for unadjusted parametric curves fit to the PFS data for 1 prior therapy from the 2nd interim analysis of the TMM1 data

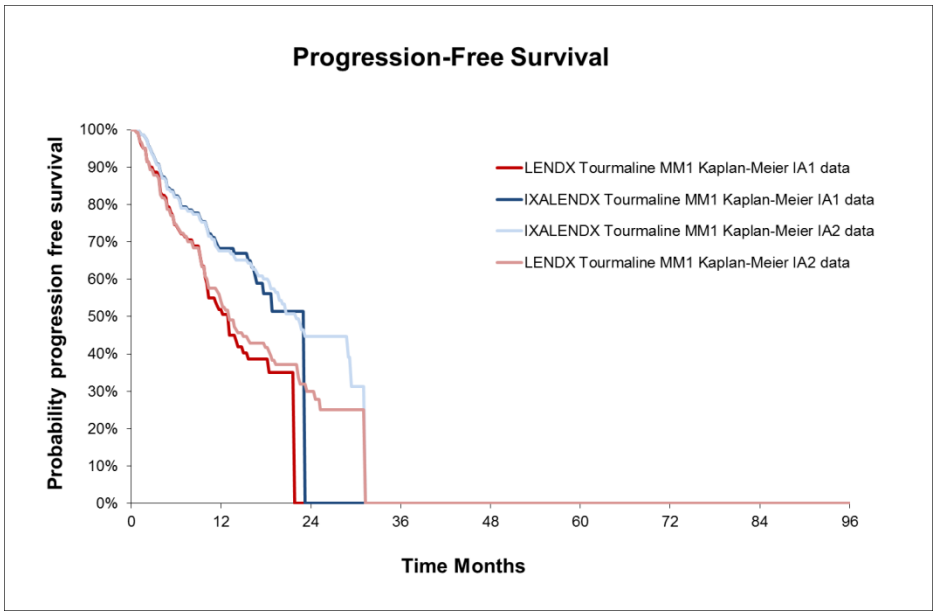
Model	N	ll(null)	ll(model)	df	AIC	BIC
Exponential	425	-950.10	-950.08	2	1904.16	1912.26
Weibull	425	-948.25	-948.23	3	1902.45	1914.61
Gompertz	425	-950.00	-949.98	3	1905.95	1918.11
Log-normal	425	-943.73	-943.72	3	1893.44	1905.60
Log logistic	425	-945.17	-945.16	3	1896.32	1908.48
Gamma	425	-943.64	-943.63	4	1895.26	1911.47
Key: AIC, Aikaike Information Criterion; BIC, Bayes Information Criterion; df, degrees of freedom; N, number						

PFS (2nd interim analysis; IA2) – 2+ prior lines population

Figure 36 compares the ***unadjusted*** PFS Kaplan-Meier data for IXA+LEN+DEX and LEN+DEX from the 1st interim analysis (IA1) and the 2nd interim analysis (IA2) for the 2+ prior lines population. The updated data from IA2 shows that the PFS benefit relative to LEN+DEX extends beyond that shown in the IA1 data, with data still immature.

Using the data from IA2 within the model increases the mean predicted PFS across the trial period for IXA+LEN+DEX (16.63 months to 19.02 months, as estimated by the model) and the mean predicted PFS across a patient's lifetime (42.75 months to 43.28 months, as estimated by the model).The mean predicted PFS across the trial period and a patient's lifetime is also increased for LEN+DEX (13.87 months to 15.58 months and 27.41 months to 28.25 months, respectively, as estimated by the model). Extrapolating the IA1 PFS data may be underestimating the true underlying impact. The uncertainty associated with extrapolating the PFS data will reduce with the IA3 data cut, expected Summer 2017 (as the analysis is event driven the exact timing cannot be confirmed).

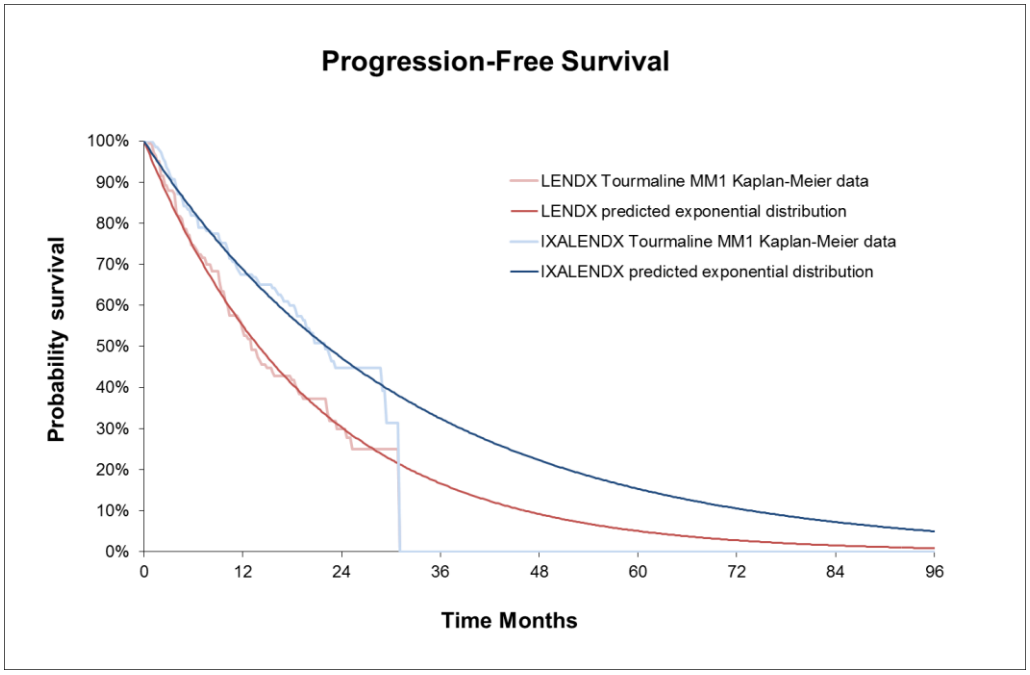
Figure 36: Comparison of unadjusted PFS Kaplan-Meier data from the IA1 and IA2 data cuts, 2+ prior lines population



Key: IXALENDX, ixazomib + lenalidomide + dexamethasone; LENDX, lenalidomide + dexamethasone; PFS, progression free survival

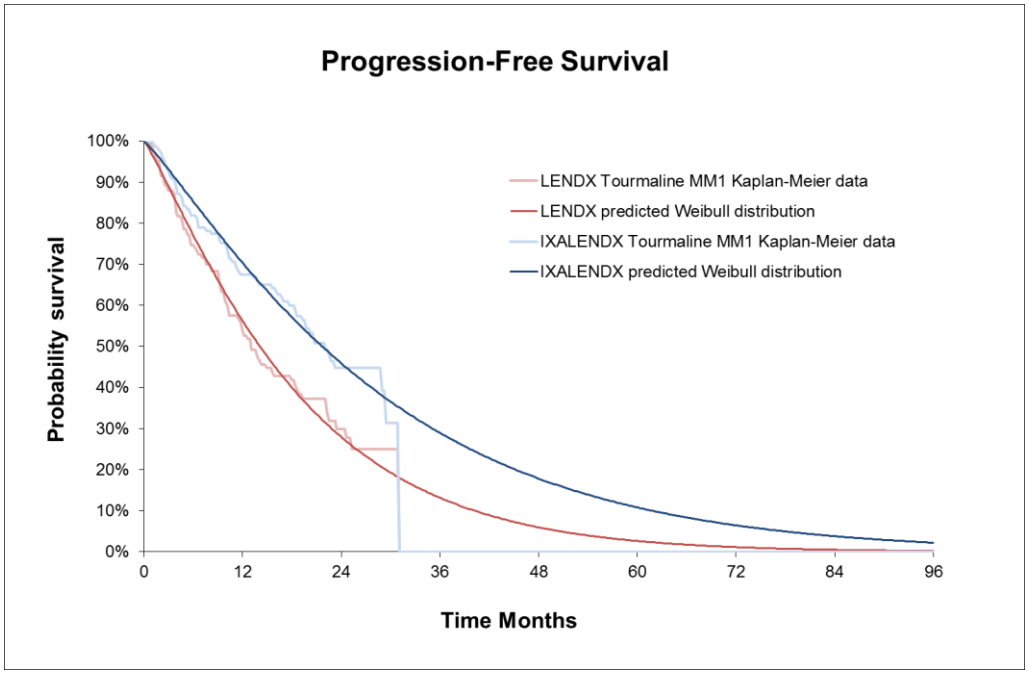
The covariate-adjusted parameterised curves for PFS, using the data for the 2+ prior lines population from the 2nd interim analysis (IA2 data cut) for the comparison with LEN+DEX, are presented in Figure 37 to Figure 42. Please note all Kaplan-Meier data presented are unadjusted and have been updated based on B13.

Figure 37: Covariate-adjusted exponential curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 2+ prior lines population



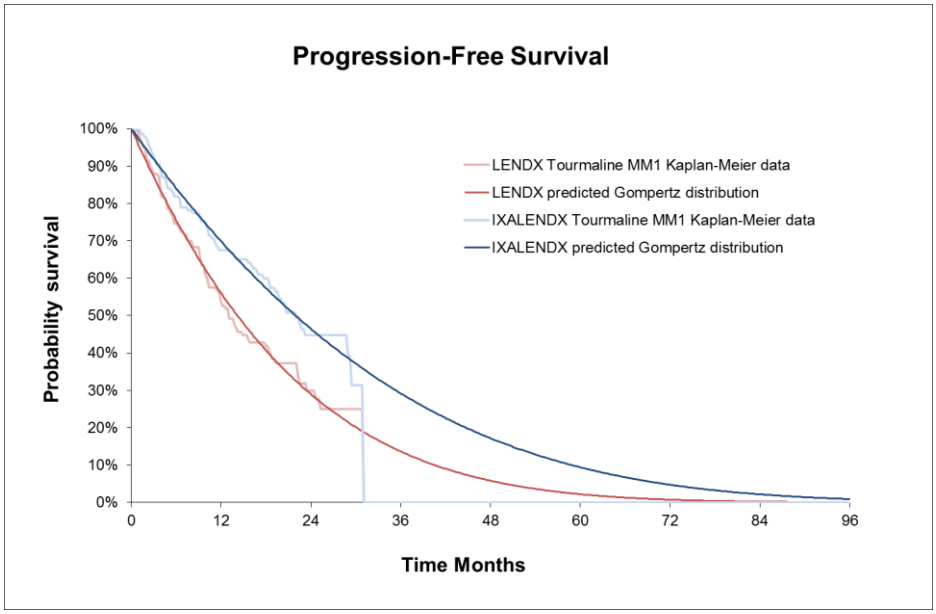
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; PFS, progression free survival

Figure 38: Covariate-adjusted weibull curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 2+ prior lines population



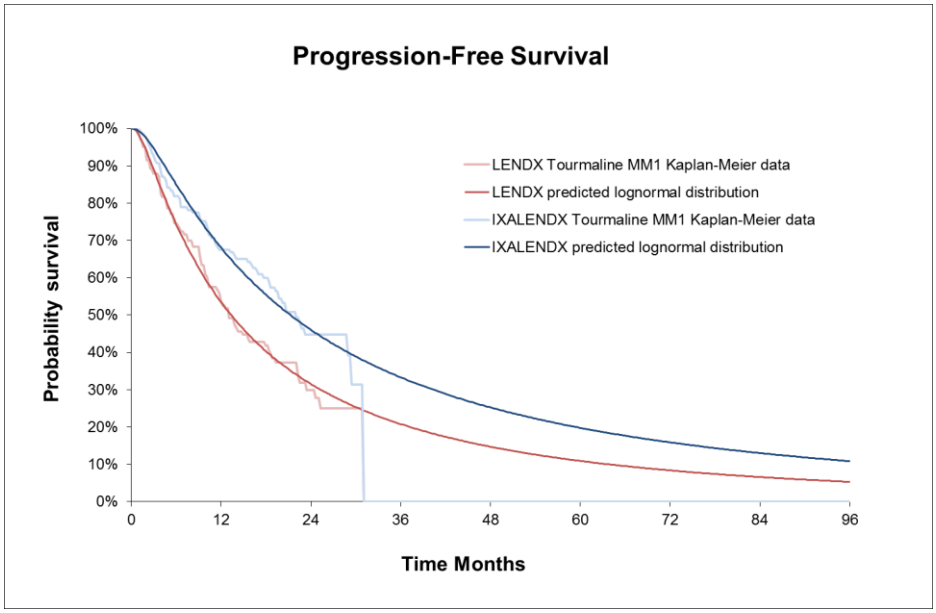
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; PFS, progression free survival

Figure 39: Covariate-adjusted gompertz curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 2+ prior lines population



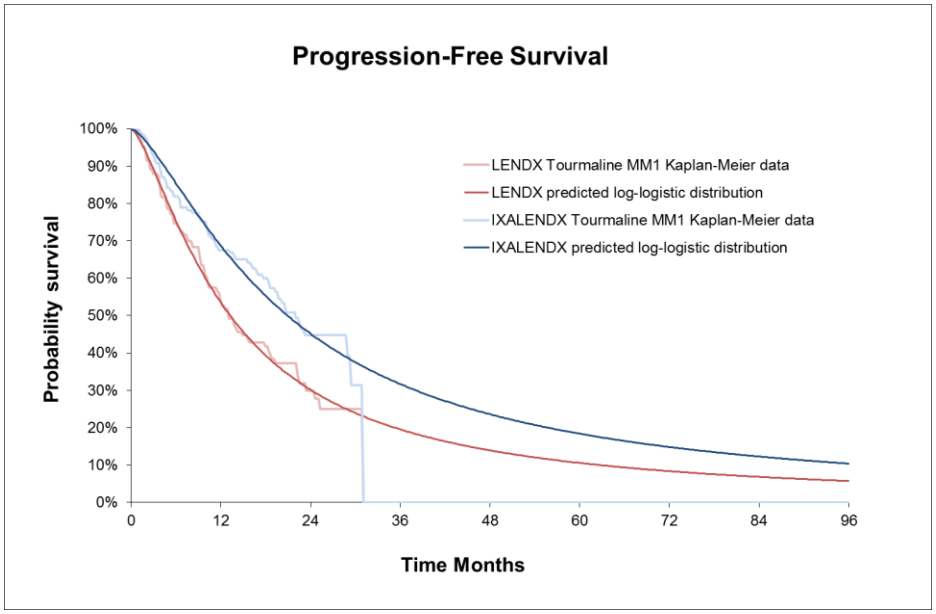
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; PFS, progression free survival

Figure 40: Covariate-adjusted log-normal curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 2+ prior lines population



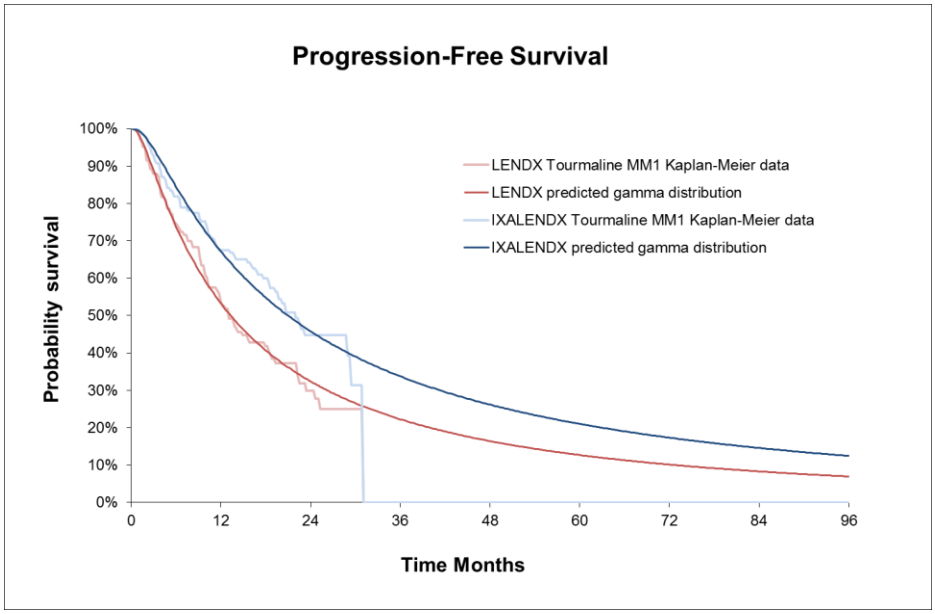
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; PFS, progression free survival

Figure 41: Covariate-adjusted log-logistic curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 2+ prior lines population



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

Figure 42: Covariate-adjusted generalised gamma curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 2+ prior lines population



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

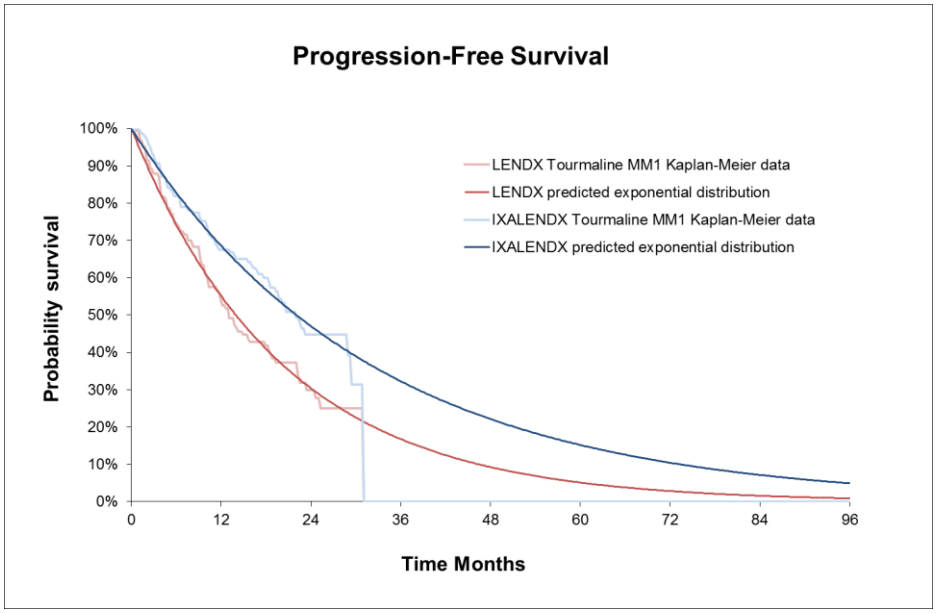
Table 32 provides the AIC and BIC estimates for the covariate-adjusted parametric curve fits, fit to the 2+ prior therapies PFS data from the 2nd interim analysis of the TMM1 clinical trial.

Table 32: AIC and BIC estimates for covariate-adjusted parametric curves fit to the PFS data for 2+ prior therapies from the 2nd interim analysis of the TMM1 data

Model	N	ll(null)	ll(model)	df	AIC	BIC
Exponential	297	-639.51	-633.87	3	1273.75	1284.83
Weibull	297	-638.23	-632.06	4	1272.12	1286.89
Gompertz	297	-639.34	-633.46	4	1274.92	1289.70
Log-normal	297	-634.45	-626.93	4	1261.87	1276.64
Log logistic	297	-636.65	-629.25	4	1266.49	1281.27
Gamma	297	-634.44	-626.80	5	1263.60	1282.07
Key: AIC, Aikaike Information Criterion; BIC, Bayes Information Criterion; df, degrees of freedom; N, number						

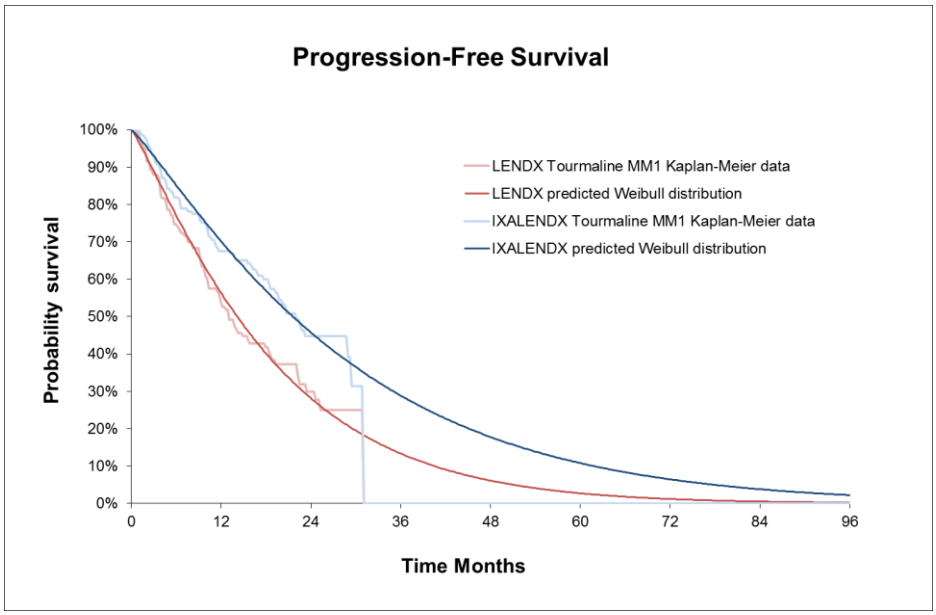
The unadjusted parameterised curves for PFS, using the data for the 2+ prior lines population from the 2nd interim analysis (IA2 data cut) from TMM1 for the comparison with LEN+DEX, are presented in Figure 43 to Figure 48. Please note all Kaplan-Meier data presented are unadjusted and haven updated based on B13.

Figure 43: Unadjusted exponential curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 2+ prior lines population



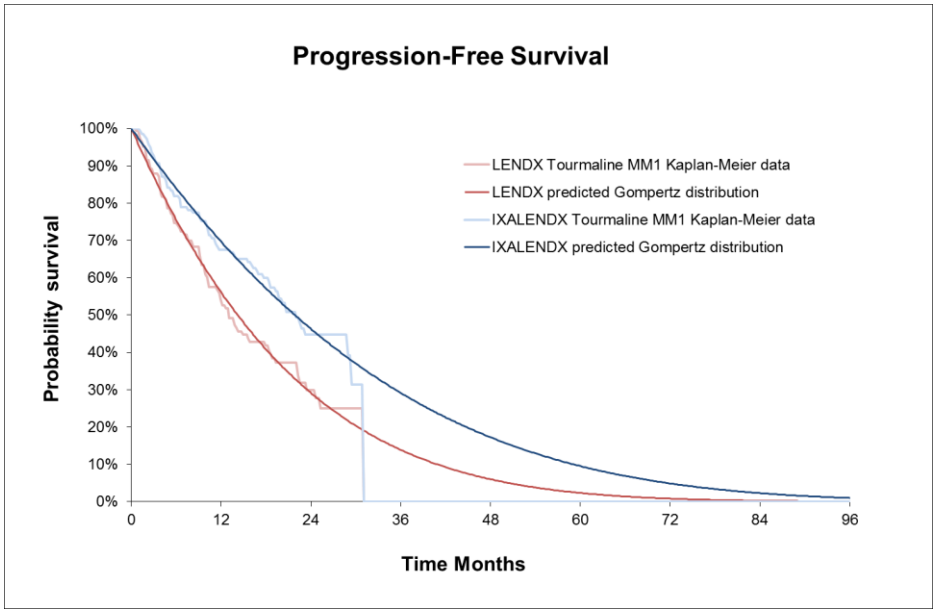
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; PFS, progression free survival

Figure 44: Unadjusted weibull curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 2+ prior lines population



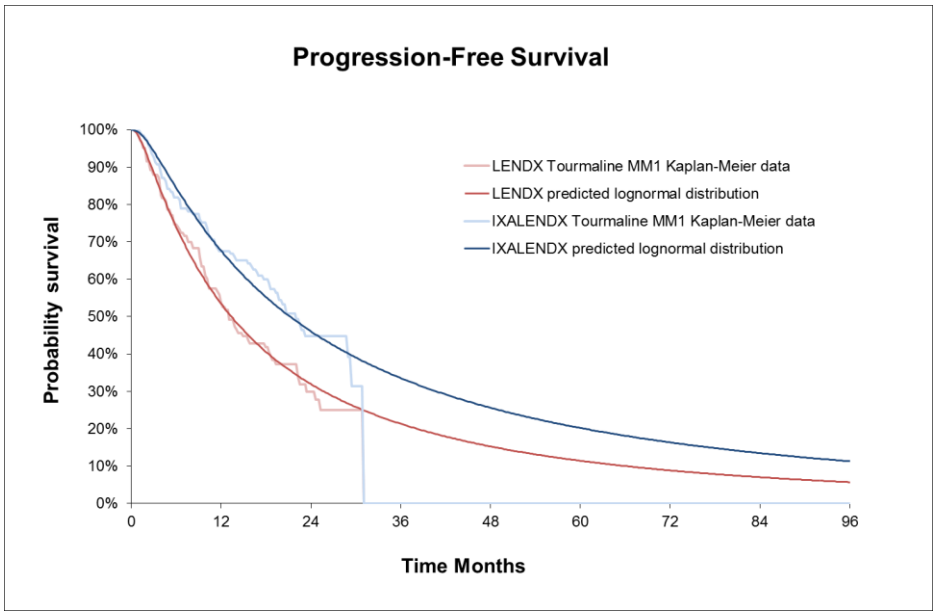
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; PFS, progression free survival

Figure 45: Unadjusted gompertz curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 2+ prior lines population



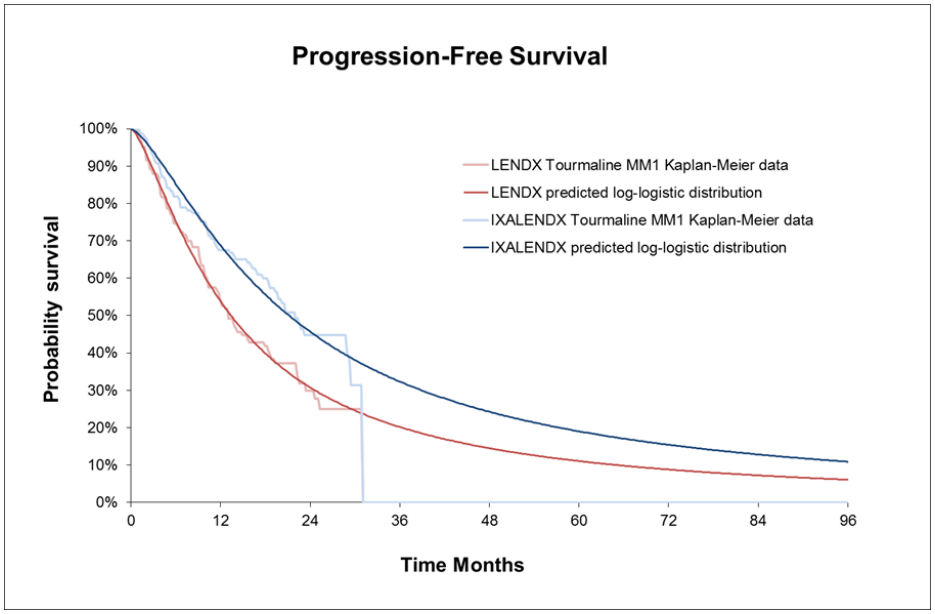
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; PFS, progression free survival

Figure 46: Unadjusted log-normal curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 2+ prior lines population



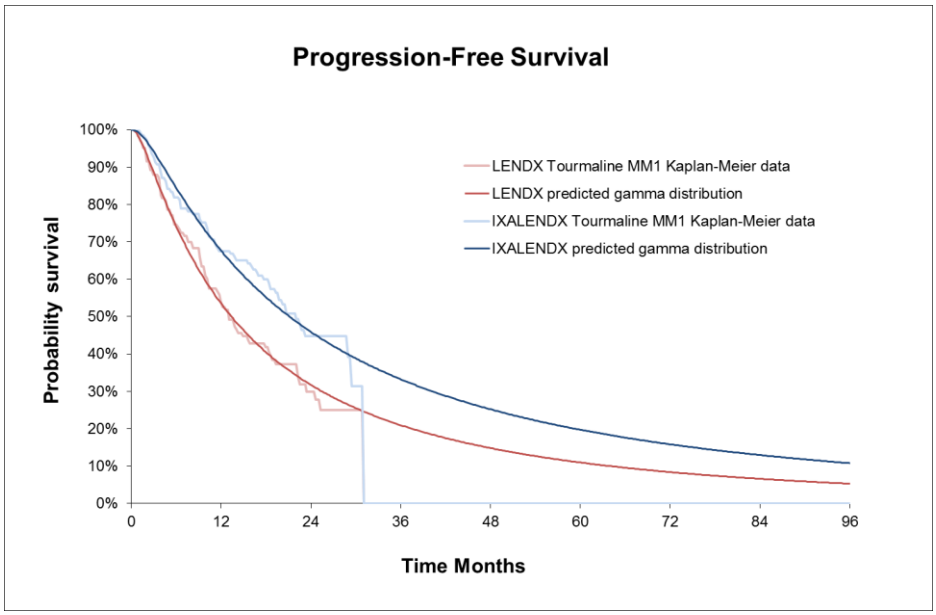
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; PFS, progression free survival

Figure 47: Unadjusted log-logistic curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 2+ prior lines population



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

Figure 48: Unadjusted generalised gamma curve fit compared with the unadjusted PFS Kaplan-Meier data (IA2), 2+ prior lines population



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

Table 33 provides the AIC and BIC estimates for the unadjusted parametric curve fits, fit to the 2+ prior therapies PFS data from the 2nd interim analysis of the TMM1 clinical trial.

Table 33: AIC and BIC values for the unadjusted parametric curve fits for PFS using the 2nd interim analysis of the TMM1 clinical trial, 2+ prior therapies

Model	N	ll(null)	ll(model)	df	AIC	BIC
Exponential	297	-639.51	-635.58	2	1275.17	1282.55
Weibull	297	-638.23	-633.88	3	1273.75	1284.83
Gompertz	297	-639.34	-635.21	3	1276.41	1287.50
Log-normal	297	-634.45	-630.61	3	1267.22	1278.30
Log logistic	297	-636.65	-632.60	3	1271.20	1282.28
Gamma	297	-634.44	-630.60	4	1269.20	1283.98
Key: AIC, Aikaike Information Criterion; BIC, Bayes Information Criterion; df, degrees of freedom; N, number						

b. the Survival (ToT – MV) and Survival (ToT – UV) for the second interim analysis, together with their AICs and BICs. What is the sensitivity of the ICERs to these curves?

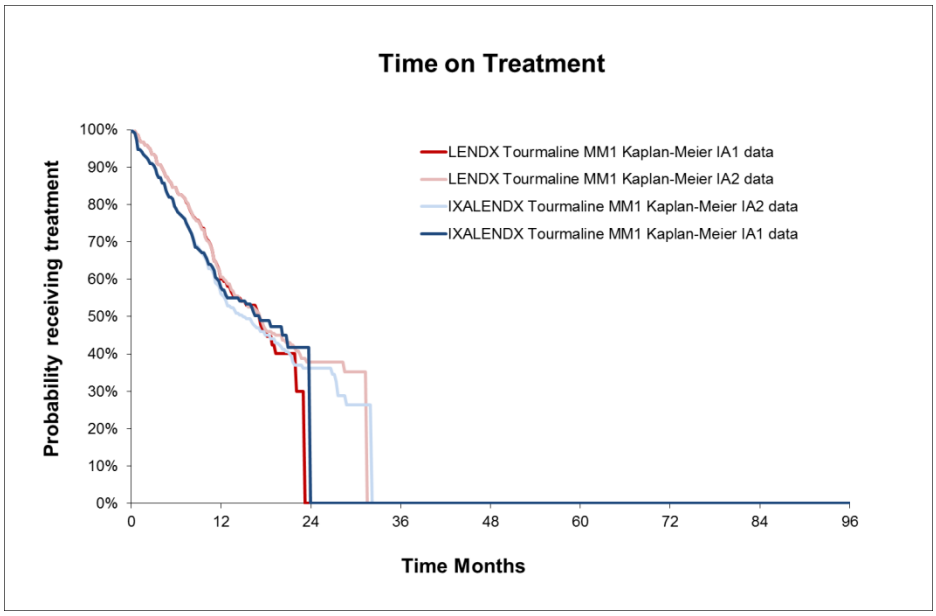
Response:

<u>ToT (2nd interim analysis; IA2) – 1 prior line population</u>

Figure 49 compares the ***unadjusted*** ToT Kaplan-Meier data for IXA+LEN+DEX and LEN+DEX from the 1st interim analysis (IA1) and the 2nd interim analysis (IA2) for the 1 prior line population. In the model, the ToT associated with LEN+DEX is a proxy for the ToT associated with BORT+DEX, prior to the stopping rule implemented as per marketing authorisation for BORT+DEX, see Section 5.3 of the original submission.

The literature and clinician feedback indicated that the ToT observed in the IA1 data cut exceeded what would be expected in current UK practice for LEN+DEX. From this it was inferred that the ToT associated with IXA+LEN+DEX may also be higher within the clinical trial setting that UK clinical practice. Whilst the later data cuts IA2 and, in Summer 2017 The next OS data cut is due for Summer 2017 (as the analysis is event driven the exact timing cannot be confirmed), IA3 address the uncertainty associated with extrapolation the ToT data, it will not address the generalisability to current UK practice. For this, further research is required.

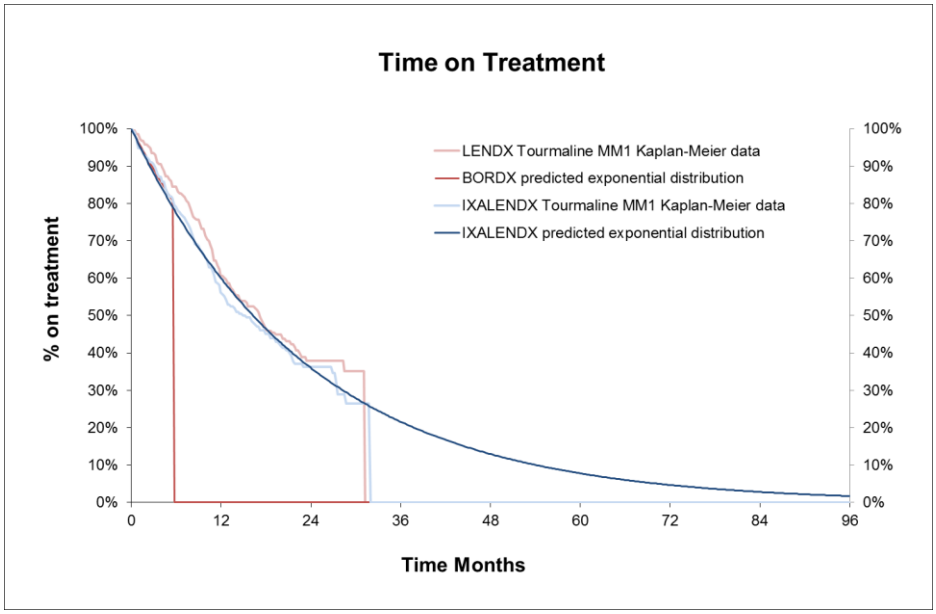
Figure 49: Comparison of unadjusted ToT Kaplan-Meier data from the IA1 and IA2 data cuts, 1 prior line population



Key: IXALENDX, ixazomib + lenalidomide + dexamethasone; LENDX, lenalidomide + dexamethasone; PFS, progression free survival

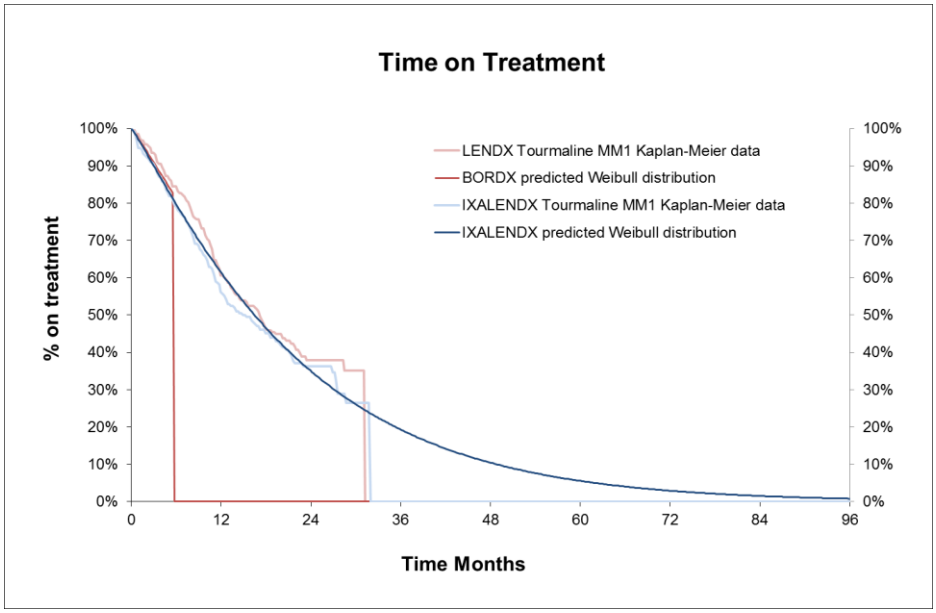
The covariate-adjusted parameterised curves for ToT, using the data for the 1 prior line population from the 2nd interim analysis (IA2 data cut) from TMM1 to enable the comparison with BORT+DEX, are presented in Figure 50 to Figure 55. Please note all Kaplan-Meier data presented are unadjusted and have been updated based on B13.

Figure 50: Covariate-adjusted exponential curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 1 prior line population



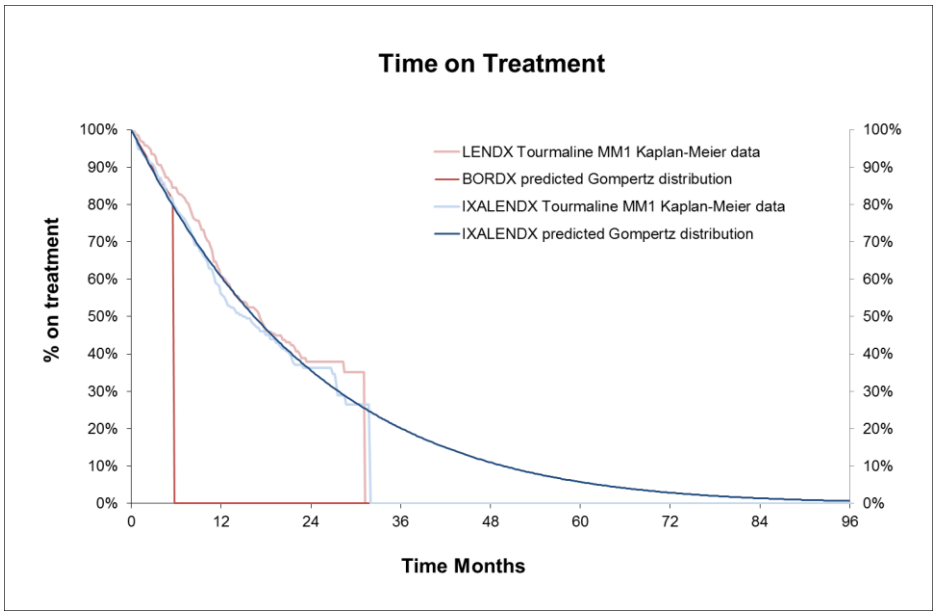
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 51: Covariate-adjusted weibull curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 1 prior line population



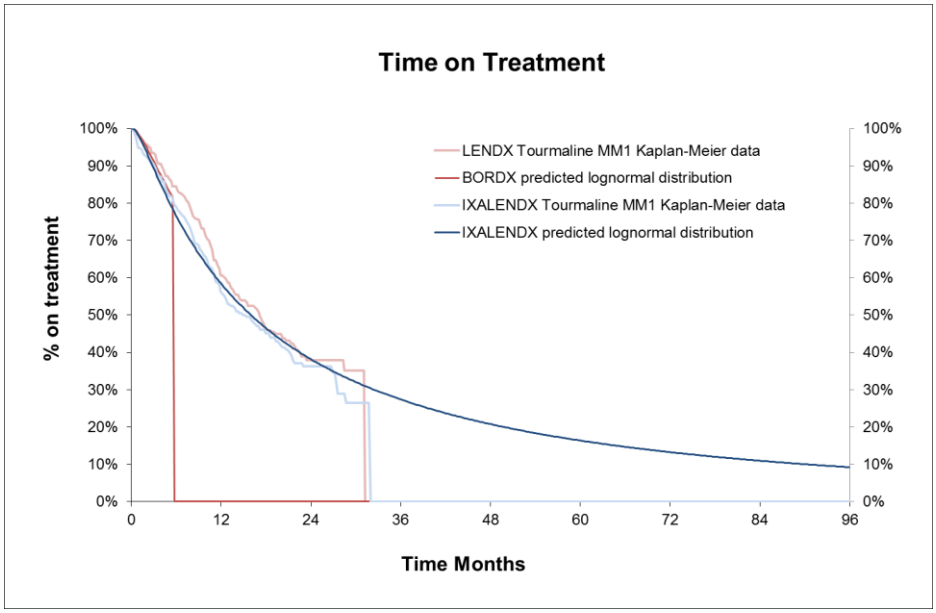
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 52: Covariate-adjusted gompertz curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 1 prior line population



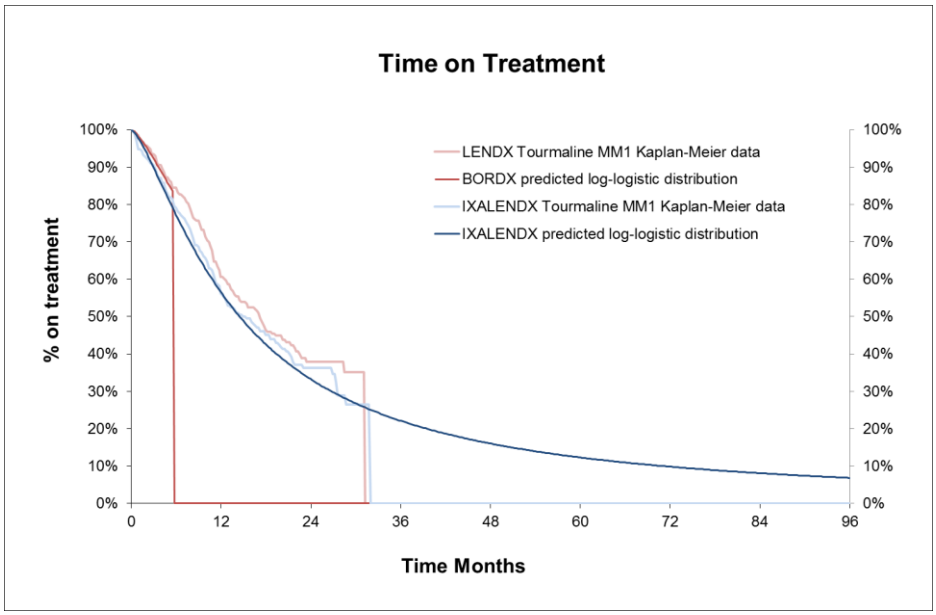
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 53: Covariate-adjusted log-normal curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 1 prior line population



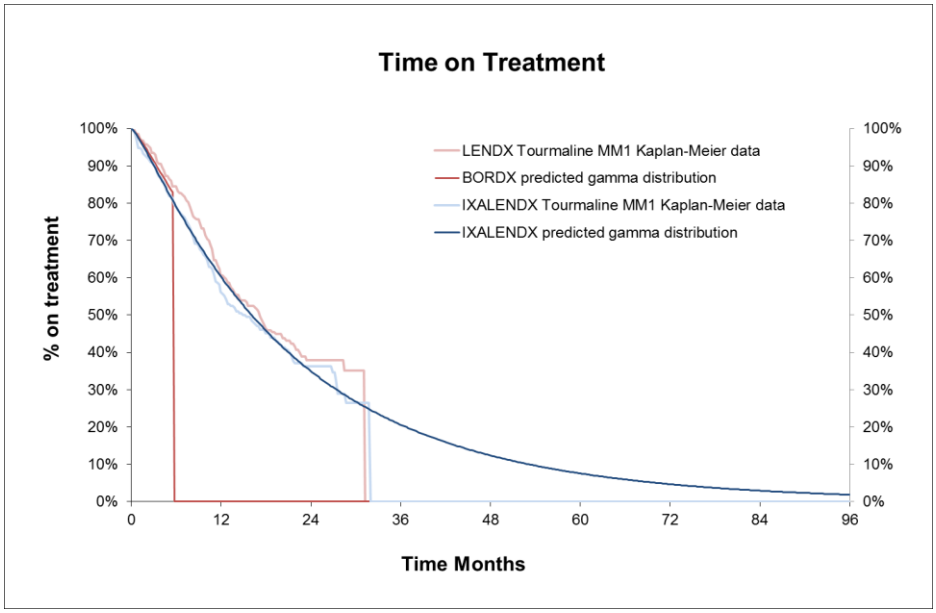
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 54: Covariate-adjusted log-logistic curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 1 prior line population



Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 55: Covariate-adjusted generalised gamma curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 1 prior line population



Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

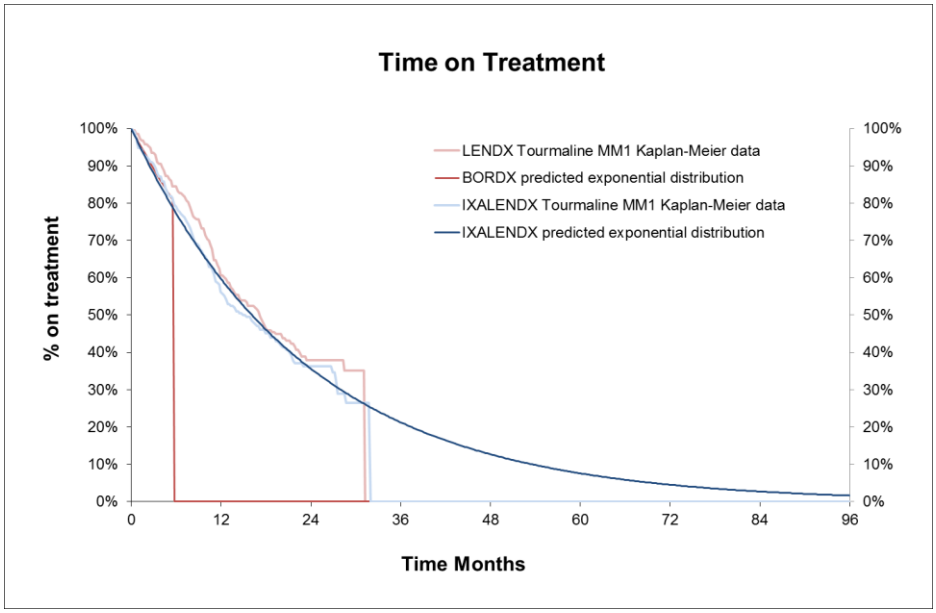
Table 34 provides the AIC and BIC estimates for the covariate-adjusted parametric curve fits, fit to the 1 prior therapy ToT data from the 2nd interim analysis of the TMM1 clinical trial.

Table 34: AIC and BIC estimates for covariate-adjusted parametric curves fit to the ToT data for 1 prior therapy from the 2nd interim analysis of the TMM1 data

Model	N	ll(null)	ll(model)	df	AIC	BIC
Exponential	423	-1475.06	-1469.71	3	2945.43	2957.57
Weibull	423	-1473.72	-1468.11	4	2944.22	2960.41
Gompertz	423	-1474.94	-1469.52	4	2947.04	2963.23
Log-normal	423	-1481.20	-1476.35	4	2960.70	2976.89
Log logistic	423	-1472.39	-1466.47	4	2940.93	2957.12
Gamma	423	-1473.04	-1467.35	5	2944.69	2964.93
Key: AIC, Aikaike Information Criterion; BIC, Bayes Information Criterion; df, degrees of freedom; N, number						

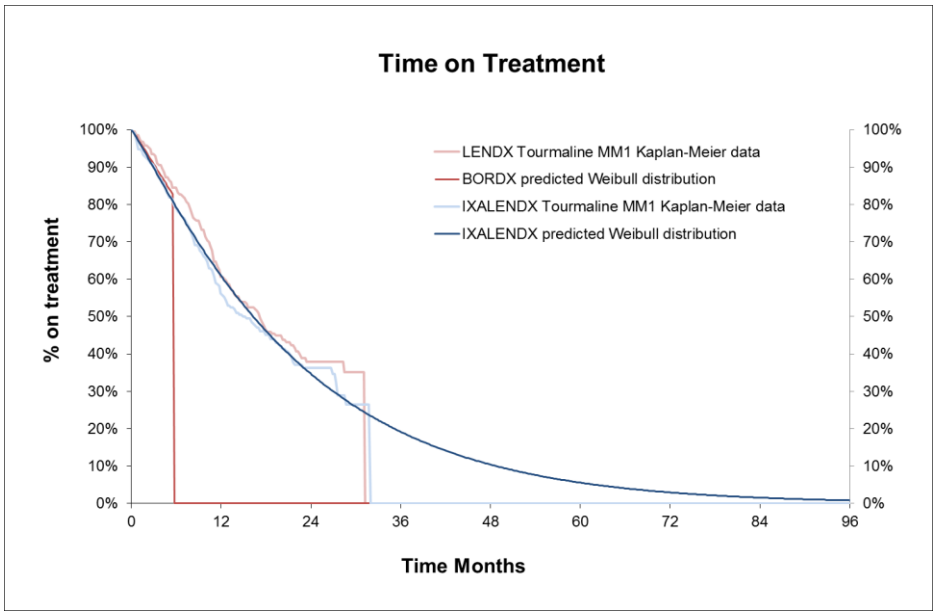
The unadjusted parameterised curves for ToT, using the data for the 1 prior line population from the 2nd interim analysis (IA2 data cut) from TMM1 to enable the comparison with BORT+DEX, are presented in Figure 56 to Figure 61. Please note all Kaplan-Meier data presented are unadjusted and haven updated based on B13.

Figure 56: Unadjusted exponential curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 1 prior line population



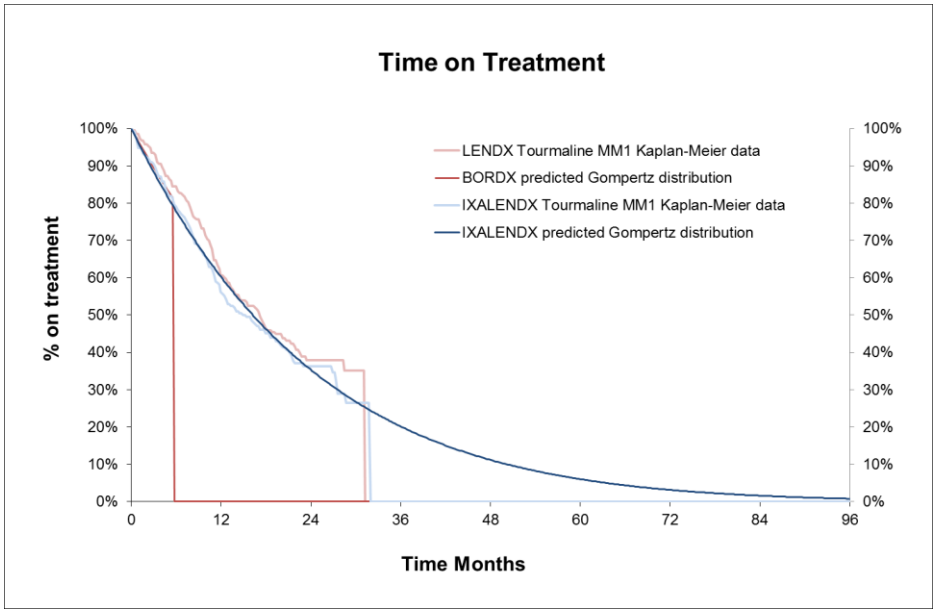
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 57: Unadjusted weibull curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 1 prior line population



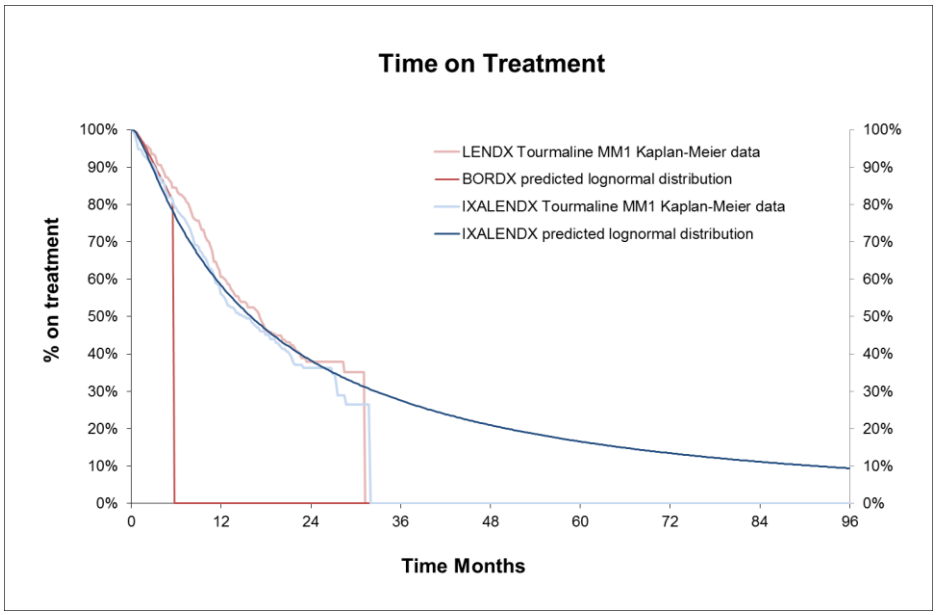
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 58: Unadjusted gompertz curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 1 prior line population



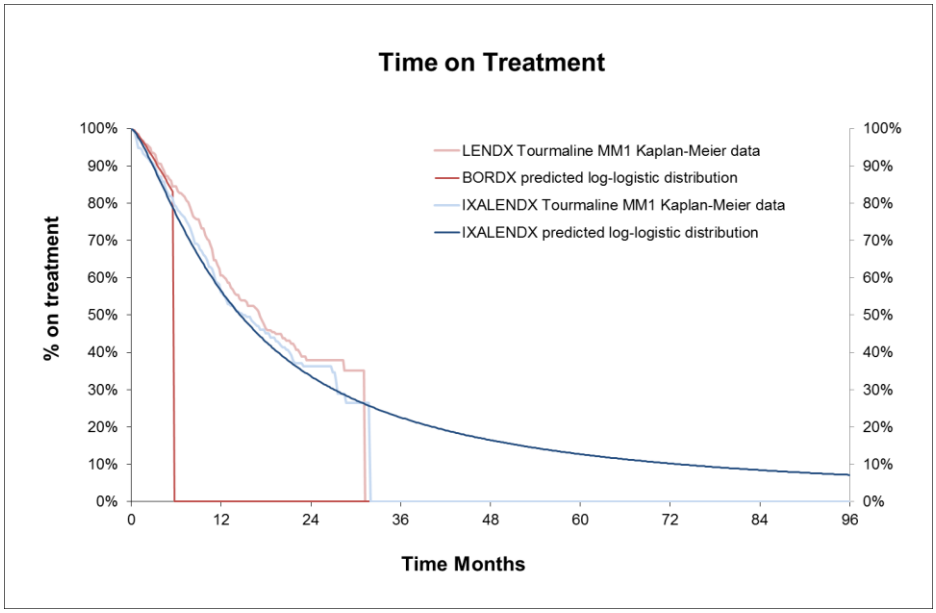
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 59: Unadjusted log-normal curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 1 prior line population



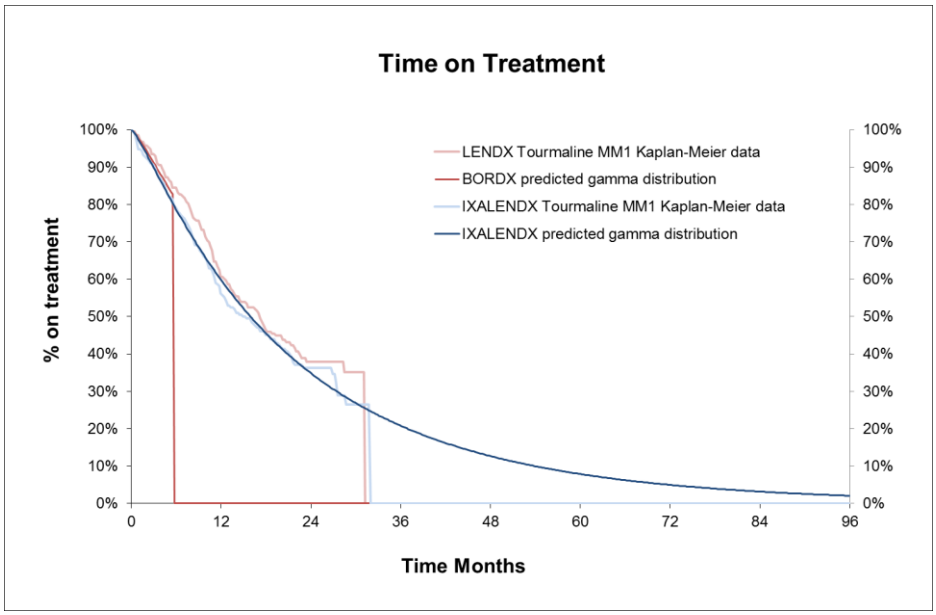
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 60: Unadjusted log-logistic curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 1 prior line population



Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 61: Unadjusted generalised gamma curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 1 prior line population



Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Table 35 provides the AIC and BIC estimates for the unadjusted parametric curve fits, fit to the 1 prior therapy ToT data from the 2nd interim analysis of the TMM1 clinical trial.

Table 35: AIC and BIC values for the unadjusted parametric curve fits for ToT using the 2nd interim analysis of the TMM1 clinical trial, 1 prior therapy population

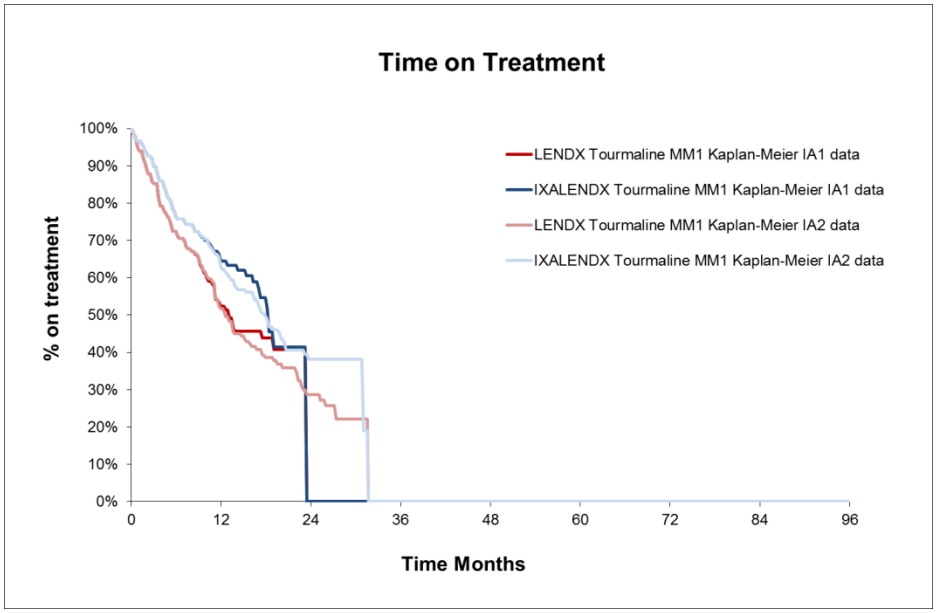
Model	N	ll(null)	ll(model)	df	AIC	BIC
Exponential	423	-1475.06	-1474.63	2	2953.25	2961.35
Weibull	423	-1473.72	-1473.30	3	2952.59	2964.73
Gompertz	423	-1474.94	-1474.51	3	2955.03	2967.17
Log-normal	423	-1481.20	-1480.15	3	2966.30	2978.44
Log logistic	423	-1472.39	-1471.72	3	2949.44	2961.59
Gamma	423	-1473.04	-1472.50	4	2953.00	2969.19
Key: AIC, Aikaike Information Criterion; BIC, Bayes Information Criterion; df, degrees of freedom; N, number						

ToT (2nd interim analysis; IA2) – 2+ prior lines population

Figure 62 compares the ***unadjusted*** ToT Kaplan-Meier data for IXA+LEN+DEX and LEN+DEX from the 1st interim analysis (IA1) and the 2nd interim analysis (IA2) for the 2+ prior lines population.

The literature and clinician feedback indicated that the ToT observed in the IA1 data cut exceeded what would be expected in current UK practice for LEN+DEX. From this it was inferred that the ToT associated with IXA+LEN+DEX may also be higher within the clinical trial setting that UK clinical practice. Whilst the later data cuts IA2 and, in Summer 2017 The next OS data cut is due for Summer 2017 (as the analysis is event driven the exact timing cannot be confirmed), IA3 address the uncertainty associated with extrapolation the ToT data, it will not address the generalisability to current UK practice. For this, further research is required.

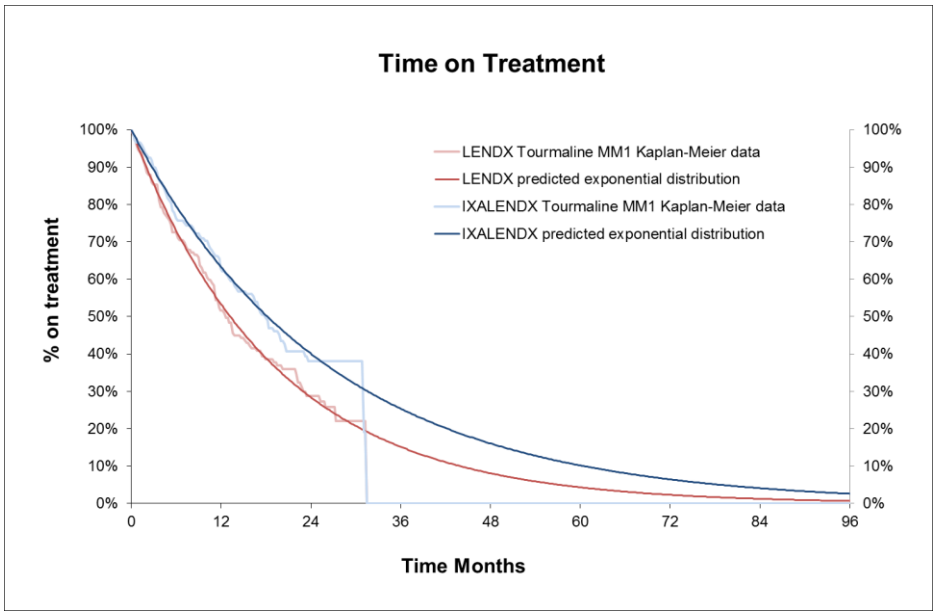
Figure 62: Comparison of unadjusted ToT Kaplan-Meier data from the IA1 and IA2 data cuts, 2+ prior lines population



Key: IXALENDX, ixazomib + lenalidomide + dexamethasone; LENDX, lenalidomide + dexamethasone; ToT, time on treatment

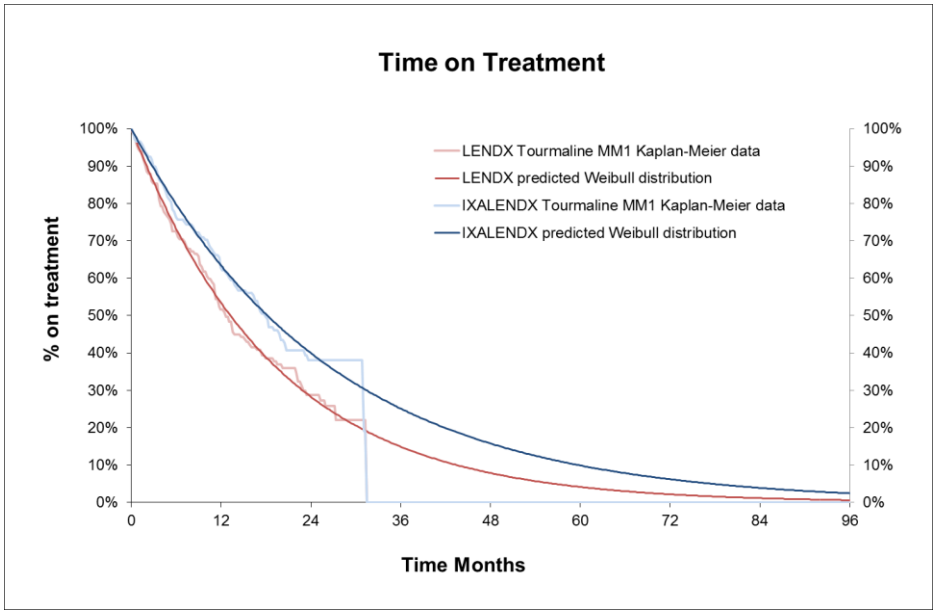
The covariate-adjusted parameterised curves for ToT, using the data for the 2+ prior lines population from the 2nd interim analysis (IA2 data cut) for the comparison with LEN+DEX, are presented in Figure 63 to Figure 68. Please note all Kaplan-Meier data presented are unadjusted and have been updated based on B13.

Figure 63: Covariate-adjusted exponential curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 2+ prior lines population



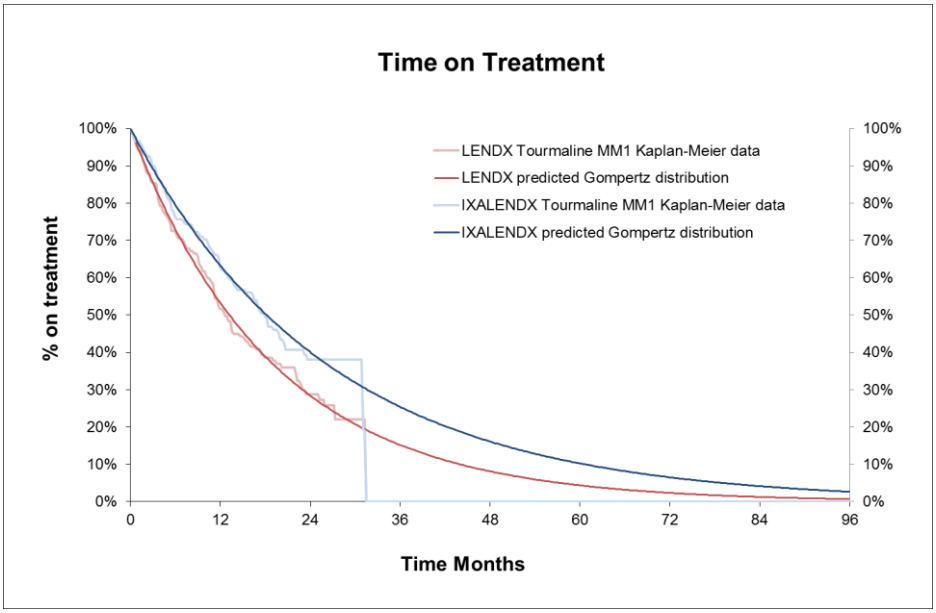
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 64: Covariate-adjusted weibull curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 2+ prior lines population



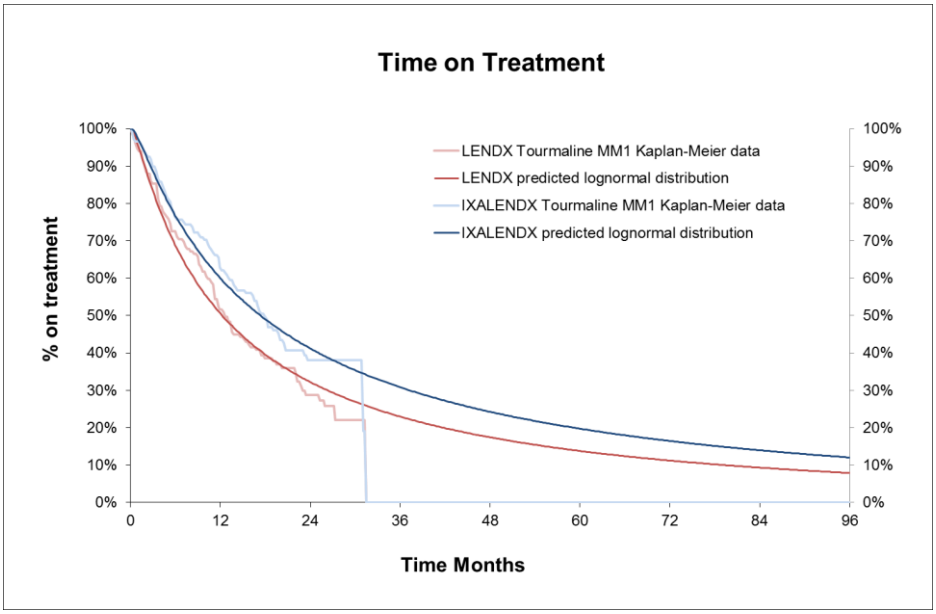
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 65: Covariate-adjusted gompertz curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 2+ prior lines population



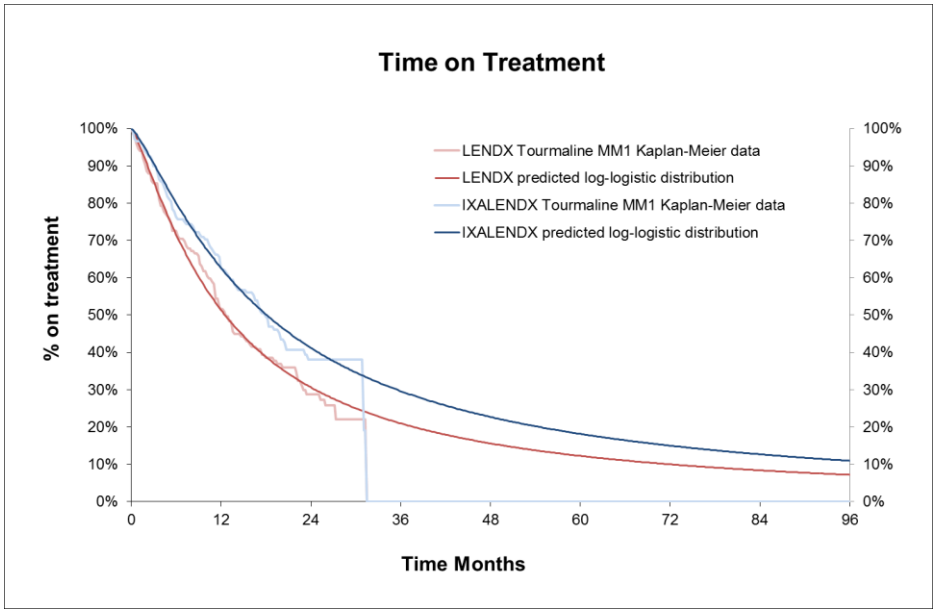
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 66: Covariate-adjusted log-normal curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 2+ prior lines population



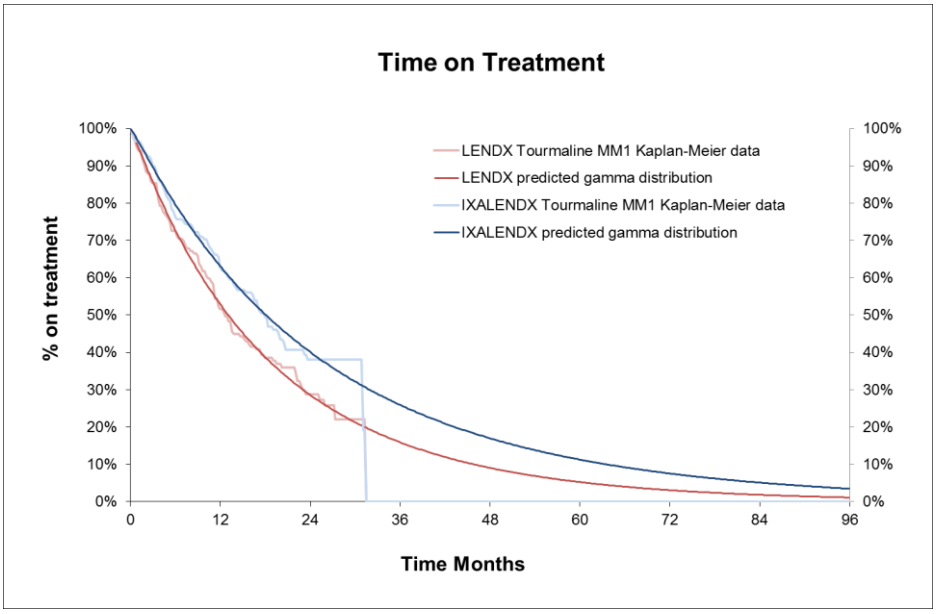
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 67: Covariate-adjusted log-logistic curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 2+ prior lines population



Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 68: Covariate-adjusted generalised gamma curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 2+ prior lines population



Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

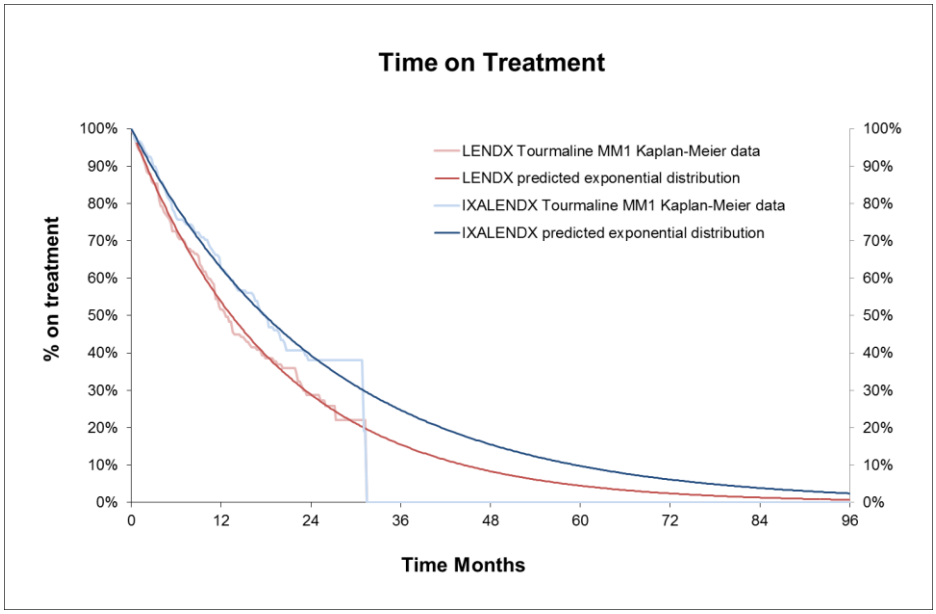
Table 36 provides the AIC and BIC estimates for the covariate-adjusted parametric curve fits, fit to the 2+ prior therapies ToT data from the 2nd interim analysis of the TMM1 clinical trial.

Table 36: AIC and BIC estimates for covariate-adjusted parametric curves fit to the ToT data for 2+ prior therapies from the 2nd interim analysis of the TMM1 data

Model	N	ll(null)	ll(model)	df	AIC	BIC
Exponential	297	-1064.60	-1056.77	4	2121.55	2136.32
Weibull	297	-1064.60	-1056.76	5	2123.52	2141.99
Gompertz	297	-1064.57	-1056.77	5	2123.55	2142.02
Log-normal	297	-1070.77	-1063.28	5	2136.55	2155.02
Log logistic	297	-1066.06	-1058.18	5	2126.36	2144.83
Gamma	297	-1064.54	-1056.62	6	2125.25	2147.41
Key: AIC, Aikaike Information Criterion; BIC, Bayes Information Criterion; df, degrees of freedom; N, number						

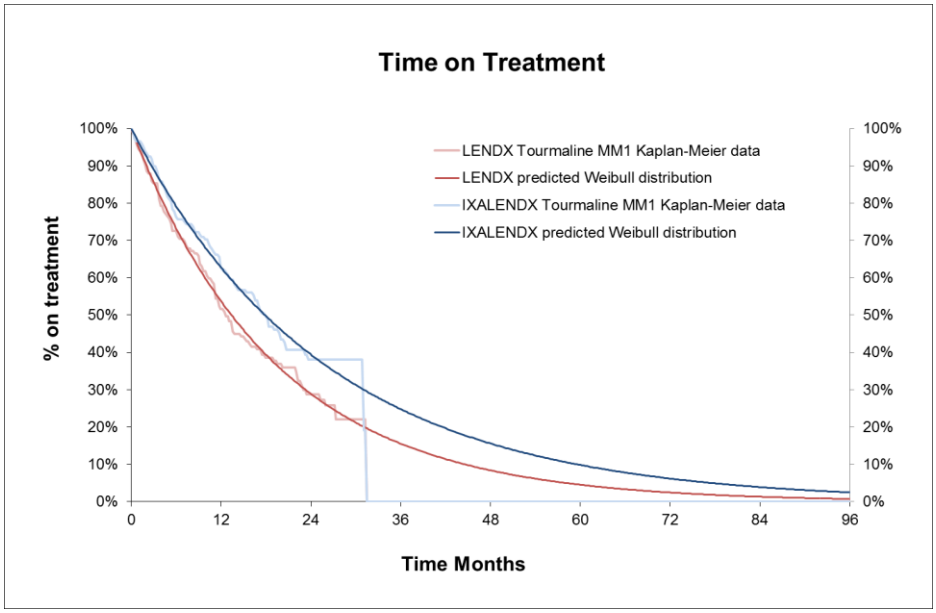
The unadjusted parameterised curves for ToT, using the data for the 2+ prior lines population from the 2nd interim analysis (IA2 data cut) for the comparison with LEN+DEX, are presented in Figure 69 to Figure 61. Please note all Kaplan-Meier data presented are unadjusted and haven updated based on B13.

Figure 69: Unadjusted exponential curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 2+ prior lines population



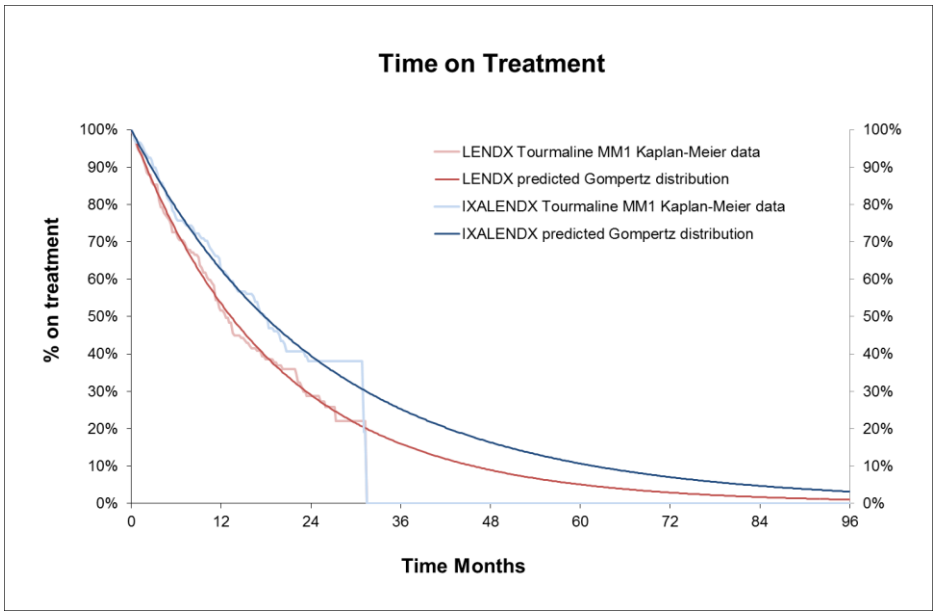
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 70: Unadjusted weibull curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 2+ prior lines population



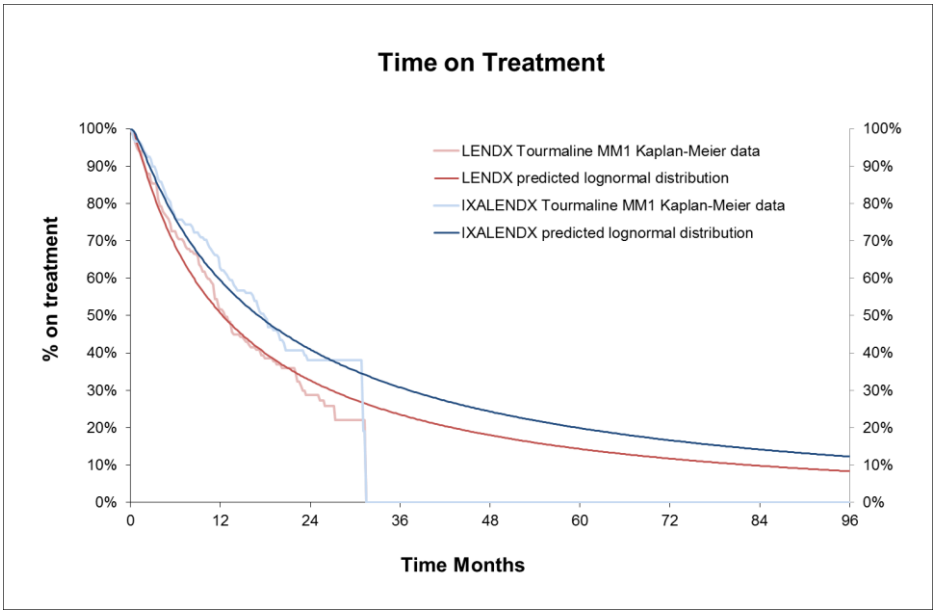
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 71: Unadjusted gompertz curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 2+ prior lines population



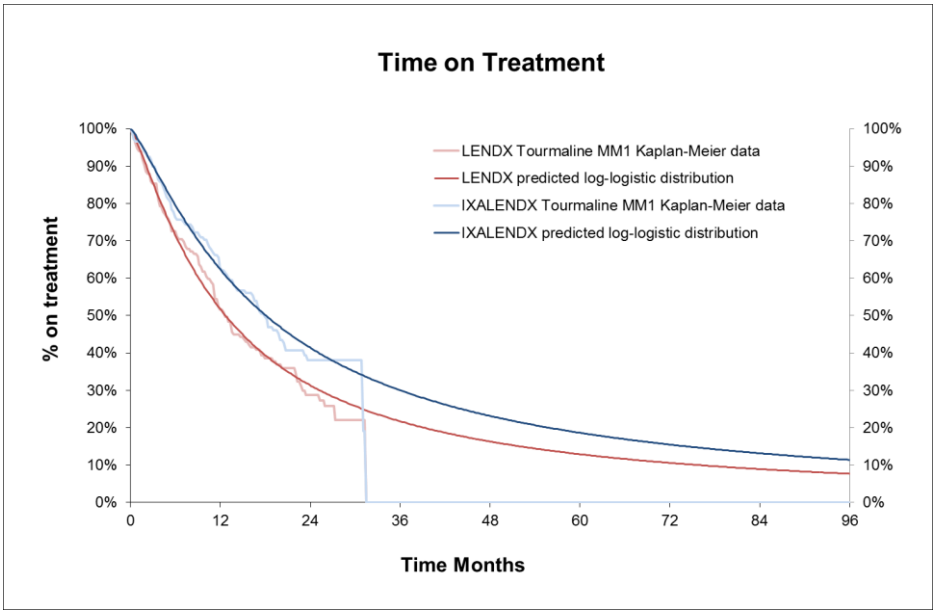
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 72: Unadjusted log-normal curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 2+ prior lines population



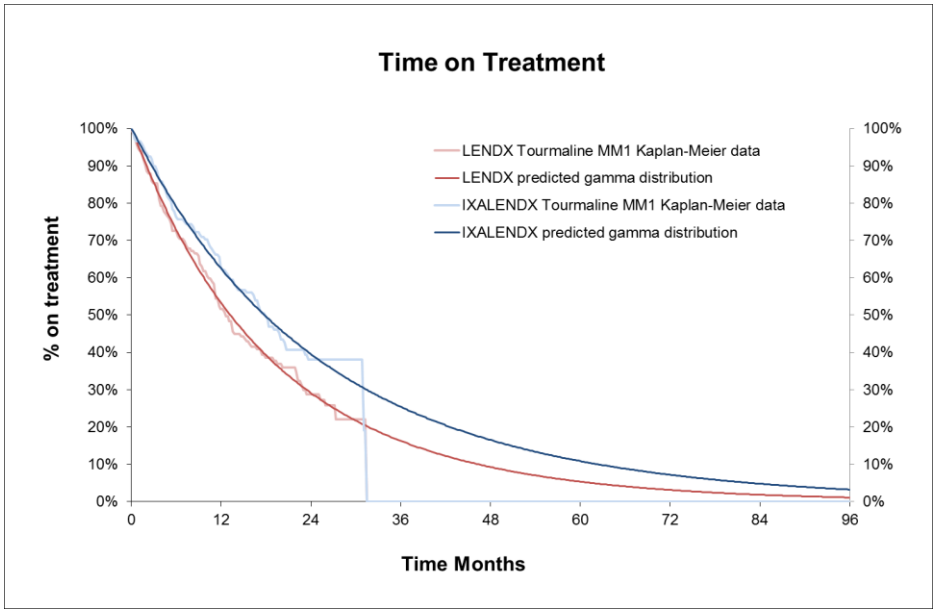
Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 73: Unadjusted log-logistic curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 2+ prior lines population



Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Figure 74: Unadjusted generalised gamma curve fit compared with the unadjusted ToT Kaplan-Meier data (IA2), 2+ prior lines population



Key: IXALENDX, ixazomib, lenalidomide and dexamethasone; LENDX, lenalidomide and dexamethasone; TOT, time on treatment

Table 37 provides the AIC and BIC estimates for the unadjusted parametric curve fits, fit to the 2+ prior therapies PFS data from the 2nd interim analysis of the TMM1 clinical trial.

Table 37: AIC and BIC values for the unadjusted parametric curve fits for ToT using the 2nd interim analysis of the TMM1 clinical trial, 1 prior therapy population

Model	N	ll(null)	ll(model)	df	AIC	BIC
Exponential	297	-1064.61	-1062.63	2	2129.25	2136.64
Weibull	297	-1064.60	-1062.63	3	2131.25	2142.33
Gompertz	297	-1064.57	-1062.61	3	2131.22	2142.30
Log-normal	297	-1070.77	-1068.90	3	2143.81	2154.89
Log logistic	297	-1066.06	-1064.16	3	2134.33	2145.41
Gamma	297	-1064.54	-1062.56	4	2133.12	2147.90
Key: AIC, Aikaike Information Criterion; BIC, Bayes Information Criterion; df, degrees of freedom; N, number						

The sensitivity of the results to different parametric curve fits to the ToT data from the 2nd interim analysis of the TMM1 clinical data is shown below in Table 38 without a PAS applied. Please note these ICERs consider OS, PFS, ToT and response data from the 2nd interim data-cut and have been corrected for the errors discussed in B3 and B13. The results with the PAS applied are shown in Table 39. In both the 1 prior line and 2+ prior line population results, the variation in ICERs arising from the different parametric forms applied to the ToT does not largely differ across the IA1 and IA2 datasets.

IA1 provided ToT data for the first 26 treatment cycles, the observed ToT over this period was considered to surpass what would be expected in UK clinical practice for LEN+DEX based on clinician opinion and the literature. From this it was inferred that the ToT for IXA+LEN+DEX may also be higher than would be expected in UK clinical practice. The 2nd

interim analysis data-cut remains immature and does not address this disparity between the ToT observed in the TMM1 clinical trial and ToT expected to be observed in UK clinical practice. Whilst the 2nd interim analysis provides longer follow-up data up to 34 treatment cycles there remains uncertainty associated with the extrapolation beyond the trial data, which may be better addressed with more mature data from later data cuts that are planned (I.e. IA3 data cut is due in Summer 2017). Whilst the later data cuts IA2 and, in Summer 2017 (as the analysis is event driven the exact timing cannot be confirmed), IA3 address the uncertainty associated with extrapolation the ToT data, it will not address the generalisability to current UK practice. For this, further research is required.

Table 38: Impact of different parametric curves fit to the ToT data, all data obtained from the 2nd interim analysis of TMM1, without PAS applied

	ICER: 1 prior therapy population, IXA+LEN+DEX vs. BORT+DEX	ICER: 2+ prior therapies population, IXA+LEN+DEX vs. LEN+DEX
Exponential parametric curve fit to the ToT data	[redacted]	[redacted]
Weibull parametric curve fit to the ToT data	[redacted]	[redacted]
Gompertz parametric curve fit to the ToT data	[redacted]	[redacted]
Log-normal parametric curve fit to the ToT data	[redacted]	[redacted]
Log-logistic parametric curve fit to the ToT data	[redacted]	[redacted]
Gamma parametric curve fit to the ToT data	[redacted]	[redacted]
Key: BORT, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; ToT, time on treatment		

Table 39: Impact of different parametric curves fit to the ToT data, all data obtained from the 2nd interim analysis of TMM1, with PAS applied

	ICER: 1 prior therapy population, IXA+LEN+DEX vs. BORT+DEX	ICER: 2+ prior therapies population, IXA+LEN+DEX vs. LEN+DEX
Exponential parametric curve fit to the ToT data	£75,981	£126,362
Weibull parametric curve fit to the ToT data	£73,878	£125,639
Gompertz parametric curve fit to the ToT data	£73,770	£126,606
Log-normal parametric curve fit to the ToT data	£95,279	£171,951
Log-logistic parametric curve fit to the ToT data	£85,717	£170,201
Gamma parametric curve fit to the ToT data	£75,812	£130,261
Key: BORT, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; ToT, time on treatment		

B10. ***PRIORITY QUESTION: Please provide the equivalent of the data in:***

a. worksheet Lifetable (OS) cells W314:Z464
b. worksheet Lifetable (PFS) cells W314:Z464
c. worksheet Lifetable (ToT) cells W314:Z464
d. worksheet BoR cells E16:I17
e. worksheet Lifetable (OS) cells C314:F464
f. worksheet Lifetable (PFS) cells C314:F464
g. worksheet Lifetable (ToT) cells C314:F464
h. worksheet BoR cells E17:I17

for the 2-prior therapy patients in the IXA-LEN-DEX arm (n=97) for the worksheets listed in bullet points a-d, and for the 2-prior therapy patients in the placebo arm (n=111) for the worksheets listed in bullet points e-h.

If this is difficult within the time available, please concentrate on the OS data.

Response:

All data requested above has been provided as an attachment to this response – please see attached zipped folder B10 response..

B11. ***PRIORITY QUESTION: Please confirm that appendix 11 is specific to the final adjusted models.***

Response:

We can confirm that appendix 11 is specific to the final (covariate) adjusted models.

a. ***Please provide a list of the covariates that were considered for the:***

i. ***1 prior therapy analyses and recursively worked through to arrive at the final 1 prior therapy models***.

Response:

As outlined in the submission, “variables from the IA1 sub-grouped data were assessed for collinearity and significance in a multivariable Cox regression model using backwards stepwise regression techniques”.

In all analyses, the following co-variates were considered for inclusion within the parametric models:

- High risk cytogenetics
- ISS stage III
- Age > 65 years
- Light chain myeloma
- Relapsed and refractory
- Primary refractory
- Proteasome inhibitor exposed
- Immunomodulation agent exposed
- ECOG performance status 2
- ASCT undertaken
- History of bone lesions
- Renal dysfunction
- Asian

A correlation matrix for the 1 prior therapy sub-population outlined evidence of co-linearity of the following pairs of variables:

- Age > 65 years and ASCT undertaken
- Proteasome inhibitor exposed and Immunomodulation agent exposed
- ECOG performance status 2 and ASCT undertaken

Overall survival

For the overall survival outcome, the covariates eliminated due to co-linearity are those with p-values denoting worsened significance. The covariates eliminated from consideration (age > 65 years, immunomodulation agent exposed and ASCT) are denoted in red within Table 40.

The remaining variables were then inserted into the regression model and subsequently eliminated (backwards stepwise) based on the least significant covariate. This process and the corresponding p-values at each iteration are outlined in Table 41. Within this table, eliminated covariates along with their p-values at time of elimination are denoted in red. Covariates retained at the end of the process and the p-value at the time of being retained are denoted in green.

Based on this process, ISS stage III (p = 0.001) was the only co-variate retained within the adjusted equation for OS within the 1 prior line-subpopulation.

Table 40: Elimination of variables due to collinearity for overall survival in the 1 prior therapy population

Variable 1		Variable 2	
Name	**p-value**	**Name**	**p-value**
Age > 65 years	**0.877**	ASCT undertaken	**0.137**
Proteasome inhibitor exposed	**0.309**	Immunomodulation agent exposed	**0.746**
ECOG performance status 2	**0.009***	ASCT undertaken	**0.137**
*: *Significant where p <= 0.05*			

Table 41: Elimination of variables based on backwards stepwise elimination method due to lowest significance for overall survival in the 1 prior therapy population

Name	Iteration 1	Iteration 2	Iteration 3	Iteration 4	Iteration 5	Iteration 6	Iteration 7	Iteration 8	Iteration 9	Iteration 10
Relapsed and refractory	**0.996**									
Light chain myeloma	0.846	**0.838**								
High risk cytogenetics	0.837	0.832	**0.819**							
Asian	0.815	0.801	0.804	**0.809**						
Primary refractory	0.669	0.670	0.671	0.660	**0.660**					
History of bone lesions	0.695	0.701	0.669	0.675	0.655	**0.653**				
Renal dysfunction	0.382	0.379	0.355	0.350	0.354	0.354	**0.349**			
Proteasome inhibitor exposed	0.274	0.269	0.272	0.277	0.278	0.301	0.289	**0.268**		
ECOG performance status 2	0.170	0.170	0.163	0.129	0.130	0.129	0.121	0.121	**0.109**	
ISS stage III	0.017*	0.017*	0.017*	0.016*	0.015*	0.016*	0.016*	0.004*	0.004*	**0.001***

*: *Significant where p <= 0.05*

Progression-free survival

For the progression-free survival outcome, age > 65 years, proteasome inhibitor exposed and ASCT were all discounted due to the collinearity with other variables (Table 42).

Upon completion of the backwards stepwise elimination method (Table 43), ISS stage III (p = 0.002), primary refractory (p = 0.044) and ECOG performance status 2 (p = 0.002) were all retained within the final adjusted equation.

Table 42: Elimination of variables due to collinearity for progression-free survival in the 1 prior therapy population

Variable 1		Variable 2	
Name	**p-value**	**Name**	**p-value**
Age > 65 years	**0.709**	ASCT undertaken	**0.024***
Proteasome inhibitor exposed	**0.668**	Immunomodulation agent exposed	**0.445**
ECOG performance status 2	**0.001***	ASCT undertaken	**0.224**
*: *Significant where p <= 0.05*			

Table 43: Elimination of variables based on backwards stepwise elimination method due to lowest significance for progression-free survival in the 1 prior therapy sub-population

Name	Iteration 1	Iteration 2	Iteration 3	Iteration 4	Iteration 5	Iteration 6	Iteration 7	Iteration 8
Relapsed and refractory	**0.995**							
Immunomodulation agent exposed	0.685	**0.718**						
Light chain myeloma	0.533	0.508	**0.478**					
Asian	0.359	0.341	0.355	**0.366**				
Renal dysfunction	0.369	0.359	0.338	0.285	**0.308**			
High risk cytogenetics	0.214	0.209	0.219	0.192	0.197	**0.201**		
History of bone lesions	0.190	0.199	0.200	0.170	0.139	0.132	**0.151**	
ISS stage III	0.023*	0.023*	0.021*	0.022*	0.017*	0.005*	0.003*	**0.002***
Primary refractory	0.049*	0.050*	0.049*	0.050*	0.050*	0.054	0.047*	**0.044***
ECOG performance status 2	0.045*	0.045*	0.045*	0.046*	0.047*	0.036*	0.017*	**0.022***

*: *Significant where p <= 0.05*

Time on treatment

For the progression-free survival outcome, age > 65 years, immunomodulation agent exposed and ASCT were all discounted due to the collinearity with other variables (Table 44)

Upon completion of the backwards stepwise elimination method (Table 45) ISS stage III (p = 0.001), was the only covariate retained within the final adjusted equation.

Table 44: Elimination of variables due to collinearity for time on treatment in the 1 prior therapy population

Variable 1		Variable 2	
Name	**p-value**	**Name**	**p-value**
Age > 65 years	**0.469**	ASCT undertaken	**0.153**
Proteasome inhibitor exposed	**0.865**	Immunomodulation agent exposed	**0.992**
ECOG performance status 2	**0.007***	ASCT undertaken	**0.153**
*: *Significant where p <= 0.05*			

Table 45: Elimination of variables based on backwards stepwise elimination method due to lowest significance for time on treatment in the 1 prior therapy sub-population

Name	Iteration 1	Iteration 2	Iteration 3	Iteration 4	Iteration 5	Iteration 6	Iteration 7	Iteration 8	Iteration 9	Iteration 10
Relapsed and refractory	**0.994**									
Proteasome inhibitor exposed	0.827	**0.801**								
History of bone lesions	0.816	0.796	**0.799**							
Primary refractory	0.608	0.612	0.633	**0.638**						
High risk cytogenetics	0.630	0.618	0.627	0.618	**0.597**					
Renal dysfunction	0.526	0.517	0.514	0.517	0.526	**0.530**				
Light chain myeloma	0.356	0.339	0.347	0.360	0.358	0.342	**0.287**			
Asian	0.216	0.199	0.199	0.205	0.205	0.209	0.215	**0.223**		
ECOG performance status 2	0.080	0.080	0.077	0.078	0.078	0.063	0.062	0.060	**0.067**	
ISS stage III	0.020*	0.020*	0.020*	0.020*	0.022*	0.019*	0.007*	0.006*	0.004*	**0.001***

*: *Significant where p <= 0.05*

i. 2+ prior therapies analyses and recursively worked through to arrive at the final 2+ prior therapies models.

Response:

A correlation matrix for this sub-population outlined evidence of co-linearity of the following pairs of variables:

- Age > 65 years and ASCT undertaken
- Age > 65 years and Renal dysfunction
- ASCT undertaken and Renal dysfunction

Overall survival

For the progression-free survival outcome, ASCT undertaken and renal dysfunction were both discounted due to the collinearity with other variables (Table 46).

Upon completion of the backwards stepwise elimination method (Table 47), age > 65 years (p = 0.012) was the only covariate retained within the final adjusted equation.

Table 46: Elimination of variables due to collinearity for overall survival in the 2+ prior therapies population

Variable 1		Variable 2	
Name	**p-value**	**Name**	**p-value**
Age > 65 years	**0.012***	ASCT undertaken	**0.367**
Age > 65 years	**0.012***	Renal dysfunction	**0.565**
ASCT undertaken	**0.367**	Renal dysfunction	**0.565**
*: *Significant where p <= 0.05*			

Table 47: Elimination of variables based on backwards stepwise elimination method due to lowest significance for overall survival in the 2+ prior therapies population

Name	Iteration 1	Iteration 2	Iteration 3	Iteration 4	Iteration 5	Iteration 6	Iteration 7	Iteration 8	Iteration 9	Iteration 10	Iteration 11
Asian	**0.997**										
Immunomodulation agent exposed	0.442	**0.664**									
Primary refractory	0.673	0.656	**0.647**								
High risk cytogenetics	0.472	0.662	0.643	**0.615**							
ECOG performance status 2	0.570	0.461	0.445	0.469	**0.479**						
Proteasome inhibitor exposed	0.397	0.331	0.290	0.273	0.247	**0.196**					
History of bone lesions	0.175	0.162	0.150	0.154	0.166	0.171	**0.156**				
Light chain myeloma	0.126	0.183	0.189	0.184	0.197	0.132	0.136	**0.119**			
ISS stage III	0.061	0.054	0.046*	0.049*	0.051	0.062	0.063	0.071	**0.108**		
Relapsed and refractory	0.136	0.165	0.150	0.133	0.142	0.119	0.101	0.090	0.089	**0.109**	
Age > 65 years	0.016*	0.017*	0.019*	0.019*	0.020*	0.009*	0.009*	0.008*	0.008*	0.008*	**0.012***

*: *Significant where p <= 0.05*

Progression-free survival

For the progression-free survival outcome, ASCT undertaken and renal dysfunction were both discounted due to the collinearity with other variables (Table 48).

Upon completion of the backwards stepwise elimination method (Table 49), light chain myeloma (p = 0.017) was the only covariate retained within the final adjusted equation.

Table 48: Elimination of variables due to collinearity for progression-free survival in the 2+ prior therapies population

Variable 1		Variable 2	
Name	**p-value**	**Name**	**p-value**
Age > 65 years	**0.292**	ASCT undertaken	**0.501**
Age > 65 years	**0.292**	Renal dysfunction	**0.837**
ASCT undertaken	**0.501**	Renal dysfunction	**0.837**
*: *Significant where p <= 0.05*			

Table 49: Elimination of variables based on backwards stepwise elimination method due to lowest significance for progression-free survival in the 2+ prior therapies population

Name	Iteration 1	Iteration 2	Iteration 3	Iteration 4	Iteration 5	Iteration 6	Iteration 7	Iteration 8	Iteration 9	Iteration 10	Iteration 11
History of bone lesions	**0.981**										
ECOG performance status 2	0.871	**0.869**									
ISS stage III	0.730	0.730	**0.727**								
Immunomodulation agent exposed	0.735	0.733	0.708	**0.731**							
Asian	0.628	0.628	0.640	0.633	**0.589**						
High risk cytogenetics	0.375	0.373	0.572	0.581	0.581	**0.620**					
Relapsed and refractory	0.559	0.559	0.515	0.514	0.521	0.546	**0.562**				
Age > 65 years	0.411	0.411	0.394	0.403	0.406	0.406	0.412	**0.402**			
Primary refractory	0.392	0.392	0.382	0.384	0.388	0.382	0.364	0.367	**0.358**		
Proteasome inhibitor exposed	0.243	0.243	0.221	0.228	0.245	0.239	0.204	0.175	0.177	**0.151**	
Light chain myeloma	0.024*	0.0248	0.017*	0.018*	0.018*	0.019*	0.021*	0.023*	0.020*	0.017*	**0.017***

*: *Significant where p <= 0.05*

Time on treatment

For the time on treatment outcome, ASCT undertaken and age > 65 years were both discounted due to the collinearity with other variables (Table 50).

Upon completion of the backwards stepwise elimination method (Table 51), light chain myeloma (p = 0.010) and renal dysfunction (p = 0.034) were the only covariates retained within the final adjusted equation.

Table 50: Elimination of variables due to collinearity for time on treatment in the 2+ prior therapies population

Variable 1		Variable 2	
Name	**p-value**	**Name**	**p-value**
Age > 65 years	**0.394**	ASCT undertaken	**0.613**
Age > 65 years	**0.394**	Renal dysfunction	**0.016***
ASCT undertaken	**0.613**	Renal dysfunction	**0.016***
*: *Significant where p <= 0.05*			

Table 51: Elimination of variables based on backwards stepwise elimination method due to lowest significance for time on treatment in the 2+ prior therapies population

Name	Iteration 1	Iteration 2	Iteration 3	Iteration 4	Iteration 5	Iteration 6	Iteration 7	Iteration 8	Iteration 9	Iteration 10
Proteasome inhibitor exposed	**0.761**									
Primary refractory	0.715	**0.698**								
Asian	0.695	0.680	**0.675**							
History of bone lesions	0.442	0.448	0.447	**0.445**						
Immunomodulation agent exposed	0.397	0.420	0.436	0.390	**0.363**					
High risk cytogenetics	0.186	0.171	0.153	0.161	0.135	**0.148**				
ECOG performance status 2	0.125	0.121	0.125	0.118	0.139	0.144	**0.146**			
ISS stage III	0.127	0.131	0.123	0.118	0.110	0.117	0.134	**0.152**		
Relapsed and refractory	0.096	0.086	0.083	0.088	0.101	0.124	0.135	0.129	**0.125**	
Renal dysfunction	0.083	0.079	0.087	0.092	0.113	0.115	0.102	0.083	0.024*	**0.034***
Light chain myeloma	0.010*	0.010*	0.009*	0.009*	0.008*	0.008*	0.011*	0.006*	0.010*	**0.010***

*: *Significant where p <= 0.05*

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b. What significance levels were used in the recursive analyses for the elimination of variables?

Response:

A significance value of p <= 0.05 (95%) was used within the elimination of covariates

c. Please supply the equivalent of appendix 11 for the unadjusted models.

Response:

Kaplan-Meier plots, log cumulative hazard plot, Schoenfeld residuals plot and QQ plot presented in Appendix 11 were based on raw ***unadjusted*** data. As the base case analysis used the covariate-adjusted curves, the AIC and BIC statistics in Appendix 11 presented the goodness of fit estimates for the ***adjusted*** curves.

The AIC and BIC statistics for the ***unadjusted*** curves are shown for PFS, OS and ToT below. As well as a comparison of the ***unadjusted*** parametric curve fits with the ***unadjusted*** Kaplan-Meier data.

Progression-free survival

Table 52 presents the AIC and BIC statistics for **the *unadjusted*** parametric curve fits to the PFS Kaplan-Meier data, for the 1 prior line and 2+ prior lines populations, respectively. Figure 75 and Figure 76 visually depict the ***unadjusted*** fitted parametric curves to the ***unadjusted*** OS Kaplan-Meier data for the 1 prior line and 2+ prior lines population, respectively.

Table 52: AIC and BIC goodness of fit statistics for PFS (unadjusted) in the 1 prior and 2+ prior therapies populations

	1 prior therapy		2+ prior therapies	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	1442.413	1450.517	988.943	996.331
Weibull	1435.726	1447.882	985.297	996.378
Gompertz	1441.027	1453.183	989.565	1000.646
Lognormal	1431.727	1443.884	979.769	990.850
Log logistic	1433.619	1445.775	983.115	994.196
Generalised gamma	1433.377	1449.586	981.751	996.526

Key: AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression free survival

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Figure 75: Comparison of fitted PFS (unadjusted) curves with unadjusted KM curves for LEN+DEX in the 1 prior therapy population

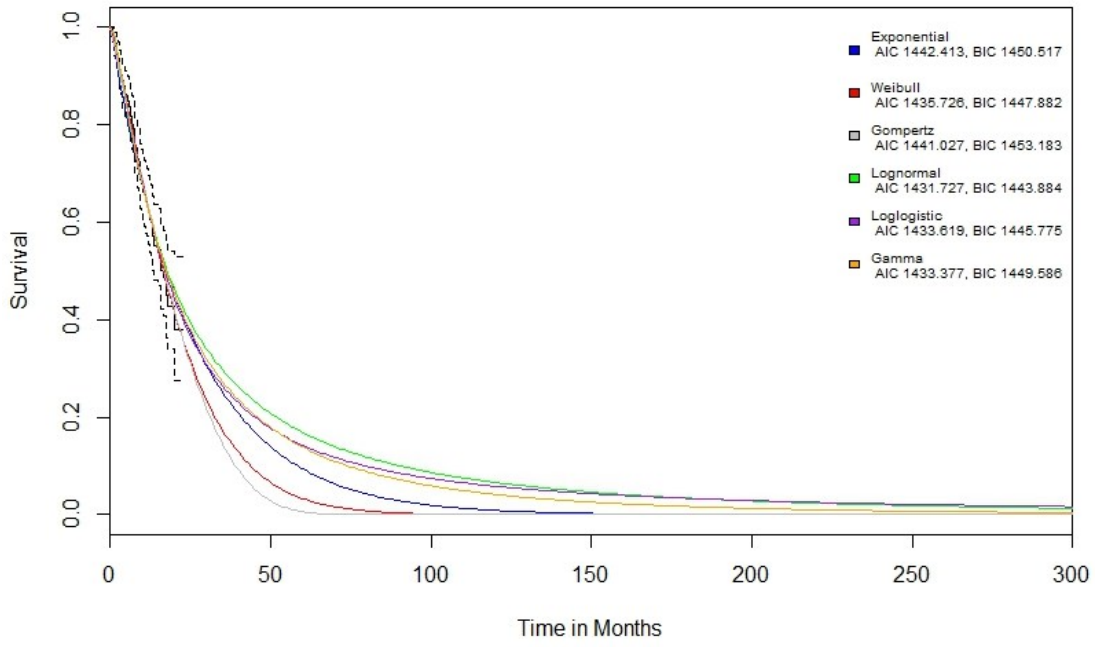
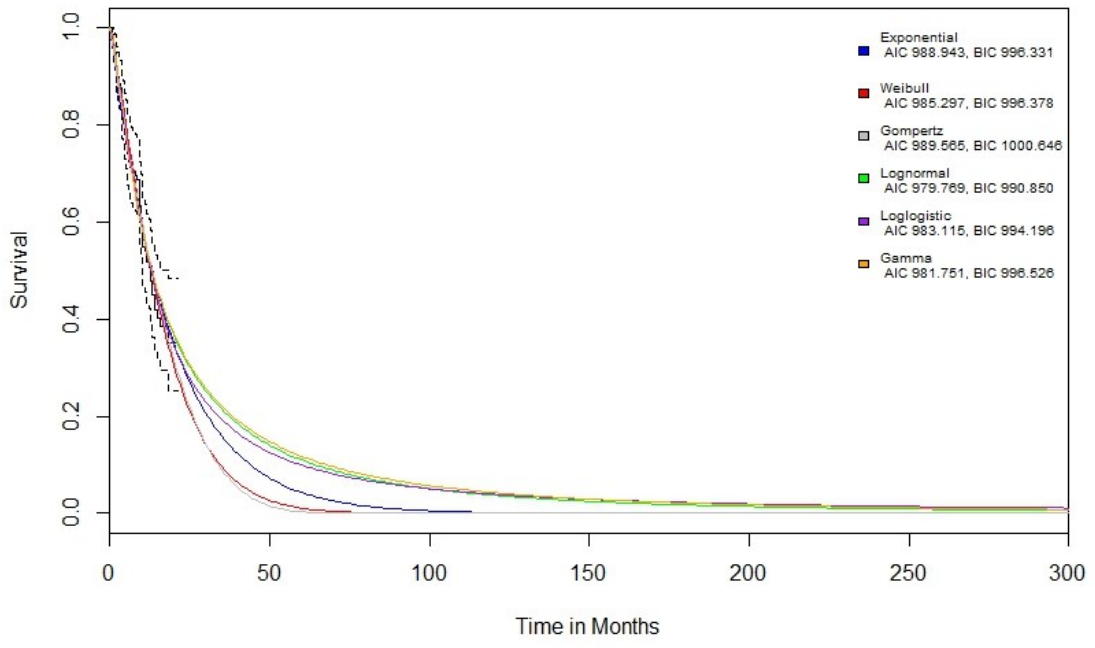


Figure 76: Comparison of fitted PFS (unadjusted) curves with unadjusted KM curves for LEN+DEX in the 2+ prior therapies population



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Overall survival

Table 53 presents the AIC and BIC statistics for the *unadjusted* parametric curve fits to the OS Kaplan-Meier data, for the 1 prior line and 2+ prior lines populations, respectively. and Figure 78 visually depict the *unadjusted* fitted parametric curves to the *unadjusted* PFS Kaplan-Meier data for the 1 prior line and 2+ prior lines population, respectively.

Table 53: AIC and BIC goodness of fit statistics for PFS (unadjusted) in the 1 prior and 2+ prior therapies population

	1 prior line		2+ prior lines	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential (>5 months)	495.537	503.550	N/A	N/A
Exponential	647.775	655.879	537.316	544.704
Weibull	646.733	658.889	535.863	546.944
Gompertz	648.474	660.630	537.886	548.968
Lognormal	645.737	657.894	534.730	545.812
Log logistic	646.345	658.502	535.517	546.599
Generalised gamma	647.702	663.911	536.721	551.495

Key: AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression free survival

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Figure 77: Comparison of fitted OS (unadjusted) curves with unadjusted KM curves for LEN+DEX in the 1 prior therapy population

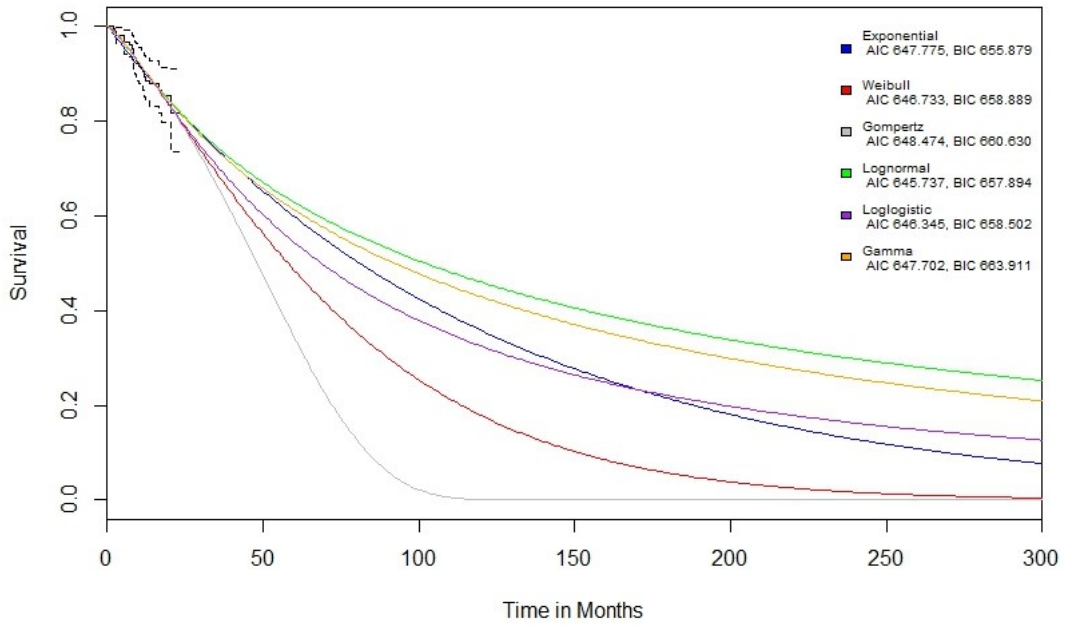
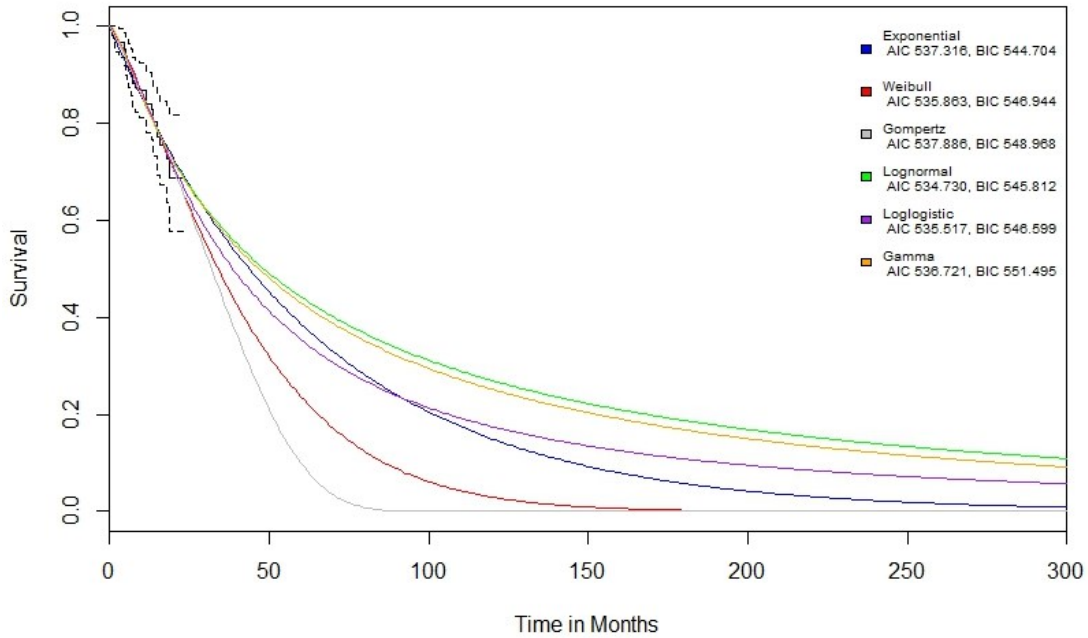


Figure 78: Comparison of fitted OS (unadjusted) curves with unadjusted KM curves for LEN+DEX in the 2+ prior therapies populations



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Time on treatment

Table 54 presents the AIC and BIC statistics for **the *unadjusted*** parametric curve fits to the ToT Kaplan-Meier data, for the 1 prior line and 2+ prior lines populations, respectively.

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Figure 79 and Figure 80 visually depict the ***unadjusted*** fitted parametric curves to the ***unadjusted*** ToT Kaplan-Meier data for the 1 prior line and 2+ prior lines population, respectively.

Table 54: AIC and BIC goodness of fit statistics for TOT (unadjusted) in the 1 prior and 2+ prior 2+ prior therapies populations

	1 prior line		2+ prior lines	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	2228.316	2236.411	1542.366	1549.753
Weibull	2225.069	2237.211	1544.045	1555.126
Gompertz	2226.413	2238.555	1543.660	1554.742
Lognormal	2242.226	2254.368	1547.471	1558.552
Log logistic	2227.167	2239.310	1543.554	1554.635
Generalised gamma	2227.046	2243.236	1545.331	1560.106

Key: AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; TOT, time on treatment

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Figure 79: Comparison of fitted TOT (unadjusted) curves with unadjusted KM curves for LEN+DEX in the 1 prior therapy population

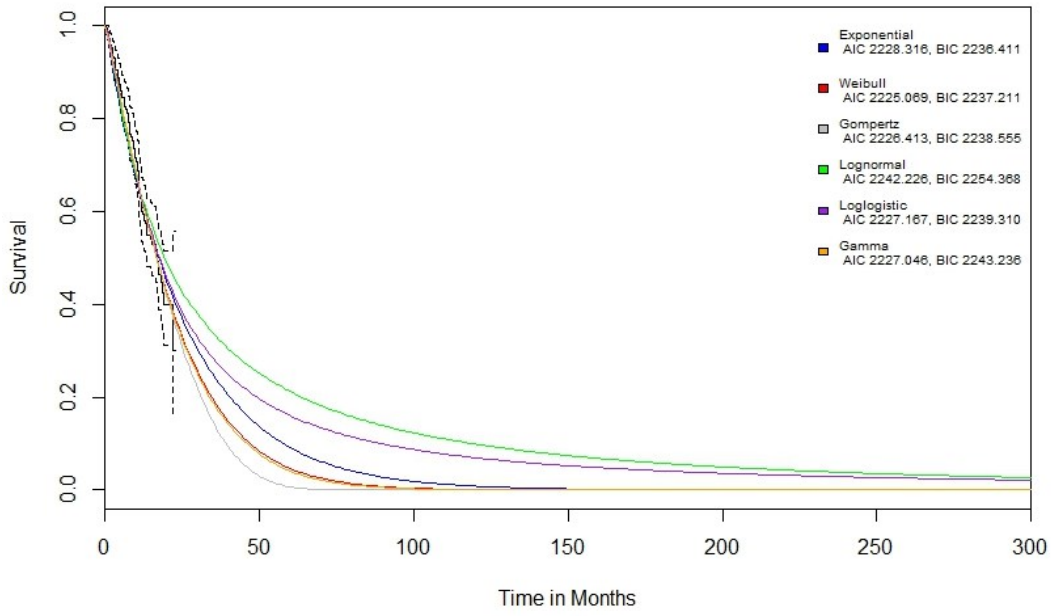
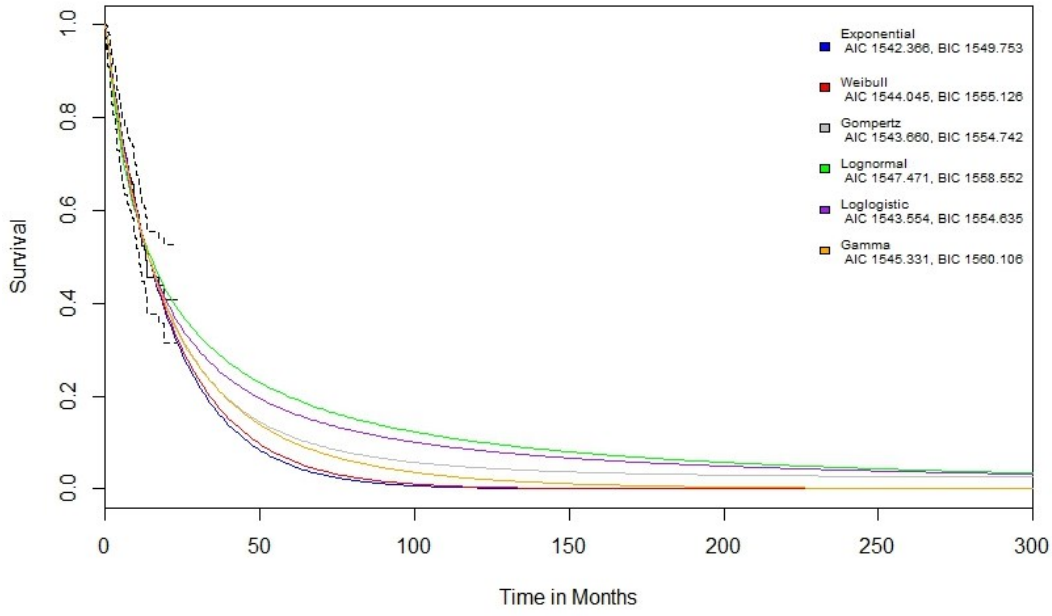


Figure 80: Comparison of fitted TOT (unadjusted) curves with unadjusted KM curves for LEN+DEX in the 2+ prior therapies population



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d. If time allows, please explore the impact on the base case ICERs of applying the unadjusted OS, PFS and ToT curves.

Response:

In the base case, data are adjusted for covariate imbalances arising between the IXA+LEN+DEX and LEN+DEX arms of the TMM1 clinical trial data. Log-rank tests found significant differences in clinical endpoints associated with several patient risk factors, including: ECOG performance score, ISS stage, light chain myeloma, age and renal dysfunction. Therefore, to allow for an unbiased comparison, it was considered appropriate to adjust for these differences within the economic model.

Results are presented in Table 55 showing the ICERs in the 1 prior line population and 2+ prior line population using covariate adjusted and unadjusted estimates without PAS applied. Table 43 presents the results with PAS applied. In line with the base case of the submission, all data are sourced from the 1st interim analysis of the TMM1 clinical trial. Please note these results take into account the updates to the model discussed in B3 and B13. The ICERs are slightly higher in the 2+ prior therapy analysis with the unadjusted models, but as stated above it is appropriate to consider the adjusted model results for the base case in order to reduce the likelihood of bias in the covariates impacting on the results.

Table 55: Comparison of results using covariate adjusted and unadjusted estimates, without PAS applied

	ICER: 1 prior line population, IXA+LEN+DEX vs. BORT+DEX	ICER: 2+ prior lines population, IXA+LEN+DEX vs. LEN+DEX
Covariate adjusted (base case)	[redacted]	[redacted]
Unadjusted	[redacted]	[redacted]

Key: BORT, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; PAS, patient access scheme

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Table 56: Comparison of results using covariate adjusted and unadjusted estimates, with PAS applied

	ICER: 1 prior line population, IXA+LEN+DEX vs. BORT+DEX	ICER: 2+ prior lines population, IXA+LEN+DEX vs. LEN+DEX
Covariate adjusted (base case)	£73,333	£135,237
Unadjusted	£72,726	£146,332

Key: BORT, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; PAS, patient access scheme

B12. ***PRIORITY QUESTION: The Cap_ToT_to_PFS curve option in the Main_Settings worksheet appears to have been hard coded through data validation rules to be set to "Off".***

a. Does this imply that treatment is not capped by PFS but is capped by OS, or something else?

Response:

In the base case, ToT is not capped by PFS. Although, the literature and clinician feedback indicated that treatment with LEN+DEX should not exceed progression in a UK setting, it was considered appropriate in the base case to maintain consistency with the OS and PFS estimates and extrapolate the trial data based on fitting parametric curves to the ToT data (and not capping based on PFS).

To maintain internal validity, the potential for the ToT curve to cross the OS curve was curtailed by applying the minimum of ToT and OS if ToT was greater than OS at a given time point. This was apparent in only early model cycles and adjusted to attain clinical validity. Please see Section 5.3.3 in the original submission for more detail.

A scenario analysis considered capping ToT at progression (using PFS) for both LEN+DEX and IXA+LEN+DEX arms; these demonstrate a negligible impact on results for IXA+LEN+DEX compared with BORT+DEX in the 1 prior line population and a marginal difference in results for IXA+LEN+DEX compared with LEN+DEX in the 2+ prior lines population. The results of these scenario analyses are shown in Section 5.8 of the original submission for the 1 prior line and 2+ prior lines populations. A summary of the impact on the ICER is shown below in Table 57 without PAS. Table 58 presents the results with PAS applied. Please note these results include the amendments to the model discussed in B3 and B13.

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Table 57: Comparison of results when ToT is capped by PFS, without a PAS applied

	ICER: 1 prior therapy population, IXA+LEN+DEX vs. BORT+DEX	ICER: 2+ prior therapies population, IXA+LEN+DEX vs. LEN+DEX
ToT not capped by PFS	[redacted]	[redacted]
ToT capped by PFS	[redacted]	[redacted]

Key: BORT, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; PAS, patient access scheme; PFS, progression free survival; ToT, time on treatment

Table 58: Comparison of results when ToT is capped by PFS, with a PAS applied

	ICER: 1 prior therapy population, IXA+LEN+DEX vs. BORT+DEX	ICER: 2+ prior therapies population, IXA+LEN+DEX vs. LEN+DEX
ToT not capped by PFS	£73,333	£135,237
ToT capped by PFS	£73,333	£136,511

Key: BORT, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; PAS, patient access scheme; PFS, progression free survival; ToT, time on treatment

b. What is the rationale behind the default "Off" value?

Response:

Please see above rationale under a.

c. What is the impact of removing the data validation rules for cell E26 in the Main_Settings worksheet setting this cell equal to "On"?

Response:

Please see above results. The updated model includes the functionality to select "On" and "Off" for this functionality.

Please see above results under a.

d. What is the sensitivity of the base case ICERs to this variable?

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Response:

This has been updated within the model. Please note this has no impact on the base case results presented in the submission. All results presented in this document use the model updated for B3 and B13 above.

B13. ***The Comp worksheet columns AZ and BA suggests that the OSModel=4 corresponds to the LogNormal, while OSModel=5 corresponds to the LogLogistic. But the treatment coefficient of AV9 suggests the reverse, and appears to be incorrect. Please clarify.***

Response:

This has been updated within the model. Please note this has no impact on the base case results presented in the submission. All results presented in this document use the model updated for B3 and B13.

B14. ***Page 184 refers to Gelber et al. (1993) when describing OS extrapolation beyond 5 months for the 1 prior therapy population. Please explain in detail how this was undertaken.***

Response:

Parametric fitting of survival data was carried out for patients with recorded events or censors beyond the 5-month time point, with this time point acting as the index time for this subset of patients for the parametric functions (i.e. such that parametric functions would be operating on a time variable of “0” at the specified time point).

Within the model, the Kaplan-Meier estimator for all data was used up to this time point. Beyond this time until the time horizon, the parametric survival function was used with no time offset required due to the constant hazard assumption, and the survival profile being scaled by the proportion of survivors indicated by the Kaplan-Meier estimate at the time point.

B15. ***Figure 37: Please clarify how the red curve for BORT-DEX was derived. It appears that a hazard ratio of 1.06 was applied; according to Table 65 this is for the comparison BORT-DEX versus LEN-DEX. Please clarify what this hazard ratio was applied to and what the result represents.***

Response:

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The NMA, described in Section 4.10 of the submission, estimated the hazard ratio for PFS [HR: 1.06, 95% CI: 0.61 – 1.85] for BORT+DEX relative to LEN+DEX. This is the hazard ratio applied within the model.

The Kaplan-Meier curves, the LCHPs, the Schoenfeld residual plots, the QQ plots and the AIC and BIC estimates indicate that the generalised gamma curve provides the most appropriate choice of model to the LEN+DEX PFS data for the 1 prior therapy population (please see Section 5.3.3 for more detail). The generalised gamma curve was therefore selected as the base case parametric curve and fitted to the LEN+DEX data for the 1 prior therapy population. To estimate the PFS associated with BORT+DEX, the hazard ratio for BORT+DEX relative to LEN+DEX was applied to this curve. The resulting estimated curve for PFS associated with BORT+DEX is presented as the red curve in Figure 37 from the original submission dossier.

The results show that, relative to LEN+DEX, BORT+DEX has lower estimated PFS. The extent of the relative reduction places the PFS associated with BORT+DEX below that of IXA+LEN+DEX

B16. ***Appendix 11 Figure 20: Please explain the difference between the fitted OS curves and unadjusted Kaplan-Meier curves; this discrepancy appears too large to be explained by covariate imbalances and looks implausible.***

Response:

Having investigated further, an issue was observed in the code used to generate the plots fitting the six adjusted parametric curves overlaid on the Kaplan-Meier curves. Please note that this issue was confined only to this type of plot (as shown in Appendix 11 and Figure 20 in the submission) and only on the adjusted form of these plots. In addition, please note that the issue was purely in the plot generation and has no impact on the underlying parametric equations in the model. The revised plots are outlined in the figures provided below. For comparative purposes, the revised plot outlined in the question (Appendix 11, Figure 20) can be seen in Figure 84 below.

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Figure 81: Comparison of fitted OS (adjusted) curves with unadjusted KM curves for LEN+DEX in the 1 prior therapy population

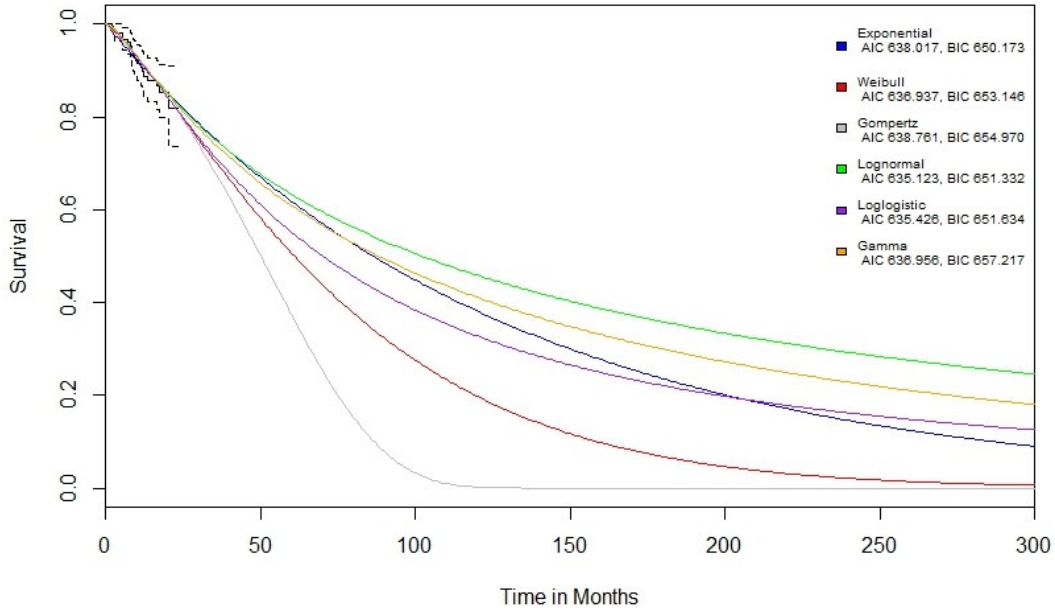

Figure 82: Comparison of fitted PFS (adjusted) curves with unadjusted KM curves for LEN+DEX in the 1 prior therapy population

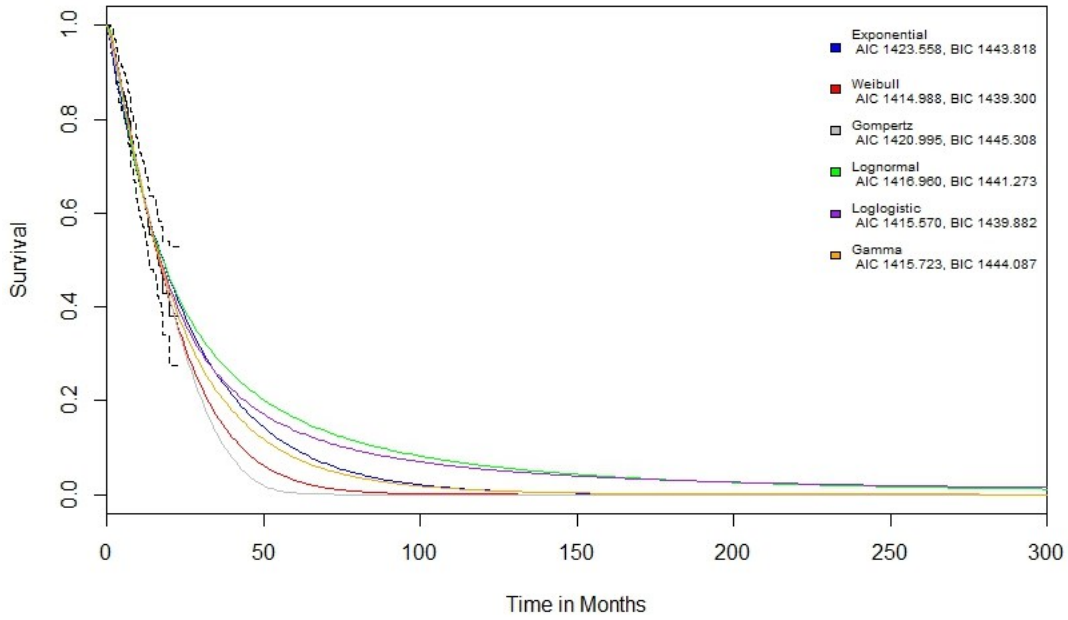

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Figure 83: Comparison of fitted TOT (adjusted) curves with unadjusted KM curves for LEN+DEX in the 1 prior therapy population

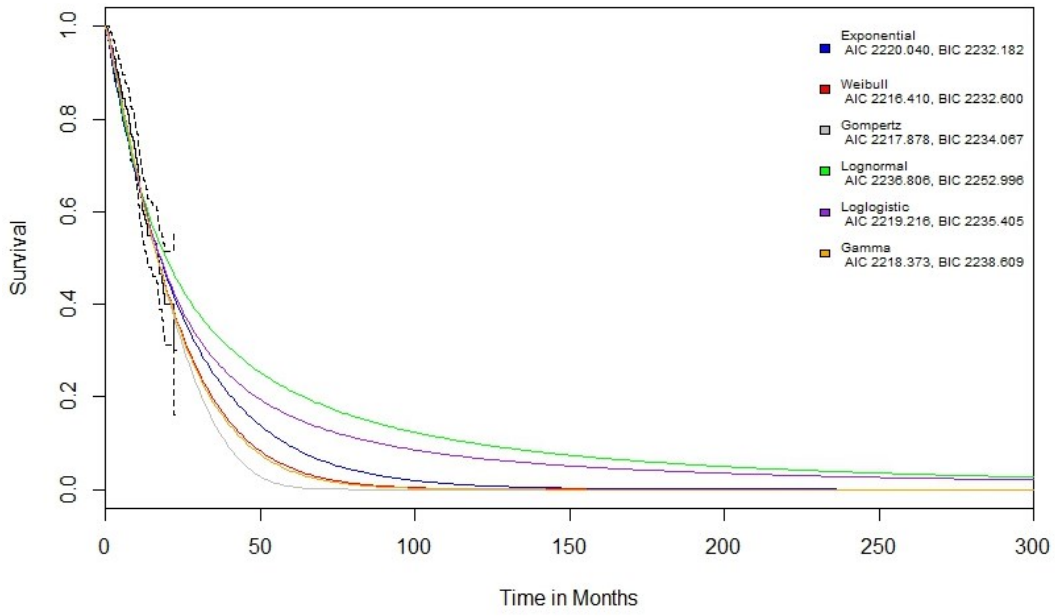

Figure 84: Comparison of fitted OS (adjusted) curves with unadjusted KM curves for LEN+DEX in the 2+ prior therapies population

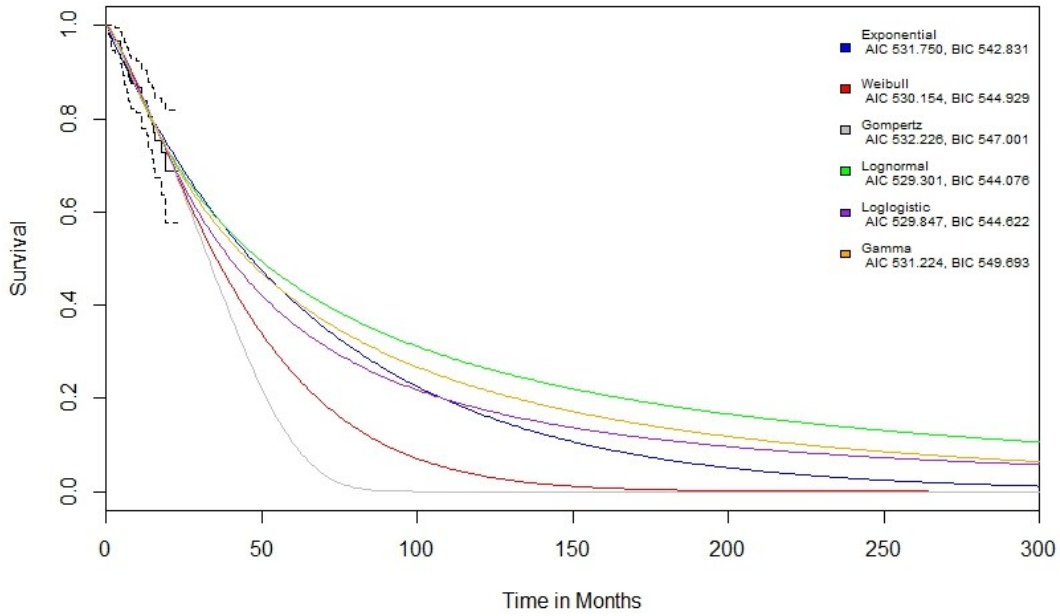

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Figure 85: Comparison of fitted PFS (adjusted) curves with unadjusted KM curves for LEN+DEX in the 2+ prior therapies population

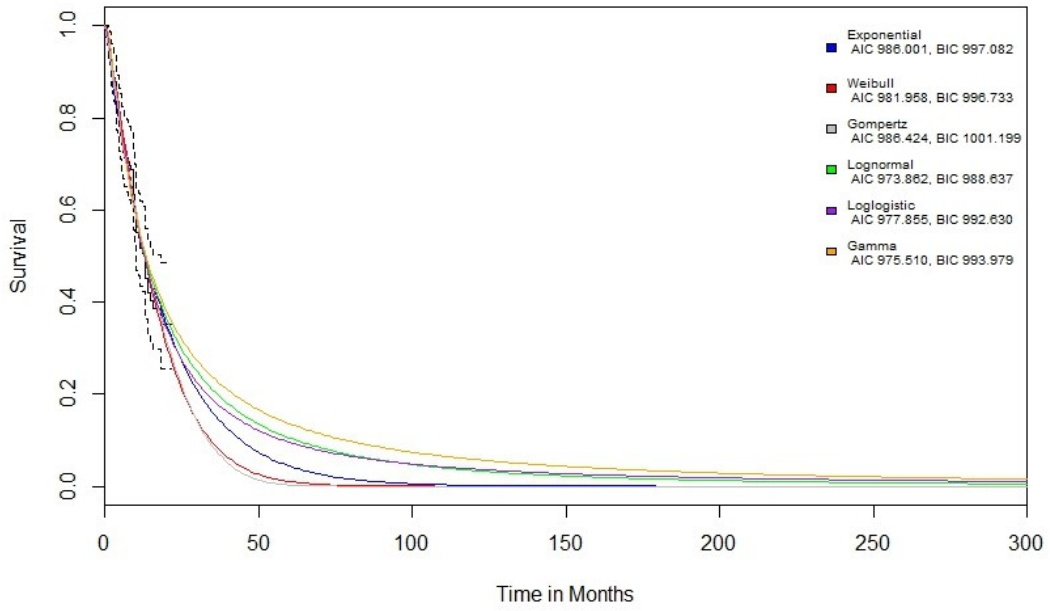
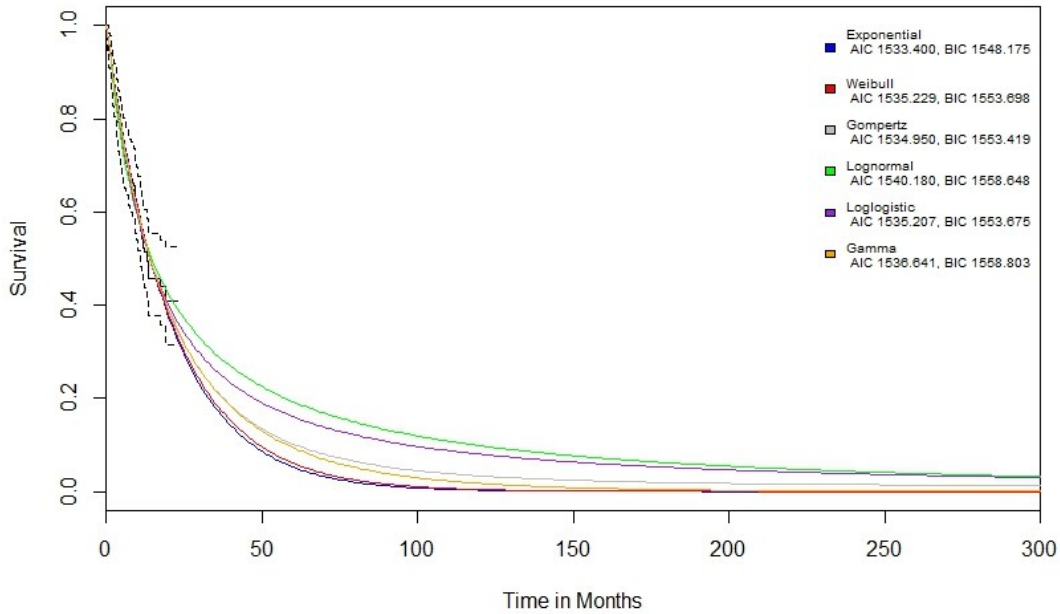


Figure 86: Comparison of fitted TOT (adjusted) curves with unadjusted KM curves for LEN+DEX in the 2+ prior therapies population



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B17. ***Page 90 (below figure 13) reports the availability of a non-inferential HR for PFS at a median follow-up of 23 months. Please provide the results of sensitivity analyses for both populations in the cost-effectiveness analyses (1 prior and 2+ prior therapies) using the HR for PFS from the second interim analysis.***

Response:

A non-inferential PFS analysis was conducted at a median follow up of 23 months with 372 PFS events. The HR of PFS was 0.98 (95% confidence interval [0.76, 1.27]) and 0.63 (95% confidence interval [0.46, 0.87]) for IXA+LEN+DEX relative to LEN+DEX for the 1 prior line and 2+ prior lines population. The impact on the ICER of using these hazard ratios from the analysis of the 2nd interim data cut, alongside the OS, ToT and response data from the 1st interim data-cut, is shown in Table 59 without PAS applied. Table 60 shows the comparison with PAS applied.

The hazard ratios for PFS for IXA+LEN+DEX relative to LEN+DEX obtained from the 2nd interim data-cut of the TMM1 clinical trial cause a minimal impact on ICERs. OS was shown to be the main driver of results in the model in the one-way sensitivity analyses (see Section 5.8 in the original submission dossier). The 2nd interim analysis provides us with further follow-up data for OS, however, these data are still relatively immature and do not reflect the full OS benefit to be expected given the PFS benefit (see Section 5.3.5 of the original submission). The next OS data cut is due for Summer 2017 (as the analysis is event driven the exact timing cannot be confirmed), with final OS analysis planned for Q3 2019 and is expected to provide more informative evidence on relative OS outcomes.

Table 59: Comparison of results when hazard ratios for IXA+LEN+DEX relative to LEN+DEX are obtained from the 2nd interim analysis, without a PAS applied

	ICER: 1 prior therapy population, IXA+LEN+DEX vs. BORT+DEX	ICER: 2+ prior therapies population, IXA+LEN+DEX vs. LEN+DEX
Base case, all data from the 1st interim data-cut	[redacted]	[redacted]
Hazard ratios from the 2nd interim analysis for PFS. OS, ToT and response data from the 1st interim data-cut.	[redacted]	[redacted]

Key: BORT, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; PAS, patient access scheme; PFS, progression free survival; ToT, time on treatment

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Table 60: Comparison of results when hazard ratios for IXA+LEN+DEX relative to LEN+DEX are obtained from the 2nd interim analysis, with a PAS applied

	ICER: 1 prior therapy population, IXA+LEN+DEX vs. BORT+DEX	ICER: 2+ prior therapies population, IXA+LEN+DEX vs. LEN+DEX
Base case, all data from the 1st interim data-cut	£73,333	£135,237
Hazard ratios from the 2nd interim analysis for PFS. OS, ToT and response data from the 1st interim data-cut.	£73,020	£135,768

Key: BORT, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; PAS, patient access scheme; PFS, progression free survival; ToT, time on treatment

B18. ***Figure 39: The BORT-DEX OS curve shown might be obtained by applying [a] the NMA HR for BORT-DEX compared with LEN-DEX (3.11, Table 65) to the OS model for LEN-DEX (not shown in Figure 39), or [b] by applying the NMA HR for BORT-DEX compared with IXA-LEN-DEX (1/0.31, Table 45 and section 1.3.5) to the model of OS for IXA-LEN-DEX shown in Figure 39.***

Please confirm which method was used and provide a rationale for this method. Please provide the results from the alternative methods.

Response:

In the base case, the hazard ratio for BORT+DEX relative to LEN+DEX was applied to the delayed exponential (Kaplan-Meier data used up to month 5 and exponential curve fit to the data from month 5) parametric curve fit to the LEN+DEX data for the 1 prior line population. Data sourced from the 1st interim analysis of the TMM1 data. Hence, approach [a] above was adopted.

This method was deemed most appropriate, as the delayed exponential parametric curve for LEN+DEX was fit as a single parametric model. Whereas, the parametric curves for IXA+LEN+DEX were calculated based on an estimated treatment effect relative to LEN+DEX. Separate independent parametric curves were not fit to the LEN+DEX and IXA+LEN+DEX data as the validity of the proportional hazards assumption supported fitting a Cox proportional hazards model to the data. Hence, we have not provided results from alternative methods as the Cox proportional hazards model was shown to provide a good fit to the data using standard goodness of fit techniques, including log cumulative hazard plots, Schoenfeld residuals and visual assessment.

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B19. ***Executable model: in the survival worksheets (life tables OS and PFS), the total number of patients is not equal to the total number of events and censorings. Please clarify.***

Using the data from these worksheets the ERG has not been able to reproduce the Kaplan-Meier and risk table plots shown in Appendix 11. Please confirm whether the plots in Appendix 11 have been derived using data shown in the model survival worksheets.

Response:

We have reviewed this and found that the total number of events and censors not equalling the number of patients was due to an oversight in how the statistical package (i.e. survfit in R) implemented weekly cycles. The events/censors that were omitted from the table were those that occurred in the final week only if incomplete. When generating the KM tables, these events/censors were omitted due to this final week being dropped due to the pre-defined weekly interval not being met.

We have addressed this and have incorporated the updated KM tables within the revised model, see "Ixazomib CEA Model – UK Adaptation (IA1) 02022017_updated.xlm".

The plots provided in Appendix 11 were generated from the same statistical package and reference object used to generate the raw Kaplan-Meier data. Visual comparisons have been made between the Appendix 11 plots and plots generated based on the KM data (survival curve) exclusively within Excel and no discrepancy has been found. The visual comparisons of the ***unadjusted*** Kaplan-Meier data between the statistical software and Microsoft Excel can be found below in to **Figure 87** Figure 92

Figure 87 Kaplan-Meier plots for unadjusted PFS – 1 prior therapy (IA1)

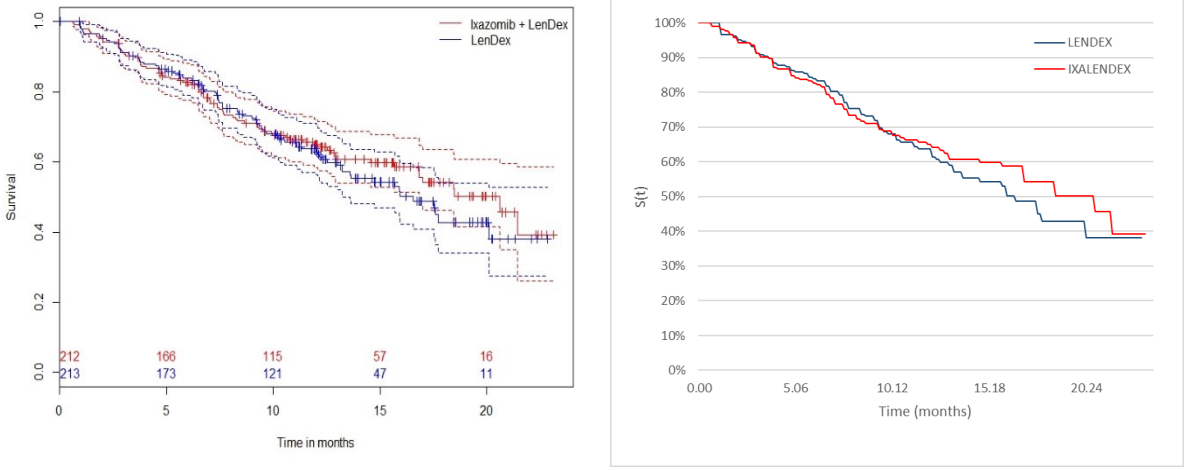

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Figure 88: Kaplan-Meier plots for unadjusted PFS – 2+ prior therapies (IA1)

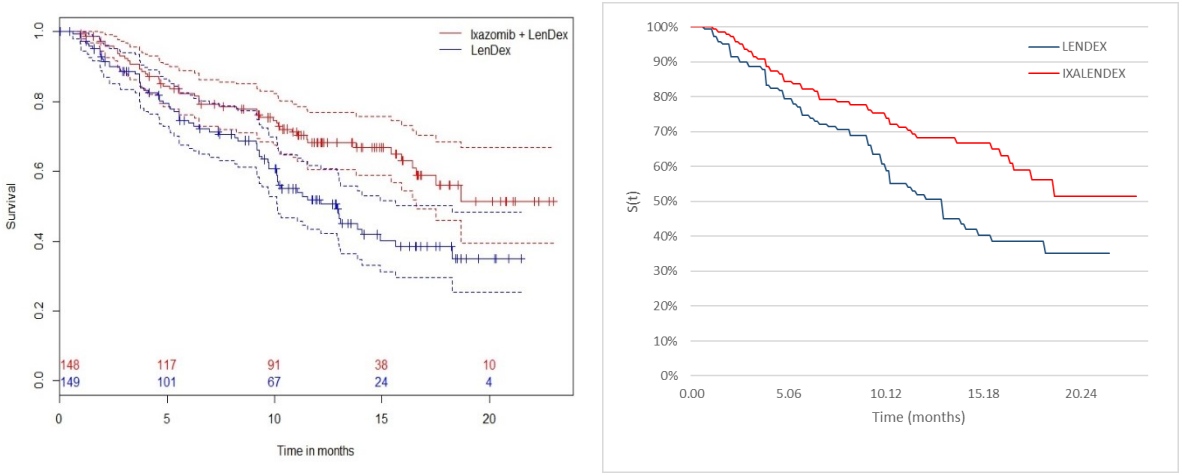

Figure 89: Kaplan-Meier plots for unadjusted OS – 1 prior therapies (IA1)

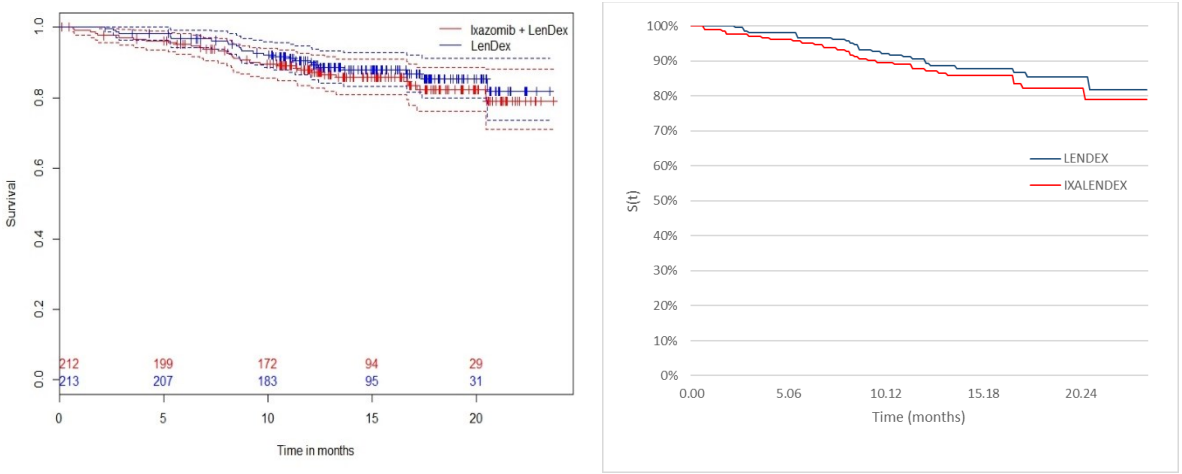

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Figure 90: Kaplan-Meier plots for unadjusted OS – 2+ prior therapies (IA1)

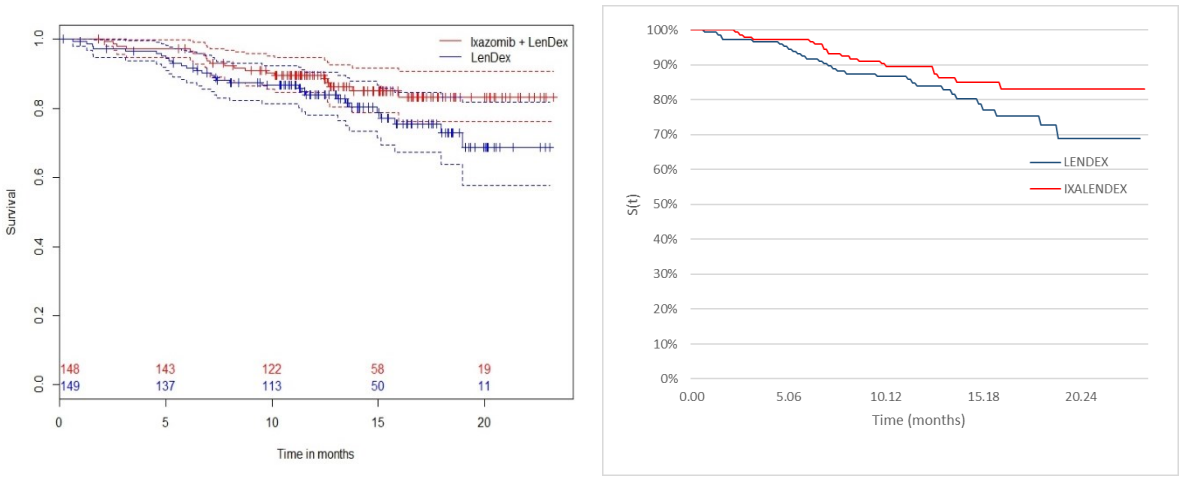

Figure 91: Kaplan-Meier plots for unadjusted TOT - 1 prior therapy (IA1)

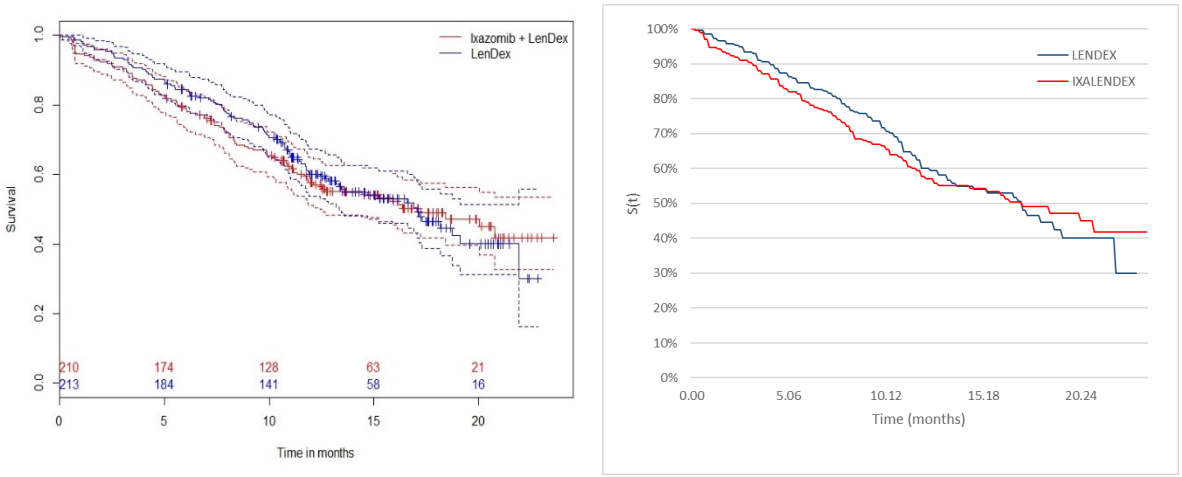

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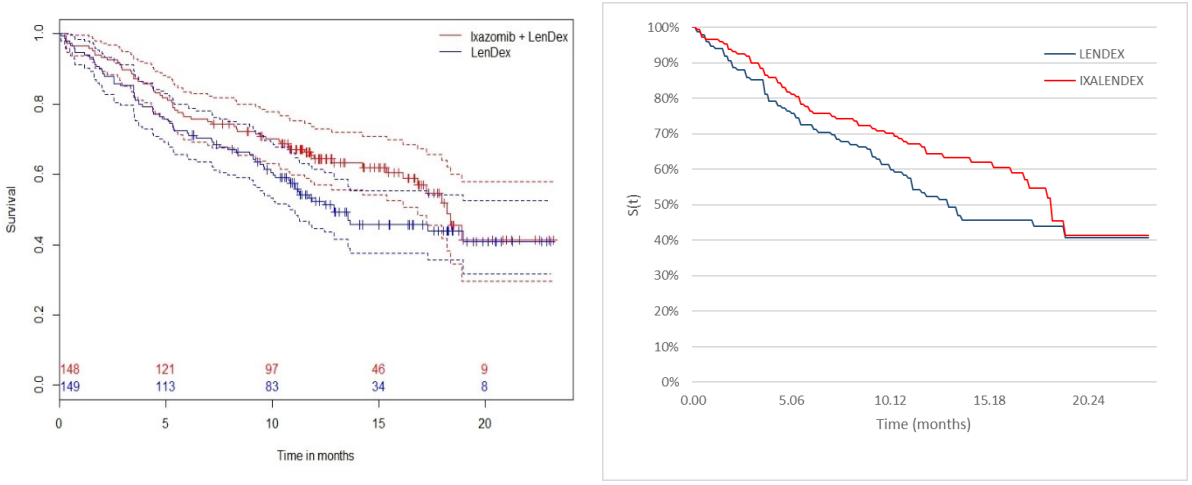
Figure 92: Kaplan-Meier plots for unadjusted TOT 2+ prior therapies (IA1)



B20. ***In the NEJM paper for TMM-1 the methods state ; "Patients were randomly assigned, in a 1:1 ratio, to receive…. in 28-day cycles", and "Assessments of the response to the study regimen were performed every cycle until disease progression." AND "All patients were followed for survival after disease progression (every 12 weeks until death or termination of the study)".***

However in the model worksheets for survival (e.g. OS, PFS) the events and censorings occur at weekly intervals rather than monthly (28 day) intervals. Timing of data collection is unclear, and it appears data has been aggregated to weekly intervals for purposes of the economic model. Please clarify.

Response:

The term cycle within the NEJM paper refers to treatment cycles whereas in the model cycles refer exclusively to one week. Within the survival analysis, a time variable (in weeks) was created based on the index date and the date of event/censor from the patient-level data of the TOURMALINE-MM1 trial. Therefore, although assessments were performed at 4 week/12 week intervals, the data used within the survival analysis were all aggregated to weekly intervals for the purposes of the model.

B21. ***Appendix 11: the horizontal axis of figures for "Log cumulative hazard plots" are labelled "ln(Time)". However, the the axis displays time, and this appears to be plotted on a logarithmic axis scale, which apperas to be log to the base 10 (rather than natural log base). Please clarify.***

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Response:

The x-axis label is incorrectly labelled as ln(time) and instead should be labelled as time. The x-axis is plotted on a natural logarithmic scale.

Health-related quality of life (HRQoL) analysis:

B22. ***PRIORITY QUESTION: Please clarify if people with an EQ-5D response who do not have PD, PR (not VGPR+) or SD are by definition in VGPR+. How was missing data handled in the HRQoL analysis, with particular reference to these variables? Please also clarify whether the response data relating to an EQ-5D response was measured at the same time as the EQ-5D, or within a 2 week window of it, or was the BoR***.

Response:

The HRQoL was based on patients best overall response (BOR) obtained during the study induction period and therefore wasn't necessarily the response observed at the time of the EQ-5D assessment.

Within the TMM1 data, a patient's BOR could be categorised as stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD) and progressed disease (PD). For the purposes of the HRQoL analysis, sCR, CR and VGPR were all re-coded as VGPR+ resulting in 4 categories (i.e. VGPR+, PR, SD, PD). Patients who progressed were re-categorised as PD from the time of progression.

Missing BOR which accounted for 45 of the 722 patients was not re-coded but regarded as missing for the purposes of fitting the generalised linear model (genmod in SAS) so that the respective EQ-5D data, hospitalisations and TRAE were still considered.

B23. ***Please provide the following EQ-5D data separately for when patients are reporting VGPR+, PR but not VGPR+ and SD (3 data subsets): the number of patients, number of EQ-5D responses among those patients and mean (s.d.) EQ-5D values among those patients (see table below). Provide data separately for the 1 prior therapy group and the 2+ prior therapies group, and separately by TMM-1 arm (ie 4 tables for each of the 3 data subsets). A patient may move between data subsets over time; e.g. be in SD at baseline, PR but not VGPR+ at week 4 and VGPR+ at week 8***.

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Response:
It was not possible to complete this analysis in the allocated time. The company is taking every effort to complete the requested analysis which may be submitted at a later date.

B24. ***Please provide the number of patients with progressive disease, number of EQ 5D responses among those patients and mean (s.d.) EQ-5D values among those patients (see table below). Provide data separately for the 1 prior group and the 2+ prior group, and separately by TMM-1 arm (ie 4 tablesPlease provide the number of patients with progressive disease, number of EQ-5D).***

Response:
It was not possible to complete this analysis in the allocated time. The company is taking every effort to complete the requested analysis which may be submitted at a later date.

B25. ***PRIORITY QUESTION: Please provide the data in the table below from the EQ-5D data set, split by 1 prior and 2+ prior subgroups and by TMM-1 arm (4 tables).***

Response:

Please refer to Table 61 for the information requested which outlines the number of EQ-5D assessments based on the outlined criteria. Table 62 which outlines the number of responses stratified by TRAE experienced at time of assessment has been provided for validation purposes.

Table 61: Number of EQ-5D assessments (total and with new primary malignancy) stratified by treatment arm, prior lines of therapy and BOR

Disease state	Number of responses, and responses with new prim. malig.	
	N EQ-5D responses	Of which resp. with new prim. malig.
Patients within the IXALENDEX arm with 1 prior line of therapy		
VGPR+	1377	0
PR	694	0
SD	174	0
PD	281	0

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Disease state	Number of responses, and responses with new prim. malig.	
	N EQ-5D responses	Of which resp. with new prim. malig.
Patients within the LENDEX arm with 1 prior line of therapy		
VGPR+	1291	0
PR	736	0
SD	236	0
PD	346	0
Patients within the IXALENDEX arm with 2+ prior lines of therapy		
VGPR+	1056	1
PR	457	0
SD	85	0
PD	146	1
Patients within the LENDEX arm with 2+ prior lines of therapy		
VGPR+	640	2
PR	521	0
SD	180	0
PD	263	0

Table 62: Number of EQ-5D assessments stratified by TRAE at time of assessment

TRAE	N EQ-5D responses
Anaemia	97
Cardiac failure	3
Diarrhoea	34

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TRAE	N EQ-5D responses
Fatigue	32
Infection	1
Nausea/Vomiting	2
Neuropathy peripheral	5
Neutropenia	159
New Primary Malignancy	4
No TRAE	8250
Pneumonia	15
Rash	15
Renal failure	11
Thrombocytopenia	26
Upper respiratory tract infection	2
VTE	22

B26. ***HRQoL was considered to be affected by a treatment-related adverse event (TRAE) only if the utility assessment occurred up to two weeks before or up to 2 weeks after the date of the adverse event.***

a) Did the hospitalisation variable also have to be within a 4-week window of the EQ-5D measure?

Response:

Hospitalisations were considered only if the EQ-5D assessment fell between the date of hospital admission and the date of discharge.

b) Please confirm whether the hospitalisation variable in the quality of life regression includes hospitalisations for any reason or hospitalisation for any reason other than TRAE.

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Response:

Hospitalisations citing 'adverse event/toxicity' as the reason were excluded from resource use calculations to prevent double counting. The reasons (aside from TRAE) for hospitalisation observed were as follows:

- Chemotherapy
- Disease-related signs and symptoms
- Medication
- Procedure
- Pre-planned surgery
- Radiotherapy
- Other*

*Other included: transplantation, rehabilitation, pneumonia, back pain, appendicitis, thyroidectomy, blood transfer, terminal care, knee problems, influenza, angina pectoris, renal insufficiency, atrial fibrillation and chest pain.

c) Please also clarify what windows the new primary malignancy had to be within.

Response:

New primary malignancy was considered over a 2 year period from the day first experienced.

B27. ***PRIORITY QUESTION: Please provide an updated HRQoL analysis which excludes hospitalisations and TRAEs. Please provide an updated HRQoL analysis which excludes hospitalisations, TRAEs and new primary malignancies. If time allows, please include the updated HRQoL analysis in the model and present the new ICERs as a sensitivity analysis***.

Response:

The model excluding hospitalisations and TRAEs is outlined in Table 63. The model additionally excluding new primary malignancies is outlined in Table 64. It was unfortunately not possible to complete a sensitivity analysis with updated model and ICERs based on the updated HRQoL analysis in the allocated time.

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Table 63: Revised HRQoL model excluding hospitalisations and TRAEs (including NPM)

Parameter	Coefficient	SE	U95% CI	L95% CI	Z	Pr > |Z|
Intercept	-1.2441	0.0380	-1.3185	-1.1696	-32.75	<.0001
PD	0.1920	0.0546	0.0850	0.2990	3.52	0.0004
PR	0.1288	0.0566	0.0180	0.2397	2.28	0.0227
SD	0.1927	0.0614	0.0724	0.3131	3.14	0.0017
New Primary Malignancy	0.7081	0.0528	0.6046	0.8115	13.42	<.0001
EOL 0-3 months pre-death	0.3867	0.0817	0.2265	0.5468	4.73	<.0001

Table 64: Revised HRQoL model excluding hospitalisations, TRAEs and NPM

Parameter	Coefficient	SE	U95% CI	L95% CI	Z	Pr > |Z|
Intercept	-1.2428	0.0380	-1.3172	-1.1684	-32.74	<.0001
PD	0.1912	0.0545	0.0843	0.2980	3.51	0.0005
PR	0.1265	0.0566	0.0156	0.2374	2.24	0.0254
SD	0.1921	0.0614	0.0719	0.3124	3.13	0.0017
EOL 0-3 months pre-death	0.3975	0.0807	0.2393	0.5558	4.92	<.0001

Resource use

B28. ***What resource use items were collected during TMM-1? Was this resource use data also collected after progression? Please provide the resource use data split by 1 prior therapy and 2+ prior therapies subgroups, by treatment arm, and by pre- and post-progression (to the extent that this is possible).***

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Response:

The following resource use items were collected during TOURMALINE MM-1:

- Number of hospitalizations
- Number of Acute Care Unit Stays (other than ICU)
- Number of Palliative Care Unit Stays
- Number of ICU Stays
- Number of Hospice Care Stays
- Total length of stay (hospitalisations)
- Number of All Outpatient Visits
- Number of Emergency Room Stays
- Number of Study Physician or Site Visits
- Number of Other Physician or Clinic Visits
- Number of Laboratory Department Visits
- Number of Radiology/Biomedical Imaging Department Visits
- Number of Other Outpatient Visits
- Number of Missing Days of Work or Other Activities by Subjects

The resource items listed above were captured pre- and post- progression, as is demonstrated by Table 87 of the *Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma ID 807* company evidence submission. TMM1 also captured concomitant therapy use and subsequent therapies post-progression, shown in Table 89 and Table 90 of the company evidence submission, respectively.

These data are not readily set up to provide resource use by progression status, treatment arm and by prior line of therapy. Therefore, whilst the subgroup analyses associated with resource use can be achieved, it has not been possible in the time available. These analyses can be available at further request.

Section C: Textual clarifications and additional points

C1. Please clarify why the Kaplan--Meier plots in Figures 33, 34, 35, 37, 39, 41 of the company submission are different to the corresponding Figures 5, 15, 27, 1, 11 and 23 presented in Appendix 11.

Response:

All of these Kaplan-Meier plots present the unadjusted data in a Kaplan-Meier format. The two main differences between the graphs presented in the submission and those presented in the appendices are:

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1. The length of time considered on the x-axis; the raw Kaplan-Meier data are only presented up until ~24 months and as such the plots in the appendices only consider 0-24 months. Whereas, the plots in the submission dossier include the extrapolated curves which are depicted from 0-96 months.

2. The content of each graph; the Kaplan-Meier data presented in appendices include the curves for IXA+LEN+DEX and LEN+DEX, censoring information and 95% confidence intervals, the plots presented in the submission dossier present the Kaplan-Meier data relevant to the population (i.e. 1 prior therapy considers IXA+LEN+DEX only and 2+ prior therapies considers both IXA+LEN+DEX and LEN+DEX) and the base case parametric curve fit.

C2. ***In the text above figure 22, it is stated "x studies contributing to a comparison". Please clarify this***.

Response:

The section in the submission should read:

"For this network were 11 studies of which 9 were RCTs and 2 were observational studies, with 8 studies directly contributing to a comparison of ixazomib + lenalidomide + dexamethasone vs. bortezomib + dexamethasone, vs. lenalidomide + dexamethasone (see Table 4 in Appendix 5 for study and patient characteristics of these trials)."

Table 27 in the original submission dossier presents the comparators considered in each of the studies included in the NMA.

C3. Please list the comparators included in the earlier Takeda Global NMA as alluded to in section 4.10.3.1 of the submission, and provide the report of this NMA.

Response:

In the response to an earlier question requesting additional references we stated that the earlier systematic review was superseded by the systematic review report that we provided to replace the references to the earlier systematic review. The systematic review we provided on 6 January 2017 to NICE directly supports the NMA presented in the submission. The NMA reported in the submission covered comparators of interest to the NICE scope and other HTA bodies in the UK for a 2nd and 3rd or later line positioning for the ixazomib regimen. In the decision problem table in the submission (Table 1), the relevant comparators were argued to be BORT+DEX in the 1 prior therapy population (for a 2nd line positioning), and LEN+DEX in the 2+ prior therapies population (representing a 3rd line position). These comparators were included in the NMA, as were several other RRMM therapies that were included in the original NICE scope or may be relevant comparators in other UK regions,

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such as Scotland (SMC) or in the Republic of Ireland (NCPE), or were considered to be potential relevant comparators in the next year or so depending on HTA decisions and uptake in clinical practice (but weren't considered relevant comparators for the NICE appraisal). These other RRMM therapies in the NMA networks submitted to NICE included: carfilzomib + lenalidomide + dexamethasone, carfilzomib + dexamethasone, dexamethasone monotherapy, bortezomib monotherapy, pomalidomide monotherapy, pomalidomide + dexamethasone and panobinostat + bortezomib + dexamethasone. The results for comparisons with these drugs were not reported in the submission as these were either not covered by the scope, or revised decision problem table submitted.
The original global NMA report alluded to in the submission is not relevant for the current submission, and has been superseded by the NMA provided in the submission which was decision focussed to include comparators of potential relevance in the UK and/or Republic of Ireland. The advantage of this approach was to use the essential evidence for the networks and comparators of interest and minimise noise associated with larger global NMA's. The only reason the earlier global NMA was alluded to was that it informed us that there was insufficient evidence in order to include HRQoL as an outcome in the protocol for our decision focussed NMA.

C4. Please provide a copy of the report underlying the TMM-1 EQ-5D analysis that informed table 71 of the company submission.

Response:

There is no separate report on the underlying EQ 5D analysis performed using TMM-1 data, and we would refer the ERG to section 5.4.1.1 in the submission that describes the choice of distribution that informed the parameters in table 71 of the submission.

C5. Please provide a copy of the report(s) of the recursive analyses that result in the final covariate adjusted parameterised curves presented in the executable model.

Response:

There is no separate report of the recursive analyses that result in the final covariate adjusted parameterised curves presented in the model. However, the text below provides more detail into the methodology.

Although the TMM1 study was randomly assigned, various imbalances have the potential to exist between the two treatment arms. This is particularly relevant when investigating sub-populations of ITT (i.e. 1 prior therapy, 2+ prior therapies) which yield low sample sizes. To cater for any potential imbalances, both unadjusted (univariate) and adjusted (multivariate) analyses were run with functionality within the model to choose between the two approaches.

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The variables considered for the multivariable parametric regression models were based on the variables identified in the multivariable Cox regression model. For each sub-population of interest (1 prior therapy and 2+ prior therapies populations), the method of identifying these variables from the candidate variables (Table 65) was as follows:

1. The proportion of patients matching the criteria of the candidate variables was analysed for strong differences between treatment arms.
2. A correlation matrix was produced to determine relationships between covariates. Covariates which were highly correlated (i.e. <-0.5 and >0.5) were identified and were input within the regression model with the covariate with the best significance being retained.
3. The remaining covariates were input into the linear regression model with the least significant covariate being removed). This process was repeated (i.e. backwards stepwise) until all the covariates retained were significant contributors to the model.

The retained variables based on the method outlined are specific to both the sub-population (1 prior therapy or 2+ prior therapies) and the outcome (OS, PFS or ToT) being investigated.

Table 65: Candidates for covariate imbalances within the TMM1 trial

	Option 1	**Option 2**
Prior therapies*	1 prior therapy	2/3 prior therapies
High risk cytogenetics (del (17), t(4:14) OR t(14:16))	Not high risk	High risk
ISS stage	Stage I or II	Stage III
Age	<= 65 years	> 65 years
Light chain myeloma	No	Yes
Relapsed and refractory	No	Yes
Primary refractory	No	Yes
PI	Naive	Exposed
Immunomodulation agent	Naive	Exposed
ECOG performance status	0 or 1	2
ASCT undertaken	No	Yes
History of bone lesions	No	Yes
Renal dysfunction	No	Yes
Race	Not Asian	Asian
Key: ASCT, autologous stem cell transplant; ECOG, Eastern Cooperative Oncology group; ISS, international staging system; PI, proteasome inhibitors		

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Covariate adjusted parameterised PFS curves

The adjusted survival analysis considered three stages to ensure imbalances in the characteristics of the population were accounted for. The first of these stages considered whether there were any strong differences between treatment arms (Table 66).

Table 66: Risk factor proportions stratified by treatment arm

	IXA+LEN+DEX	LEN+DEX	p-value
1 prior therapy population (n=425)			
High risk cytogenetics = Yes	45 (56.96%)	34 (43.04%)	0.204
ISS = Stage III	26 (50.00%)	26 (50.00%)	1.000
Age > 65 years	112 (50.68%)	109 (49.32%)	0.807
Light chain myeloma = Yes	35 (38.89%)	55 (61.11%)	0.026
Relapsed and refractory = Yes	1 (33.33%)	2 (66.67%)	1.000
Primary refractory = Yes	13 (52.00%)	12 (48.00%)	0.990
Proteasome inhibitor = Exposed	137 (49.64%)	139 (50.36%)	0.972
Immuno agent = Exposed	93 (47.69%)	102 (52.31%)	0.463
ECOG performance status = 2	8 (47.06%)	9 (52.94%)	1.000
ASCT undertaken = Yes	126 (51.64%)	118 (48.36%)	0.458
History of bone lesions = Yes	143 (50.00%)	143 (50.00%)	1.000
Renal dysfunction = Yes	18 (35.29%)	33 (64.71%)	0.038*
Race = Asian	15 (57.69%)	11 (42.31%)	0.536
2+ prior therapies population (n=297)			
High risk cytogenetics = Yes	30 (51.72%)	28 (48.28%)	0.861
ISS = Stage III	20 (52.63%)	18 (47.37%)	0.845
Age > 65 years	80 (50.96%)	77 (49.04%)	0.769
Light chain myeloma = Yes	32 (50.79%)	31 (49.21%)	0.976
Relapsed and refractory = Yes	40 (50.00%)	40 (50.00%)	1.000
Primary refractory = Yes	11 (52.38%)	10 (47.62%)	0.987
Proteasome inhibitor = Exposed	113 (49.78%)	114 (50.22%)	1.000
Immuno agent = Exposed	100 (49.50%)	102 (50.5%)	0.968
ECOG performance status = 2	10 (40.00%)	15 (60.00%)	0.413
ASCT undertaken = Yes	86 (51.50%)	81 (48.5%)	0.594
History of bone lesions = Yes	111 (51.15%)	106 (48.85%)	0.536
Renal dysfunction = Yes	18 (43.90%)	23 (56.10%)	0.501
Race = Asian	12 (44.44%)	15 (55.56%)	0.700

Key: ASCT, autologous stem cell transplant; ECOG, Eastern Cooperative Oncology group; ISS, international staging system; PI, proteasome inhibitors
*significant to p<0.05

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Renal dysfunction was the only risk factor where there was a significant difference between treatment arms within the 1 prior therapy sub-population and there were no risk factors where a significant difference was observed between treatments in the 2+ prior therapies sub-population.

The second stage was to determine if there were any relationships between covariates in which collinearity exists. Collinearity must be avoided when addressing imbalances in subgroups to ensure two or more variables aren't modelling the same factor. To achieve this, a series of Pearson correlation matrices were created.

Significant relationships (as denoted by a value > 0.5 for strong positive and <-0.5 for strong negative relationships) observed were as follows:

- 1 prior therapy sub-population (Table 67)
    - Proteasome inhibitor exposed vs Immuno agent exposed (-0.625)
    - ASCT undertaken vs Age > 65 years (-0.757)
    - ASCT undertaken vs ECOG performance status 2 (-0.611)
- 2+ prior therapies sub-population (Table 68)
    - ASCT undertaken vs Age > 65 years (-0.766)
    - Renal dysfunction vs Age > 65 years (0.533)
    - Renal dysfunction vs ASCT undertaken (-0.611)

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Table 67: Pearson's correlation matrix for 1 prior therapy population (IA1 data cut)

	Treatment arm IXA+LEN+DEX	High risk cytogenetics Yes	ISS stage 3	Age >65 years	Light chain myeloma Yes	Relapsed and refractory Yes	Primary refractory Yes	Proteasome inhibitor exposed	Immunoagent exposed	ECOG performance status 2	ASCT undertaken Yes	History of bone lesion Yes	Renal dysfunction Yes	Race Asian
Treatment arm IXA+LEN+DEX		0.070	-0.110	-0.040	-0.323	-0.350	-0.042	-0.042	-0.099	-0.133	0.076	-0.076	-0.301	0.081
High risk cytogenetics Yes			0.000	-0.002	-0.080	-0.144	-0.135	0.034	-0.039	0.084	-0.018	-0.320	-0.071	0.103
ISS stage 3				0.095	0.004	-0.156	0.144	0.015	-0.211	0.456	-0.268	-0.006	0.443	-0.207
Age >65 years					0.019	-0.382	0.027	-0.278	-0.108	0.373	-0.757	0.012	0.341	-0.238
Light chain myeloma Yes						-0.111	-0.126	0.097	-0.178	0.032	-0.075	0.105	0.218	0.023
Relapsed and refractory Yes							-0.071	0.267	-0.012	-0.129	0.145	-0.154	-0.110	0.365
Primary refractory Yes								-0.384	0.165	0.049	-0.248	-0.045	0.063	-0.075
Proteasome inhibitor exposed									-0.625	-0.073	0.274	-0.174	0.032	0.121
Immunoagent exposed										-0.129	0.021	0.041	-0.296	-0.298
ECOG performance status 2											-0.611	0.043	0.248	-0.138
ASCT undertaken Yes												-0.131	-0.495	0.127
History of bone lesion Yes													-0.011	-0.340
Renal dysfunction Yes														-0.028
Race Asian														

Key: ASCT, autologous stem cell transplant; DEX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; IXA, ixazomib; LEN, lenalidomide

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Table 68: Pearson's correlation matrix for 2+ prior therapies sub-population (IA1 data cut)

	Treatment arm IXA+LEN+DEX	High risk cytogenetics Yes	ISS stage 3	Age >65 years	Light chain myeloma Yes	Relapsed and refractory Yes	Primary refractory Yes	Proteasome inhibitor exposed	Immunoagent exposed	ECOG performance status 2	ASCT undertaken Yes	History of bone lesion Yes	Renal dysfunction Yes	Race Asian
Treatment arm IXA+LEN+DEX		-0.018	-0.030	-0.038	-0.073	-0.108	-0.041	-0.033	-0.086	-0.202	0.052	-0.015	-0.220	-0.125
High risk cytogenetics Yes			-0.114	0.017	-0.247	0.015	-0.237	0.233	-0.200	-0.186	-0.145	-0.332	-0.037	0.043
ISS stage 3				0.215	-0.276	0.044	0.173	-0.233	-0.090	0.130	-0.384	-0.112	0.429	-0.024
Age >65 years					-0.026	0.229	0.159	-0.191	0.038	0.343	-0.766	-0.179	0.533	-0.133
Light chain myeloma Yes						-0.140	-0.059	-0.011	-0.019	-0.008	-0.045	0.044	-0.030	0.044
Relapsed and refractory Yes							0.032	-0.303	0.176	0.052	-0.257	-0.183	0.240	-0.131
Primary refractory Yes								-0.286	0.101	0.132	-0.360	-0.101	0.200	-0.012
Proteasome inhibitor exposed									-0.489	-0.177	0.121	0.020	-0.225	0.012
Immunoagent exposed										-0.004	0.026	-0.190	-0.056	-0.322
ECOG performance status 2											-0.341	0.142	0.069	-0.157
ASCT undertaken Yes												0.194	-0.611	-0.117
History of bone lesion Yes													-0.094	-0.022
Renal dysfunction Yes														0.087
Race Asian														

Key: ASCT, autologous stem cell transplant; DEX, dexamethasone; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; IXA, ixazomib; LEN, lenalidomide

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All the relationships observed were considered understandable in regards to their collinearity. Taking ASCT for example, strong correlations are expected between ECOG performance score (i.e. often used to determine ASCT eligibility), age and renal dysfunction (i.e. older patients are less likely to have transplants due to extra risk factors).

To determine the structure of the final equations, the retained covariates were input into the linear regression model and the covariate with the least impact on the equation (i.e. the value with the highest p-value) was removed. This process was repeated until the remaining covariates were deemed significant where $p < 0.05$.

Following this backwards stepwise method, the retained covariates for PFS within each sub-population of interest were:

- 1 prior therapy sub-population
    - ECOG performance score = 2
    - ISS = Stage III
    - Primary refractory = Yes
- 2+ prior therapies sub-population
    - Light chain myeloma = Yes

Covariate adjusted parameterised OS curves

The adjusted survival analysis considered three stages to ensure imbalances in the characteristics of the population were accounted for. The first of these two stages were based off relationships between covariates and as such were consistent over the three outcomes (OS, PFS and TOT) and as such the findings were consistent with those outlined within the adjusted PFS survival analysis.

Consistent with the PFS analysis, the retained covariates were input into the linear regression model and the covariate with the least impact on the equation (i.e. the value with the highest p-value) was removed. This process was repeated until the remaining covariates were deemed significant where $p < 0.05$. Because of this backwards stepwise method, the retained covariates for OS within each sub-population of interest are as follows:

- 1 prior therapy sub-population (delayed)
    - ECOG performance score = 2
    - ISS = Stage III
- 2+ prior therapies sub-population
    - Age > 65 years

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Covariate adjusted parameterised ToT curves

The adjusted survival analysis considered three stages to ensure imbalances in the characteristics of the population were accounted for. The first of these two stages were based off relationships between covariates and as such are consistent over the three outcomes (OS, PFS and TOT) and as such the findings are consistent with those outlined within the adjusted PFS survival analysis.

Consistent with the PFS analysis, the retained covariates for TOT within each sub-population of interest are as follows:

- 1 prior therapy sub-population
    - ISS = Stage III
- 2+ prior therapies sub-population
    - Renal dysfunction = Yes
    - Light chain myeloma = Yes

C6. TMM-1 baseline characteristics: table 37 of the company submission states that 441 people in the trial had received 1 prior treatment, whereas section 4.8.1 states 425. There is a corresponding discrepancy for the number of people who had received 2-3 prior treatments. Which statement is correct? Are the response rates in table 41 based on the correct subgroup data?

Response:

In Table 41, the n numbers correspond to the subgroups based on the stratification factors of 1 prior line, or 2/3 prior lines (also presented in Table 37 rows 11-13; between “Lines of prior therapy” and “Cytogenetics” and in the text in Section 4.5.2 [first line of second paragraph: “Of relevance for the NICE scope, 59% (n=425) of patients had received 1 prior line and 41% (n=297) had received 2 or 3 lines of prior therapy (based on stratification factors)]” and the text of Section 4.8.1 first paragraph). As explained in the footnotes of Table 37, the two do not match exactly: the “Lines of prior therapy” was determined by blinded Sponsor medical review of prior therapy data, where prior therapies were defined per Rajkumar et al. 2011 (NICE dossier reference 126: Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011 May 5;117(18):4691-5) and does not exactly match the stratification factor (lines of prior therapy: 1 versus 2 or 3).

Further explanation to these two sets of n numbers is provided in response to question A6: TMM-1 (C16010) clinical study report figure 11v . (Forest Plots of Time to Progression and Overall Response Rate in Subgroups): Please clarify how “Prior Therapies (1, 2 or 3)” and “Prior Therapies Derived (1, 2 or 3)” were derived and should be interpreted.

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The efficacy outcome data, as presented in the SmPC, the EPAR and the C16010 CSR, were based on the n numbers from the stratification factors (for example, please see: EPAR page 77 Table 27 and page 78 Table 78 or CSR Table 10d and Table 10e for baseline characteristics; and EPAR Figure 9 page 85 for forest plot of PFS by subgroups or CSR Figure 11e & Table 11K for efficacy outcome data by subgroup). We presented the n numbers by “Lines of prior therapy” in the baseline characteristics table (Table 37) for completeness because it was in the published manuscript by Moreau 2016 as well as the CSR and EPAR, but apologise for the confusion this may have caused.

C7. For the cost-effectiveness analysis in the 1 prior therapy group, the model assumes 8 cycles of subcutaneous BORT on days 1, 4, 8 and 11. Was the stopping rule in NICE technology appraisal 129 included in the model (i.e. BORT is continued beyond cycle 4 only in people who have a complete or partial response)?

Response:

The model assumed 8 x 21-day cycles of subcutaneous BORT on days 1, 4, 8 and 11 in line with the summary of product characteristics (SPC) published by the European Medicines Agency (EMA). The proportion of patients remaining on treatment across these 8 treatment cycles was defined by the LEN+DEX ToT observed in the TMM1 clinical trial.
The stopping rule where BORT is continued beyond cycle 4 only in people who have a complete or partial response was not considered, in line with the SPC. However, the progression-based refund was included, whereby the treatment of patients progressing prior to the 4th treatment cycle was refunded.

Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma [ID807] 2nd round of clarification questions

Submitted by Takeda UK Ltd.

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

Submitted 10th February 2017

1. Overview

This document contains the responses to the 2nd round of clarification questions from the evidence review group (ERG) sent to Takeda on 8th February 2017.

2. Response to clarification questions

A5 The clarification response to A5 highlights that the original submission contains scenario analyses that use the later interim data cut with 23 months data. The ERG cannot identify how to arrive at these results within the submitted model(s) and would be grateful if the company could outline how to undertake these analyses.

Response
This scenario analysis uses IA2 data incorporated into a separate but identical (aside from the TMM1 clinical data cut) economic model which can be found in "Ixazomib CEA Model – UK Adaptation (IA2) - 10022017". The IA2 model has been corrected for errors presented in questions B3, B13 and B19, the updated results are shown in Table 1 (Table 2 with PAS) and Table 3 (Table 4 with PAS) for the 1 prior line and 2+ prior line population, respectively.

Table 1: Corrected results for IXA+LEN+DEX vs. BORT+DEX (1 prior line population) using 2nd interim analysis (without PAS)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental cost/QALY (ICER)
IXA+LEN+DEX	[redacted]	3.93			
BORT+DEX	[redacted]	1.61	[redacted]	2.33	[redacted]
Key: BORT, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; PAS, patient access scheme; QALY, quality adjusted life year					

Table 2: Corrected results for IXA+LEN+DEX vs. BORT+DEX (1 prior line population) using 2nd interim analysis (with PAS)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental cost/QALY (ICER)
IXA+LEN+DEX	£235,044	3.93			
BORT+DEX	£38,673	1.61	£196,370	2.33	£84,370
Key: BORT, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; PAS, patient access scheme; QALY, quality adjusted life year					

Table 3: Corrected results for IXA+LEN+DEX vs. LEN+DEX (2+ prior lines population) using 2nd interim analysis (without PAS)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental cost/QALY (ICER)
IXA+LEN+DEX	[redacted]	4.83			
BORT+DEX	[redacted]	3.75	[redacted]	1.09	[redacted]
Key: BORT, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; PAS, patient access scheme; QALY, quality adjusted life year					

Table 4: Corrected results for IXA+LEN+DEX vs. LEN+DEX (2+ prior lines population) using 2nd interim analysis (with PAS)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental cost/QALY (ICER)
IXA+LEN+DEX	£227,312	4.83			
BORT+DEX	£97,269	3.75	£130,043	1.09	£119,803
Key: BORT, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; PAS, patient access scheme; QALY, quality adjusted life year					

B11c It appears that the AIC and CIC values of the 1-prior group of the unadjusted curves OS curves supplied at clarification in response to B11c are the same as those of the adjusted curves of appendix 11 table 9. The ERG would be grateful if these could be cross checked

Response

Table 9 in the submitted Appendix 11 is incorrect and the correct AIC and BIC estimates for the adjusted curves for OS are shown in **Table 5**.

Table 5:: AIC and BIC goodness of fit statistics for OS (adjusted) in the 1 prior and 2+ prior therapies populations. Correction of Table 9 in Appendix 11.

	1 prior therapy		2+ prior therapies	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	485.581	501.606	N/A	N/A
Weibull	638.017	650.173	531.750	542.831
Gompertz	636.937	653.146	530.154	544.929
Lognormal	638.761	654.970	532.226	547.001
Log logistic	635.123	651.332	529.301	544.076
Generalised gamma	635.426	651.634	529.847	544.622
Key: AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression free survival				

The AIC and BIC statistics for the ***unadjusted*** curves are shown for PFS, OS and ToT below. As well as a comparison of the ***unadjusted*** parametric curve fits with the ***unadjusted*** Kaplan-Meier data.

Progression-free survival

Table 6 presents the AIC and BIC statistics for **the *unadjusted*** parametric curve fits to the PFS Kaplan-Meier data, for the 1 prior line and 2+ prior lines populations, respectively. Figure 75 and Figure 76 visually depict the ***unadjusted*** fitted parametric curves to the ***unadjusted*** OS Kaplan-Meier data for the 1 prior line and 2+ prior lines population, respectively.

Table 6: AIC and BIC goodness of fit statistics for PFS (unadjusted) in the 1 prior and 2+ prior therapies populations

	1 prior therapy		2+ prior therapies	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	1442.413	1450.517	988.943	996.331
Weibull	1435.726	1447.882	985.297	996.378
Gompertz	1441.027	1453.183	989.565	1000.646
Lognormal	1431.727	1443.884	979.769	990.850
Log logistic	1433.619	1445.775	983.115	994.196
Generalised gamma	1433.377	1449.586	981.751	996.526

Key: AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; PFS, progression free survival

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma [ID807]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Myeloma UK

Your position in the organisation: [redacted]

Brief description of the organisation:

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 entirely on the fundraising efforts of our supporters and unrestricted educational grants from a range of pharmaceutical companies.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: We do not have any links with the tobacco industry.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

"Myeloma creeps up on you, engulfs you and, if you win the battle, leaves you wondering when it will come back."

"My prognosis was the most shattering thing I'd ever been through in my life."

Myeloma is an incurable 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.

Due to increasing treatment options, survival in myeloma has improved greatly, but it remains a challenging cancer to treat, with high mortality rates. There is an urgent and continual need for new treatments to ensure that patient survival rates keep improving.

Myeloma is a highly individual, relapsing and remitting cancer which evolves over time and becomes resistant to treatment. This takes a considerable toll on patients' physical and emotional well-being. Patients particularly can experience an increasing sense of despair and resignation when they relapse and are faced with limited treatment options.

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. Given the non-specificity of symptoms, research

highlights that myeloma patients are more likely to be diagnosed late and often present in secondary care with bone lesions, fractures and in the worst cases collapsed vertebrae. This compounds the distress of their diagnosis, presents treatment challenges and impacts negatively on pain levels, mobility and their ability to complete everyday tasks.

Treatment side-effects and frequent hospital visits can 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.

That said, many myeloma patients, even those who have had two previous treatments can be relatively asymptomatic – if their myeloma is effectively controlled and further damage to their body is prevented. Relapsed myeloma patients can have durable and deep responses to treatment and can experience good quality of life – but only if they have access to new, effective and innovative treatments.

Impact on myeloma carers

A recent Myeloma UK study[1] into the experiences of carers and family members found that looking after someone with myeloma has a significant emotional, social and practical impact.

- Carers and family members can carry a heavy emotional burden: 94 per cent of carers reported that caring impacted on their emotional life; 84 per cent always put the needs of their relative or friend with myeloma before their own; and 52 per cent of all carers find emotional support the hardest type of support to give. "*You're trying to support them and your heart's breaking too"*

- Carers' lives can change dramatically because of their caring responsibilities: 60 per cent of carers reported that their social life had changed for the worse and 25 per cent of those in work had been unable to work or had to retire early to care for the person with myeloma. *"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"*

- The impact of myeloma on the well-being of carers is often overlooked; 42 per cent of carers were not given enough information at diagnosis about how myeloma may affect them and only 6 per cent of carers are asked how they are by healthcare professionals when attending appointments with their relative or friend

Living with myeloma is therefore often extremely challenging emotionally and physically for patients, carers and family members.

[1] The study, conducted between May and June 2016, was designed with the input of carers and involved a survey of 374 carers and a second stage of interviews to explore issues in more depth.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Through our regular programme of health services research, Myeloma UK continually asks patients about what they value from new treatments. We have recently commissioned a number of studies to better understand patient preferences and how decisions are made on new medicines. In addition, to inform our response to this NICE appraisal Myeloma UK conducted a number of informal interviews with patients about what it would mean to them to have ixazomib approved in this setting.

Myeloma patients and their carers place a very high value on treatments that put their myeloma into remission for a long time and prolong their life. It is also very important to them that treatments allow them to enjoy normal day-to-day life doing the things they enjoy. Key points about myeloma patient and carer treatment preference are as follows:

- Treatment outcomes patients and carers value most are those to do with length and quality of life. *"When it comes to the crunch, most people would want to choose the option that gives them longer life"*

- Patients want treatments that increase remission (i.e. disease free periods) for the longest possible time and reduce their paraprotein to stable or non-detectable levels. Effectively controlling patients' myeloma improves quality of life for patients, and also reduces the impact on carers. *"The most important thing for me in considering treatment is to get a good remission time and to get back to normal life"*
- In a recent patient preference survey involving 560 myeloma patients, a multi-criteria decision analysis with the European Medicine Agency and the University of Groningen, the majority of myeloma patients considered progression free survival (PFS) to be the most important attribute to consider when making a decision on a new treatment. This preference did not depend on any social, demographic or clinical differences between patients
- In the same survey, we also measured differences in patient preference between severe toxicity (i.e. side-effects) and moderate chronic toxicity. In decision-making on new medicines, myeloma patients put PFS over and above their concerns for either moderate chronic toxicity or severe toxicity. However, patients were more likely to give more consideration to toxicity if they had children, were working or had past experience of severe side-effects from previous treatments
- To build on the above points relating to survival, we also know from patients that any incremental gain in survival from treatment is seen as

a “bridge” to further treatments coming down the line. Survival benefits of one treatment cannot be seen in isolation to others*. “A drug like this can be a gateway to other treatments that can extend your life even further”*

- 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. This increases in significance as patients experience multiple relapses and may suffer from the cumulative effects of previous treatments. “*The aim is to maintain the best possible quality of life for as long as possible”*

What is your organisation’s experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

The individual and heterogeneous nature of myeloma means that it is difficult to compare treatments in head-to-head terms as some patients may tolerate a treatment well and others may not.

It is therefore essential to have a range of treatments and treatment combinations available to ensure that doctors can treat myeloma flexibly and improve outcomes.

Options for myeloma patients at second line (first relapse) treatment are currently very limited, with only bortezomib approved at this stage. If patients have received bortezomib as a front-line therapy, particularly in combination with thalidomide, there are no effective novel treatment options available. There is a continuous need to develop and bring new drugs and drug combinations to market that prolong progression free and overall survival in myeloma. There is also a need to use NICE approved treatment in increasingly innovative ways. There is also a need for more oral versions of treatment to ensure that patients can be offered personalised care that meets their needs; in this case a treatment that can be taken at home, minimising impact on work and family commitments.

Below we cover our experience of each of the comparators mentioned in the final scope for the appraisal. We cover the advantages and disadvantages of each. We cannot state which are preferred by patients, as this varies on a patient-by-patient basis.

Velcade® (bortezomib) with or without dexamethasone

NICE guidance (TA129) recommends Velcade monotherapy as a treatment in patients at second line (first relapse), although clinical trial data and practice demonstrate its effectiveness at all stages of myeloma. The use of Velcade retreatment at first relapse is restricted in NHS England. As Velcade has been approved in England and Wales since 2007, doctors are very experienced in its administration and use in myeloma patients.

Advantages

Most myeloma patients who receive Velcade outline that it is well tolerated and report an improvement in myeloma-related symptoms and complications, overall general health and quality of life. In the majority of patients, Velcade is effective at putting their myeloma into a quick remission and their side-effects are well managed.

Velcade is also very well tolerated in patients with impaired kidney function as a result of their myeloma, so it is a treatment of choice in these patients. Although NHS England do not fund this as a retreatment.

Velcade is given to patients in up to eight cycles, so it is a relatively short treatment frequency compared to other myeloma drugs which are given on a treat until disease progression basis. This allows patients to have treatment breaks, which are valued by patients.

Disadvantages

Some patients report that a number of the side-effects of Velcade are difficult to deal with and can be debilitating.

The most commonly reported side-effect of Velcade is peripheral neuropathy (mild to severe tingling and numbness in the hands and feet), affecting up to 30% of patients. However, this has been greatly improved through the development of subcutaneous formation of the drug.

Other complications are anaemia, fatigue, skin rashes and gastrointestinal disturbances – although in the majority of cases these are appropriately managed by a healthcare professional.

As Velcade is given subcutaneously, it means that patients have to attend hospital in order to receive treatment. This can be seen as a disadvantage in some cases as patients have to take the time out of their daily routine to attend day clinics. However, a patient preference survey conducted by Myeloma UK found that patients are divided in terms of preferences of how to receive treatment.

Revlimid® (lenalidomide) with dexamethasone

Again, myeloma doctors in England and Wales are used to prescribing Revlimid for patients at third line (second relapse), having received NICE approval in 2009. Like Velcade, whilst it is approved as a treatment in second relapse, it is well known to be effective in all stages of myeloma.

Advantages

Patients report that Revlimid in combination with dexamethasone is very effective treatment and is an easy to take formulation, particularly given the tablet form which can be taken at home. As some patients can be on Revlimid

in excess of two years, the tablet formation is better suited given the minimal impact it has on their lives. Although, as outlined above, patient preferences for where they want to receive their treatment can vary.

Myeloma UK sees and speaks to patients who respond well to Revlimid and it can be very effective in patients, keeping their disease at bay for long periods of time. It has a lesser side-effect profile than related immunomodulatory drugs (IMiDs) such as thalidomide.

Disadvantages

Side-effects of Revlimid include low blood counts and there is a risk of venous thromboembolism and blood clots whilst taking the treatment. Patients also frequently report fatigue which impacts negatively on their quality of life and peripheral neuropathy, although this is a lesser risk than in thalidomide and Velcade. Another side-effect is skin rashes.

As with other treatments these side-effects can be largely mitigated or improved through appropriate management by a healthcare professional. Revlimid is also given on a treat until progression basis, so patients do not have long treatment free breaks.

Farydak® (panobinostat) in combination with Velcade® (bortezomib) and dexamethasone

NICE guidance (TA380) recommends Farydak in combination with Velcade and dexamethasone as an option for treating relapsed or refractory myeloma patients who have received at least two prior regimens, including Velcade and an immunomodulatory agent.

Advantages

A major advantage of Farydak is that it offers an entirely new mechanism of action to other treatments that are approved for use in the disease. Adding drugs with new mechanisms of action into treatment combinations can help to treat underlying myeloma clones, improving a patient's response to treatment.

Published data has also highlighted that patients who have become refractory to Velcade, are able to respond again when it is given in combination with panobinostat.

Patients report that it improves symptoms associated with myeloma and their quality of life in the longer term and that the oral formulation is easy and convenient to take (although Velcade is administered subcutaneously or intravenously and requires hospital visits).

Disadvantages

The main disadvantage of the Farydak combination treatment is gastrointestinal problems, in particular diarrhoea. Other side-effects include neuropathy, fatigue, low blood counts and nausea. However, patients and doctors report that these have been adequately managed through communication and supportive care.

Kyprolis® (carfilzomib) in combination with Revlimid (lenalidomide) and dexamethasone and in combination with dexamethasone

NICE are currently conducting an appraisal of Kyprolis in combination with Revlimid and dexamethasone and in combination with dexamethasone (ID934) for myeloma patients who have received at least one prior therapy.

This treatment is therefore not yet available on the NHS but clinical trial data has shown that both combinations significantly extended progression free survival (PFS) in comparison to the current standard treatments in the control arm of the trial and have an acceptable side-effect profile. Carfilzomib is an IV treatment which may be less convenient for some patients, although again patient preferences on this issue vary.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Myeloma UK, patients and carers agree that access to ixazomib would improve the treatment pathway of patients in England and Wales. Ixazomib:

- **Prolongs life.** Ixazomib has been shown to give additional progression free survival of almost 6 months. In some groups of patients, including third line and high-risk patients, the PFS was longer than this. This represents a significant and prolonged period for patients and their carers and family members. Research has also demonstrated the correlation between median PFS and median overall survival (OS). *"The most important factor is the increased survival benefit"*

- **Treats underlying disease, thereby addressing symptoms and preventing complications.** Effectively controlling myeloma prevents the progressive damage that it does to the body. This has a positive impact on quality of life, enabling patients to take part in day to day activities they enjoy and find fulfilling. "*It's important to keep well for as long as possible because the chances are that treatment will work better"*

- **Addresses a lack of effective treatments at this stage in the pathway.** Approving ixazomib would give patients access to an effective proteasome inhibitor at most stages of relapse. Providing more treatment options in the relapse setting can improve patient outcomes and survival and enables doctors to treat patients on a more "personalised" basis. Adding novel agents into existing effective treatment combinations can also help to treat underlying myeloma and improve the patient's response to treatment. *"When you have myeloma and you have relapsed you need to have as many 'arrows in your quiver' as you can"*

- **Is well tolerated.** It has tolerable side-effects and patients we spoke to said that, given its survival benefit, they would be willing to accept the level of toxicity outlined in the results of the trials. Patients did not consider the side-effects to differ significantly from other treatments currently available in the treatment of myeloma. *"For me there is no question that the added survival benefit is worth it"*

- **Is innovative.** This is the first oral proteasome inhibitor, a significant breakthrough which will deliver major benefit to patients who find it difficult to attend regular hospitals appointments. *"For this to be the first all oral combination; that is a great step forward." "Having an oral treatment makes a huge difference. You feel more in control of the process"*

- **Improves emotional well-being.** Myeloma patients often feel an increasing sense of despair on relapse. Knowing an effective treatment, with a good survival benefit, is available at every stage is very important psychologically – not just for this patient population but for all myeloma patients. *"When I relapsed many years ago, there were very few treatments available. Anything that gives someone more options is fantastic"*

- **A bridge to future novel effective treatments.** The additional survival benefit given by new myeloma treatments cannot be seen in isolation, particularly for patients at first or second relapse. The cumulative survival benefits of new improved novel agents in the myeloma treatment pathway is very important to patients. *"A treatment like this can be built on. The additional time it gives you could lead to another treatment which could give you years more"*

These benefits also apply to carers and family members, for example:

- Improved psychological and emotional well-being knowing that the patient has effective treatment options
- Alleviation of symptoms and prevention of complications enables patients to be more independent and reduces day-to-day reliance on carers
- A good side-effect profile improves quality of life and improves patients' ability to live a fuller life, participating in and enjoying more activities with family and friends

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

Not applicable.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS

treatments in England.

Please list any concerns patients or carers have about the treatment being appraised.

Clinical trial data showed a slight increased incidence of peripheral neuropathy occurring as a side-effect of ixazomib in comparison to the control arm. Some patients expressed concern about this since this is a side-effect which can persist beyond treatment. However, peripheral neuropathy is a known side-effect of the current standard approved proteasome inhibitor Velcade and the majority of the cases observed in the ixazomib trial were mild. Most importantly, and in keeping with our broader findings on patient priorities, patients felt that the side-effect profile was acceptable given the survival and other benefits ixazomib delivers.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Not applicable.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

The trial data highlighted that high-risk patients, a very difficult to treat population, did respond well to the drug. Whilst this isn't a subgroup in itself and it is difficult to identify this group of patients without cytogenetic testing, this is an important development. It provides a very difficult to treat patient population with a treatment that works.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Not applicable

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☒ **Yes** ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment

as part of their routine NHS care reflects the experiences of patients in the clinical trials.

The treatment is not yet routinely available on the NHS but from our general experience, myeloma patients do better on treatments outside of the clinical trial setting. For example, adjusting dosage for patients who experience severe side-effects is easier in clinical practice than in trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

We are not aware of any limitations in how the treatment has been assessed in clinical trials.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

We understand that side effects reported through the named patient programme were largely representative of those reported in the trials and monitored in the trial setting

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☒ **Yes** ☐ No

If yes, please provide references to the relevant studies.

Myeloma UK's 'Life in Limbo' report suggests that the most common aspects of caring are: providing emotional support (98%); accompanying myeloma patients to appointments (89%); running errands (81%); and sourcing information (78%). In addition to being the most common aspect of caring, our survey indicated that emotional support was the most difficult to provide. (https://www.myeloma.org.uk/what-we-do/research/health-services-research/#1475078374303-8f12f105-1771)

Stephens et al's (2014) study into living with myeloma, reflects the findings in our 'Life in Limbo' report, reporting that carers experience fatigue and emotional distress, and a lack of time to attend to their own health needs (http://ro.uow.edu.au/cgi/viewcontent.cgi?article=3121&context=smhpapers).

Molassiotis et al (2011) additionally found that informal caregivers often neglected their own needs, leading to experiences of a heightened illness burden and difficulties with coping (http://www.ntcrp.org.uk/Myeloma_unmetNeeds_qualitative.pdf)

Muhlbacher et al. Evaluating patients' preferences for multiple myeloma therapy, a Discrete Choice Experiment (2008).

Raven D et al. Comparison if generic, condition-specific and mapped health state utility values for multiple myeloma (2012).

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Not applicable.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Not applicable

9. Other issues

Do you consider the treatment to be innovative?

☒ **Yes** ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

As the first oral treatment of its kind, ixazomib has a significant benefit for patients, especially those who are unable to regularly attend hospital appointments.

Are there any other issues that you would like the Appraisal Committee to consider?

No.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Myeloma is a highly individual, relapsing and remitting cancer which evolves and becomes resistant to treatment and it is therefore particularly important that there are a range of treatments available at all stages of the disease pathway
- The innovative benefit of ixazomib being the first oral proteasome inhibitor delivers much needed patient choice and convenience at an important point in the pathway when many patients will still be able and keen to work and undertake other normal day-to-day activities
- Approving ixazomib addresses the unacceptably limited options available to patients at this stage of their myeloma
- Adding another treatment option to the pathway, increases doctors' ability to provide treatment suited to the patient's individual circumstances and helps alleviate the psychological burden of patients, family members and carers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: UK Myeloma Forum, British Society of Haematology & Royal College of Pathologists

Are you (tick all that apply):

- **X** a specialist in the treatment of people with the condition for which NICE is considering this technology?
- **X** a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NONE TO DECLARE

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Multiple myeloma is a clonal late B-cell disorder in which malignant plasma cells expand and accumulate in the bone marrow leading to cytopenias, bone resorption, renal impairment and the production of a monoclonal protein. Myeloma represents 1.5% of all malignant diseases, with an incidence of 6.9/100,000 per year accounting for 4,500 new cases each year in the UK (representing 2,600 deaths per year)[1]. Therapeutic options for myeloma have changed for both the young and the elderly patients with the arrival of potent novel agents such as proteasome inhibitors (PI) and IMiDs. Multi-agent combination chemotherapies with both conventional (Cyclophosphamide, Corticosteroids, Melphalan) and novel agents (Bortezomib, Lenalidomide, Thalidomide) when employed together, elicit frequent, rapid, and deep responses. What is clear is that the disease-controlling effect lessens with each passing line of therapy in the majority of patients, thus early management strategies should capitalise on this effect, aiming to maximise the depth and durability of responses in first to third line therapy, where the best healthcare resource utilisation can be observed[2].

Despite these benefits in both OS and PFS, myeloma remains incurable and patients develop resistance to both proteasome inhibitors and IMiDs. A retrospective study has recently demonstrated that patients with relapsed myeloma who were refractory to bortezomib and were relapsed following, refractory to, or ineligible to receive IMiD, had a median overall survival (OS) and event-free survival (EFS) of 9 and 5 months, respectively[3]. Thus, there is

1. Office for National statistics: Cancer Statistics Registrations, England (Series MB1) , No. 42, 2011
2. San Miguel et al, Haematologica, 2015, 100, 10, 1334
3. Kumar SK, Lee JH, Lahuerta JJ, et al Leukemia 2012;26(1):149-157.

a need for new strategies for managing patients prior to this stage to augment the benefits from early intervention with novel agents.

Ixazomib is a next generation, small molecule inhibitor of the 20S proteasome, the same target validated as therapeutically important in the treatment of malignancies using VELCADE® (bortezomib)[4]. The early development of ixazomib in patients with relapsed and/or refractory MM (RRMM) examined differing dosing schedules (C16003 and C16004), aimed to defined both the dose-limiting toxicities and the efficacy of the agent. The clinical experience with ixazomib has shown signs of antitumor activity in MM as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across[5].

The current HTA application for authorisation seeks the role for Ixazomib, in combination with lenalidomide and dexamethasone (IRd), for patients with relapsed MM having received at least 1 prior line of therapy. The current treatment pathway for patients with MM is largely formulated by the sequential NICE HTA (single and multiple TAs) to date. Furthermore, NICE guidance treatment of newly diagnosed patients as this will affect the treatments that can be offered according to NICE or the Cancer Drugs Fund at 1st, 2nd and 3rd line therapy. Currently newly diagnosed patients are treated according to whether they are transplant eligible (TE) or transplant ineligible (TI), and accordingly, NICE TA311 is applicable to TE patients approving the use of bortezomib/dexamethasone or bortezomib/thalidomide/dexamethasone. NICE TA228 is applicable to TI patients and approves the use of alkylator therapy/thalidomide/corticosteroid or thalidomide substituted with bortezomib if thalidomide is contraindicated or not tolerated. Additionally, Bortezomib is approved for routine commissioning by NHSE in June 2013. This means that a significant proportion of patients will have already received a bortezomib-based treatment prior to consideration of 2nd line therapy and beyond. Furthermore, secondline use of lenalidomide is no longer available following delisting from the Cancer Drugs Fund in November 2015. As such, the use of Lenalidomide with dexamethasone (LenDex) is reserved for patients in the 3rd line (after 2 prior lines of therapy), in accordance with NICE TA171. These approvals are incorporated into the UK Myeloma forum diagnosis and treatment guidelines[6].

As a consequence, the current application for approval relates to third line, which in keeping with NICE TA171, is LenDex. The application seeks to gain approval form the addition of Ixazomib to LenDex in this clinical space, aiming to secure a more durable disease response with associated clinical benefits and patient-reported freedom from disease-related morbidity. This is a

4. Tian Z et al. Blood. 2012 Nov 8;120(19):3958-67
5. Kumar SKK et al. Lancet Oncol. 15, Dec 2014,
6. JM Bird, et al. British Journal of Haematology 154(1):32-75

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Single Technology Appraisal (STA)

technology applicable only to secondary/tertiary care, being prescribed by specialists in the care of MM patients, and not transferable to primary care (a "red" drug), especially with the special care and attention to side effect profiles and efficacy measures.

In relation to sub-groups of MM patients, two such groups have particular importance, those with genetic high risk disease and the elderly population. In terms of genetic high risk, delineated as t(4;14), TP53 gene deleted and t(14;16), then successive studies of novel agent combinations have singularly failed to demonstrate parity of efficacy with non-high risk patients. The data from TOURMALINE study however, does show parity of effect for this patient group[7]. In relation to the elderly population, the failure of novel agents to truly impact on survivorship, such as seen in seen in younger patients, may in part, relate to the ability to deliver appropriately efficacious therapy[8]. Ixazomib with LenDex offers a rapid and potent combination for depth of disease control, which not only is associated with improved patient experiences but also outcomes and thus could serve this specific population well minimising healthcare resource utilisation.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

7. Moreau et al, NEJM 2016, 374, 17, 1621
8. Palumbo et al, Blood, 2015, 125; 13, 2068.

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Single Technology Appraisal (STA)

A clear clinical advantage of the technology is the ability to produce rapid disease control, with a higher proportion of patients achieving a response with a longer PFS. The benefit of improved PFS when compared with lenalidomide and dexamethasone (current standard of care in this setting) has been demonstrated in the clinical trial. An important benefit is benefit of this combination in patients with high risk myeloma (approximately a third of patients in relapsed setting), where the IRD combination continues to show improved PFS, when compared with those receiving lenalidomide and dexamethasone. Quality of life has been maintained on the trial despite a use of triplet combination and bias has been eliminated with the study being blinded to both patients and physicians. With this technology being an all-oral combination, the uptake is likely to be higher and combination elderly myeloma patients would prefer. Disadvantages with this technology are limited. Within the trial the adverse events mostly noted are lenalidomide and dexamethasone related and has been observed in clinical practice with lenalidomide therapy. In addition low grade neuropathy rates, diarrhoea, fatigue, thrombocytopenia and rash are observed with the new technology and require vigilant monitoring in patients. As standard practice will be to review patients monthly, this should be addressed in routine follow up appointments.

Comparing this technology with the current standard of care lenalidomide and dexamethasone; there are no significant additional clinical requirements. Patients will need closer monitoring of counts and toxicities in the first 2-3 cycles. Patients will start this therapy when there is evidence of relapsed myeloma and stop either due to toxicity or disease progression while on therapy.

The use of Ixazomib/ lenalidomide and dexamethasone in relapsed myeloma patients within the trial reflects currents clinical practice in the UK. The results of TOURMALINE trial[7] can be extrapolated to UK population. Key outcomes in this trial are PFS, toxicity, QoL analysis all of which appear favourable and support its use in relapsed MM patient population.

Ixazomib use outside of clinical trials is limited in the UK. Adverse reactions described in trial are manageable and patients can be monitored for these on a month-to-month basis.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

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Single Technology Appraisal (STA)

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

NONE PERCIEVED

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No additional information available

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The proposed technology is an all-oral combination therapy. There are no additional delivery resource implications to the NHS. It is reasonable to expect that local haematology departments to draw up clinical protocols based on the evidence provided in this trial[7] on dosing, toxicity and pre requisite laboratory data prior to commencing treatment and during therapy.

Appendix D – patient/carer expert statement template

1. About you

Your name:DAVID LOBB

Name of your nominating organisation: MYELOMA UK

Do you know if your nominating organisation has submitted a statement?

X☐ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

X☐ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

X☐ Yes ☐ No

- a carer of a patient with the condition?

☐ Yes X☐ No

- a patient organisation employee or volunteer?

☐ Yes X☐ No

Do you have experience of the treatment being appraised?

☐ Yes X☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I HAVE BEEN A MYELOMA PATIENT FOR 10 YEARS AND 4 MONTHS

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

THE LONGEST POSSIBLE SURVIVAL WITH MINIMUM SYMPTONS OF THE DISEASE AND MINIMUM PHYSICAL AND EMOTIONAL SIDE EFFECTS

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

SINCE DIAGNOSIS IN DECEMBER 2006 I HAVE RECEIVED THE FOLLOWING TREATMENTS...

RADIOTHERAPY

VINCRISTINE, ADRIAMYCIN AND DEXAMETHOZONE

BLOOD TRANSFUSIONS

CYCLOPHOSPHOMIDE, DEXAMETHOZONE AND THALIDOMIDE

STEM CELL TRANSPLANT 1

TREATMENT TO DEALWITH INFECTIONS OF HICKMAN LINE

STEMCELL TRANSPLANT 2

VELCADE, CYCLOPHOPHOMIDE AND DEXAMETHOZONE

VERTEBROPLASTY

BALLOON KYPHOPLASTY

REVLIMID WITH DEXAMETHOZONE SOMETIMES ALSO WITH CYCLOPHOSPHOMIDE

All of the above have meant countless visits to and/or stays in hospital, insertion and removal of hickman lines, and many many MANY needles stuck into me!

But all these treatments have been successful to a greater or lesser extent and I am grateful that as a result I am still alive after ten plus years.

4. What do you consider to be the advantages of the treatment being appraised?

1 .It is an ORAL treatment, therefore involving few visits to hospital and NO NEEDLES!

2 . It proves another option at a point in the pathway when the options fade away. THIS IS VERY IMPORTANT. When the options start to disappear, you think **"if this doesn't work I am going to die**". If there are more options, you think **"if this doesn't work at least there are other options now that could keep me alive".**

Please list the benefits that you expect to gain from using the treatment being appraised.

As above.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

As above.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

Not applicable

5. What do you consider to be the disadvantages of the treatment being appraised?

Not applicable

Please list any concerns you have about current NHS treatments in England.

Limited options for later stage relapsed patients – with myeloma, you know that eventually every treatment stops being effective.

Please list any concerns you have about the treatment being appraised.

Not applicable

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Not applicable

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

I do not know

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

I do not know

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes x☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

Not applicable

9. Other issues

Do you consider the treatment to be innovative?

x☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

It is an ORAL treatment for later stage patients, for whom the options for treatment are running out

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Trials show it is effective
- It provides a new option at a point when few or no others are available, thereby giving hope of survival to many patients.
- It is an ORAL treatment
- FEWER NEEDLES
- Fewer visits to hospital

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma [ID807]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Karthik Ramasamy

Name of your organisation: UK Myeloma forum, BSH, Royal College of Pathologists
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? Executive Member

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: No

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed or refractory multiple myeloma [ID807]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Multiple myeloma is a clonal late B-cell disorder in which malignant plasma cells expand and accumulate in the bone marrow leading to cytopenias, bone resorption, renal impairment and the production of a monoclonal protein. Myeloma represents 1.5% of all malignant diseases, with an incidence of 6.9/100,000 per year accounting for 4,500 new cases each year in the UK (representing 2,600 deaths per year)[1]. Therapeutic options for myeloma have changed for both the young and the elderly patients with the arrival of potent novel agents such as proteasome inhibitors (PI) and IMiDs. Multi-agent combination chemotherapies with both conventional (Cyclophosphamide, Corticosteroids, Melphalan) and novel agents (Bortezomib, Lenalidomide, Thalidomide) when employed together, elicit frequent, rapid, and deep responses. What is clear is that the disease-controlling effect lessens with each passing line of therapy in the majority of patients, thus early management strategies should capitalise on this effect, aiming to maximise the depth and durability of responses in first to third line therapy, where the best healthcare resource utilisation can be observed[2].

1. Office for National statistics: Cancer Statistics Registrations, England (Series MB1) , No. 42, 2011
2. San Miguel et al, Haematologica, 2015, 100, 10, 1334

Despite these benefits in both OS and PFS, myeloma remains incurable and patients develop resistance to both proteasome inhibitors and IMiDs. A retrospective study has recently demonstrated that patients with relapsed myeloma who were refractory to bortezomib and were relapsed following, refractory to, or ineligible to receive IMiD, had a median overall survival (OS) and event-free survival (EFS) of 9 and 5 months, respectively[3]. Thus, there is a need for new strategies for managing patients prior to this stage to augment the benefits from early intervention with novel agents.

Ixazomib is a next generation, small molecule inhibitor of the 20S proteasome, the same target validated as therapeutically important in the treatment of malignancies using VELCADE® (bortezomib)[4]. The early development of ixazomib in patients with relapsed and/or refractory MM (RRMM) examined differing dosing schedules (C16003 and C16004), aimed to defined both the dose-limiting toxicities and the efficacy of the agent. The clinical experience with ixazomib has shown signs of antitumor activity in MM as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across[5].

The current HTA application for authorisation seeks the role for Ixazomib, in combination with lenalidomide and dexamethasone (IRd), for patients with relapsed MM having received at least 1 prior line of therapy. The current treatment pathway for patients with MM is largely formulated by the sequential NICE HTA (single and multiple TAs) to date. Furthermore, NICE guidance treatment of newly diagnosed patients as this will affect the treatments that can be offered according to NICE or the Cancer Drugs Fund at 1st, 2nd and 3rd line therapy. Currently newly diagnosed patients are treated according to whether they are transplant eligible (TE) or transplant ineligible (TI), and accordingly, NICE TA311 is applicable to TE patients approving the use of bortezomib/dexamethasone or bortezomib/thalidomide/dexamethasone. NICE TA228 is applicable to TI patients and approves the use of alkylator therapy/thalidomide/corticosteroid or thalidomide substituted with bortezomib if thalidomide is contraindicated or not tolerated. Additionally, Bortezomib is approved for routine commissioning by NHSE in June 2013. This means that a significant proportion of patients will have already received a bortezomib-based treatment prior to consideration of 2nd line therapy and beyond. Furthermore, secondline use of lenalidomide is no longer available following delisting from the Cancer Drugs Fund in November 2015. As such, the use of Lenalidomide with dexamethasone (LenDex) is reserved for patients in the 3rd line (after 2 prior lines of therapy), in accordance with NICE TA171. These approvals are incorporated into the UK Myeloma forum diagnosis and treatment guidelines[6].

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3. Kumar SK, Lee JH, Lahuerta JJ, et al Leukemia 2012;26(1):149-157.
4. Tian Z et al. Blood. 2012 Nov 8;120(19):3958-67
5. Kumar SKK et al. Lancet Oncol. 15, Dec 2014,
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As a consequence, the current application for approval relates to third line, which in keeping with NICE TA171, is LenDex. The application seeks to gain approval form the addition of Ixazomib to LenDex in this clinical space, aiming to secure a more durable disease response with associated clinical benefits and patient-reported freedom from disease-related morbidity. This is a technology applicable only to secondary/tertiary care, being prescribed by specialists in the care of MM patients, and not transferable to primary care (a "red" drug), especially with the special care and attention to side effect profiles and efficacy measures.

In relation to sub-groups of MM patients, two such groups have particular importance, those with genetic high risk disease and the elderly population. In terms of genetic high risk, delineated as t(4;14), TP53 gene deleted and t(14;16), then successive studies of novel agent combinations have singularly failed to demonstrate parity of efficacy with non-high risk patients. The data from TOURMALINE study however, does show parity of effect for this patient group[7]. In relation to the elderly population, the failure of novel agents to truly impact on survivorship, such as seen in seen in younger patients, may in part, relate to the ability to deliver appropriately efficacious therapy[8]. Ixazomib with LenDex offers a rapid and potent combination for depth of disease control, which not only is associated with improved patient experiences but also outcomes and thus could serve this specific population well minimising healthcare resource utilisation.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

7. Moreau et al, NEJM 2016, 374, 17, 1621
8. Palumbo et al, Blood, 2015, 125; 13, 2068.

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What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

A clear clinical advantage of the technology is the ability to produce rapid disease control, with a higher proportion of patients achieving a response with a longer PFS. The benefit of improved PFS when compared with lenalidomide and dexamethasone (current standard of care in this setting) has been demonstrated in the clinical trial. An important benefit is benefit of this combination in patients with high risk myeloma (approximately a third of patients in relapsed setting), where the IRD combination continues to show improved PFS, when compared with those receiving lenalidomide and dexamethasone. Quality of life has been maintained on the trial despite a use of triplet combination and bias has been eliminated with the study being blinded to both patients and physicians. With this technology being an all-oral combination, the uptake is likely to be higher and combination elderly myeloma patients would prefer. Disadvantages with this technology are limited. Within the trial the adverse events mostly noted are lenalidomide and dexamethasone related and has been observed in clinical practice with lenalidomide therapy. In addition low grade neuropathy rates, diarrhoea, fatigue, thrombocytopenia and rash are observed with the new technology and require vigilant monitoring in patients. As standard practice will be to review patients monthly, this should be addressed in routine follow up appointments.

Comparing this technology with the current standard of care lenalidomide and dexamethasone; there are no significant additional clinical requirements. Patients will need closer monitoring of counts and toxicities in the first 2-3 cycles. Patients will start this therapy when there is evidence of relapsed myeloma and stop either due to toxicity or disease progression while on therapy.

The use of Ixazomib/ lenalidomide and dexamethasone in relapsed myeloma patients within the trial reflects currents clinical practice in the UK. The results of TOURMALINE trial[7] can be extrapolated to UK population. Key outcomes in this trial are PFS, toxicity, QoL analysis all of which appear favourable and support its use in relapsed MM patient population.

Ixazomib use outside of clinical trials is limited in the UK. Adverse reactions described in trial are manageable and patients can be monitored for these on a month-to-month basis

Any additional sources of evidence

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Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Ixazomib is available through a compassionate use programme across Europe. Most UK hospitals have experience in using this combination within the label of the product.

Ixazomib Lenalidomide and dexamethasone induction followed by ASCT and consolidation was tested in a phase II trial by the IFM collaborative. The data was presented at ASH meeting in December 2016

IRD COMBINATION BEFORE AND AFTER ASCT FOLLOWED BY IXAZOMIB MAINTENANCE IN PATIENTS WITH NDMM: A PHASE 2 STUDY FROM THE INTERGROUPE FRANCOPHONE DU MYÉLOME (IFM)
Abstract 674, Oral, Prof. Moreau

The treatment was well tolerated with CR rate of 44% and VGPR rate of 79% post consolidation. No Grade 3-4 neuropathy was evident. This confirms the safety and efficacy of this combination. We await results of Phase III newly diagnosed Ixazomib / lenalidomide/ Dexamethasone vs Lenalidomide and dexamethasone in transplant ineligible newly diagnosed patients.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

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The proposed technology is an all-oral combination therapy. There are no additional delivery resource implications to the NHS. It is reasonable to expect that local haematology departments to draw up clinical protocols based on the evidence provided in this trial[7] on dosing, toxicity and pre requisite laboratory data prior to commencing treatment and during therapy

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Nil

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Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Kwee L Yong

Name of your organisation: Royal College of Pathologists, UK Myeloma Forum

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? No
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

Not applicable

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Response

Newly diagnosed patients with myeloma are generally (70-80%) treated with a bortezomib containing regimen if they are transplant eligible, the remaining receiving a thalidomide regimen or chemotherapy. For older, non-transplant eligible patients, around 50% will be treated on a bortezomib regimen (usually with an alkylating agent and prednisolone), the rest will receive a thalidomide regimen (usually in combination with cyclophosphamide and steroid), or chemotherapy. This is in accordance with NICE guidance.

Relapsed or relapsed/refractory myeloma is also currently treated according to NICE-guidance. This means that for second line treatment (at first relapse), bortezomib is used in patients who have previously not received bortezomib in front line therapy, otherwise thalidomide or chemotherapy (eg. cyclophosphamide) is used. At second relapse (third line), lenalidomide and dexamethasone is most commonly used, and at third relapse (fourth line), there are the options of bortezomib with panobinostat in patients previously treated with bortezomib, or pomalidomide and dexamethasone, or bendamustine. The choice of regimen, and dosing schedule, is often made by the physician depending on patient fitness, co-morbidities and disease tempo and biology. With increasing lines of therapy, there is more variability in the choice of regimens, because patient variability with regard to these factors also increases, as do patient priorities. In general, physicians treating patients with myeloma do not differ greatly in their opinions about current practice, nor is there much geographical variability except for the use of clinical trials in the large teaching hospitals, that allow patients to access agents that are unlicensed or not reimbursed.

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Among the current alternatives to the technology would be bortezomib or thalidomide combinations at second line, and Lenalidomide and Dexamethasone at third line. We expect that the technology will be used in third line, as this would be in accordance with NICE guidance regarding Lenalidomide. Thalidomide regimens have considerable toxicity in the form of neuropathy, thrombo-embolic risk and constipation. The added toxicity of the technology, when combined with Lenalidomide and dexamethasone, is minimal (nausea, abdominal discomfort, fatigue), over and above the side effects of Lenalidomide/dexamethasone. The triplet combination is generally well tolerated, provided appropriate dose reductions are in place, eg. for haematological toxicities.

A major advantage of the technology, when compared with currently available alternatives, is that it offers patients the opportunity to receive combination treatment with *a proteasome inhibitor (PI) and an Immunomodulatory Drug (IMiD)*, a combination that is fast becoming standard of care for patients globally. Notably, the technology is the only all oral PI+IMiD combination that is licensed. In an older and often less mobile patient population, all oral regimens reduce the health care burden of hospital visits for subcutaneous or intravenous alternatives, hence likely improving patient wellbeing.

Patients with relapsed or relapsed/refractory myeloma will differ in their disease biology, this is commonly termed “risk”. Around 25-40% of patients at relapse will be high risk. High risk patients are generally identified by their disease tempo (e.g. early relapse), result of cytogenetic tests, and International Staging System (ISS) stage. Results from the phase three Tourmaline study suggest that such high risk patients may benefit more from the technology, which is to say that high risk patients receiving the technology had similar outcomes to standard risk patients, while the outcomes for high risk patients receiving the control arm were inferior to those in standard risk patients.

The technology should be used in specialist clinics. Input from nurse specialist and oncology pharmacists is required, but this is no different from any other cancer treatment. Patient counselling regarding likely side effects and supportive medication are not different from alternative therapies.

The technology is currently available as part of a named patient programme, where it is used according to its licensed indication.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements

for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Response

The advantages and disadvantages of the technology
The technology will be just as easy to use as the current alternative, Lenalidomide and Dexamethasone. It is oral, with a simple dosing schedule (3 weekly doses each 4-week cycle), has mainly Grade 1-2 side effects and is well tolerated, as indicated by the QOL data from the phase 3 Tourmaline study. Patients are unlikely to need additional concomitant medications, or blood tests; thus the technology is as easy to use as the alternative, Lenalidomide and Dexamethasone.

The phase 3 study was conducted in relapsed/refractory patients, whose characteristics and circumstances reflect current UK practice and patient population. In such a patient population, the most important outcomes are progression free survival (PFS), and overall survival (OS). Given the long OS in relapsed patients today, the use of PFS as a surrogate marker of benefit is appropriate, as recently reported (Fisher et al, 2013). Another relevant endpoint is the analysis of subgroups defined by cytogenetic features, and the quality of life data.

Side effects and adverse reactions of the technology
These are, in general, mild: nausea, rash, fatigue, diarrhoea and low platelet counts, all of which are easily managed with patient education and supportive medications, and do not add significantly to the toxicity of Lenalidomide and dexamethasone alone. The once weekly schedule of an oral medication has the advantage of convenience, improved lifestyle for patients, and reduces the healthcare burden of hospital visits for intravenous/subcutaneous therapy. No additional monitoring is required, and I am not aware of any adverse effects that have come to light during clinical use of the technology on the NPP, that were not apparent in clinical trials.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

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- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Response
There are as far as I know, no implications of this appraisal for the equality legislation.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Real life experience of the technology, accrued using the named patient programme (n=30), has been submitted to the European Haematology Association meeting in June 2017, and confirms good safety profile and tolerability, with similar responses and PFS to that reported for the phase 3 study.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

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How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Response

Positive NICE guidance for this technology would markedly improve patient outcomes and experience, by making available an all oral, well tolerated, convenient and effective treatment regimen for patients with relapsed disease. It would improve the delivery of care for these patients, by releasing healthcare resources to be utilised elsewhere. This is particularly important given the increasing use of intravenous therapies for patients with cancer, impacting on hospital day care resources. Thus this would make a major contribution to patient care, potentially not just for patients with myeloma, but to the wider patient population.

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Title: Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed refractory multiple myeloma

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Declared competing interests of the authors

The authors have no conflicts of interest.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed refractory multiple myeloma: A Single Technology Appraisal. Warwick Evidence, 2017.

Contributions of authors: Xavier Armoiry (Senior Research Fellow) conducted the critique of clinical effectiveness evidence and co-ordinated the project; Ewen Cummins (Health Economist) conducted, reviewed and critiqued the cost-effectiveness evidence; Martin Connock (Senior Research Fellow) conducted the critique of clinical effectiveness evidence and undertook additional analyses; Alexander Tsertsvadze (Senior Research Fellow) conducted the critique of clinical effectiveness evidence and the NMA; G.J. Melendez-Torres (Assistant Professor) conducted the critique of clinical effectiveness evidence and the NMA; Rachel Court (Information specialist) and Pam Royle (Research Fellow) conducted the critique of the company searches; Karoline Munro conducted the critique of the background section and decision problem and contributed to the reporting of clinical effectiveness data; and Aileen Clarke (Professor of Public Health and Health Services Research) co-ordinated the project and provided comments on the report.

Word count: 65,667.

Please note that: Sections highlighted in yellow and underlined are [redacted] Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

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LIST OF ABBREVIATIONS

ASCO	American Society of Clinical Oncology
BORD	Bortezomib + Dexamethasone
BORT	Bortezomib
BSC	Best Supportive Care
CARF	Carfilzomib
CEAF	Cost-effectiveness Acceptability Frontier
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CR	Complete Response
CS	Company Submission
CYCLO	Cyclophosphamide
DEX	Dexamethasone
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQol – 5 Dimensions
ERG	Evidence Review Group
FAD	Final Appraisal Determination
FDA	U.S.Food and Drug Administration
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio

IV	Intravenous
IXA	Ixazomib
IXAL	Ixazomib + Lenalidomide + Dexamethasone
KM	Kaplan Meier
LEN	Lenalidomide
LEND	Lenalidomide + Dexamethasone
LYG	Life Years Gained
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
OR	Odds Ratio
ORR	Objective Response Rate
OS	Overall Survival
PANO	Panobinostat
PFS	Progression-Free Survival
POM	Pomalidomide
PPS	Post-Progression Survival
PR	Partial Response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Services
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomised Controlled Trial
RoB	Risk of Bias

RR	Response rates
RRMM	Relapsed Refractory Multiple Myeloma
SD	Standard Deviation
SPC	Summary of Product Characteristics
TMM-1	Tourmaline MM1 trial (pivotal trial)
TTNT	Time to next treatment
TTP	Time To Progression
UK	United Kingdom
VGPR	Very Good Patient Response

1 SUMMARY

1.1 Critique of the decision problem in the company submission

The CS decision problem matches the population, the interventions and outcomes described in the final NICE scope, as seen in Box 1. The CS decision problem differs from the NICE scope on the comparators, with lenalidomide + dexamethasone, bortezomib retreatment, and panobinostat with bortezomib and dexamethasone being excluded from the decision problem. While the NICE scope indicated a group of comparators for patients who have had at least 1 therapy, the Company considered a group of comparators for patients who have had one prior therapy.

Ixazomib 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. A positive opinion granting marketing authorisation of Ixazomib was adopted by the Committee for Medicinal Products for Human Use in September 2015. This opinion was preceded by an initial negative opinion by the CHMP.

	Final scope issued by NICE
Population	People with relapsed or refractory multiple myeloma who have had at least 1 therapy
Intervention	Ixazomib in combination with lenalidomide and dexamethasone
Comparator (s)	For people who have had at least 1 therapy: -bortezomib (with or without dexamethasone) -bortezomib retreatment (with or without dexamethasone) -lenalidomide with dexamethasone (subject to ongoing NICE appraisal) For people who have had at least 2 therapies: -lenalidomide with dexamethasone -panobinostat with bortezomib and dexamethasone
Outcomes	-Progression-free survival -Overall survival -Response rates -Time to next treatment -Adverse effects of treatment -Health-related quality of life

Box 1: NICE final scope

1.2 Summary of submitted clinical effectiveness evidence

The CS undertook a systematic review to search for evidence of relevance to the decision problem, including searches for studies on the intervention and separate searches for comparator studies for a network meta-analysis.

The CS includes direct evidence of ixazomib in combination with lenalidomide and dexamethasone compared with placebo and lenalidomide and dexamethasone from one phase 3

RCT. The CS presents outcomes of survival (progression free survival, overall survival), time to progression, response rates, health-related quality of life (HRQoL) and adverse events. The Tourmaline MM1 trial was of good quality, with a low risk of bias in most domains.

- For progression-free survival (PFS), the HR from the first interim analysis suggested a 26% reduction in risk (HR 0.74, 95% CI 0.5, 0.94) with ixazomib, which led to the approval of this drug. At the second data cut, corresponding to more mature data, a non-inferential analysis showed a reduced treatment effect for ixazomib (HR 0.82, 95% CI 0.67, 1.0; p=0.054).
- For overall survival (OS), the hazard ratio indicated similar outcome in those treated with ixazomib compared with placebo in both first (HR for death 0.90 95% CI 0.62, 1.32) and second (HR 0.87, 95% CI 0.64, 1.18) interim analyses. Further analyses, not yet available, using more mature data will indicate whether ixazomib improves OS.
- Overall response rate (ORR) was higher with ixazomib than with placebo in the first interim analysis: ORR was 78.3% in the ixazomib group and 71.5% in the placebo (OR 1.44, 95%CI 1.03, 2.03; p=0.04). The benefit of ixazomib on ORR was not sustained in the second interim analysis (OR 1.35, 95%CI 0.96, 1.91).
- Very good response and complete response were higher with ixazomib than with placebo in the first interim analysis (48.1% in the ixazomib group and 39.0% in the placebo group; OR 1.45, 95%CI 1.08, 1.95). The benefit of ixazomib on this outcome was sustained in the second interim analysis (OR 1.35, 95%CI 1.01, 1.81).
- There were no significant differences observed between groups on measures of HRQoL.
- Discontinuation due to adverse events occurred in 17% vs. 14% in the IXA+LEN+DEX group vs. LEN+DEX. The most common haematologic adverse events were neutropenia (33% vs. 31% for IXA vs. placebo, with grade 3 events at 18% vs. 18% and grade 4 at 5% vs. 6%) and thrombocytopenia (31% vs. 16% for IXA vs. placebo), with grade 3 events at 12% vs. 5% and grade 4 at 7% vs.4% (CS, 143, 144, table 55). Rash (any grade), occurred in 36% vs. 23% of patients in the IXA vs. placebo group.
- The Company undertook several subgroup analyses including one comparing the clinical outcomes per number of prior line. In the 1 prior therapy population, the Tourmaline MM1 trial showed no benefit of ixazomib on PFS (HR $_{\text{1st interim analysis}}$ 0.88, 95% CI 0.65, 1.20) or on OS (HR $_{\text{2nd interim analysis}}$ 1.11, 95%CI, 0.74, 1.66). In the 2+ prior therapies population, the benefit of ixazomib was greater on PFS (HR $_{\text{1st interim}}$

$_{\text{analysis}}$ 0.58, 95%CI 0.40, 0.84). Further analyses using more mature data will indicate whether the trend toward an increased survival with ixazomib is confirmed ($HR_{\text{2nd interim analysis}}$ 0.65, 95%CI, 0.41, 1.02) in this sub-population. Of note, the greater benefit of ixazomib in the 2+ prior therapies population seems largely driven by an increased benefit of ixazomib in heavily pre-treated patients (fourth line) and less by the group of people with 2 prior therapies (third line). The third line is where the Company would mainly position ixazomib within the NHS consistently with the current use of lenalidomide + dexamethasone.

The CS presented indirect evidence for comparisons with bortezomib + dexamethasone in the 1+ prior therapy group via a network meta-analysis (NMA). The network included a wider range of comparator treatments for relapsed refractory multiple myeloma (RRMM). The ERG has a number of major concerns about the NMA, its reporting and methodology as discussed subsequently. Results presented by the CS are:

- Ixazomib + lenalidomide+dexamethasone showed a significantly greater PFS than lenalidomide+dexamethasone in line with the results of the TMM-1 trial. The comparison of ixazomib + lenalidomide+dexamethasone with bortezomib + dexamethasone shows no statistically significant difference in PFS (0.72, 95%CrI 0.41, 1.19). The ERG critiqued these results since the NMA used a non-RCT of poor methodological quality with irrelevant interventions including cyclophosphamide (lenalidomide+dexamethasone+cyclophosphamide versus bortezomib + dexamethasone +cyclophosphamide instead of lenalidomide+dexamethasone versus bortezomib + dexamethasone) to indirectly compare ixazomib + lenalidomide+dexamethasone with bortezomib + dexamethasone.
- Ixazomib + lenalidomide+dexamethasone showed no benefit on OS over lenalidomide+dexamethasone in line with the results of the TMM-1 trial. The indirect comparison of ixazomib + lenalidomide+dexamethasone with bortezomib + dexamethasone shows a statistically significant difference in OS (HR 0.31, 95%CrI, 0.13, 0.65), suggesting that ixazomib + lenalidomide+dexamethasone reduces the risk of death by 69%. The ERG has presented in a subsequent section a critique of this result, given the strongly implausible magnitude of the benefit in OS of ixazomib, and identified an unfortunate error on the inputs that were used by the Company in its NMA: within the Company's NMA inputs, the HR for death of dexamethasone versus bortezomib was 0.57 while 0.57 corresponded, as reported in the APEX trial, to the HR for death of bortezomib versus dexamethasone.

- Ixazomib + lenalidomide+dexamethasone showed a significantly greater ORR than lenalidomide+dexamethasone in line with the results of the TMM-1 trial. The comparison of ixazomib + lenalidomide+dexamethasone with bortezomib + dexamethasone shows no statistically significant difference in ORR (OR 0.88, 95%CrI 0.35, 1.85).
- Other results were presented for Best Overall Response and Discontinuation due to AEs.

The CS was unable to present indirect evidence for comparisons with bortezomib + dexamethasone in the 1 prior therapy group via a NMA on the ground that there insufficient data to connect the network. The ERG has critiqued this and additional searches have enabled us to identify records that would allow connection of the network interventions and therefore to undertake an NMA.

1.3 Summary of the ERG's critique of submitted clinical evidence

The ERG considered the systematic review to be of reasonable quality and substantially agreed with the CS appraisal of the pivotal phase 3 trial that compared ixazomib+lenalidomide+dexamethasone with one of the scoped comparators, lenalidomide+dexamethasone. The outcomes and analytical approach to the phase 3 trial were appropriate. The population in the trial appear to be relevant to those treated in the NHS and the ERG does not have any reason to consider the results of the trial to be significantly biased. However, clinical effectiveness data are characterised by a high degree of immaturity since the benefit of ixazomib on OS cannot yet be determined.

The ERG noted several issues with the submitted clinical evidence.

- The ERG has concerns regarding the exclusion of a scoped comparator, lenalidomide+dexamethasone, from the decision problem. Lenalidomide in the RRMM population is currently being considered by NICE in an ongoing appraisal. For this reason the CS considers that lenalidomide+dexamethasone is not a relevant comparator as it is not currently used in NHS practice for second line treatment. The ERG has considered the clinical effectiveness evidence for this potential comparator owing to the presence of a direct comparison for these two regimen.
- The evaluation of the NMA is restricted, in part owing to the limited details provided as regards some aspects of the analysis and results.
- As indicated earlier, the ERG has major concerns with regards to the NMA presented by the Company. First, the studies included within the NMA are characterized by a

high level of heterogeneity. Secondly, the comparison of ixazomib + lenalidomide+dexamethasone with bortezomib + dexamethasone was possible only using non-RCT studies. Lastly, and as indicated in previous section, the ERG has identified several major flaws in the NMA's results related to the main outcomes of interest (PFS, OS).

1.4 Summary of submitted cost effectiveness evidence

The economics considers two patient groups:

- Those at 2nd line: This is modelled using the TMM-1 1 prior subgroup
- Those at 3rd line: This is approximated by the TMM-1 2+ prior subgroup.

For the 1 prior the comparator for ixazomib+lenalidomide+dexamethasone (IXA+LEN+DEX) is bortezomib+dexamethasone (BORT+DEX). For the 2 prior subgroup the comparator is lenalidomide+dexamethasone (LEN+DEX)

The company submits a partitioned survival model with a weekly cycle length and a 25 year time horizon. The perspective and discounting is as per the NICE reference case. In common with many cancer models, patients are modelled as being in either progression free survival (PFS), post progression survival (PPS) or dead. The OS curve of a treatment defines those alive and those dead through time. The PFS curve of the treatment subdivides the proportion modelled as alive into those in PFS and those in PPS.

Subgroup specific parameterised curves adjusted for a range of covariates are estimated from the TMM-1 patient data. The company uses the 1st interim data cut for its analysis.

The company notes that some patients were treated beyond progression. This is the apparent justification for the additional element of the time on treatment (ToT) which determines the treatment costs. Treatment holidays and missed doses are separately accounted for and are not part of the ToT, with ToT only considering treatment cessation. The effect of this is mainly to further partition the PFS into those on treatment and those who have ceased treatment. This substantially reduces the treatment costs to less than that which would be estimated using the PFS, particularly for IXA+LEN+DEX.

Those in PFS are further subdivided by their Best Overall Response (BoR) which can be either very good partial response or complete response (VGPR+), partial but not very good response (PR) or stable disease (SD). The distribution between BoR states is treatment specific and assumed to apply to patients over their entire PFS.

To estimate the curves for BORT+DEX the company applies hazard ratios to the LEN+DEX curves:

- OS: An HR of 3.11 from the NMA
- PFS: An HR of 1.06 from the NMA
- ToT: An HR of 1.00 by assumption due to a lack of data

The BoR distribution for BORT+DEX is estimated using the NMA odds ratio of 2.28 compared to LEN+DEX and the LEN+DEX 1 prior subgroup 78% response rate.

Quality of life values are estimated through a repeated measure model using the TMM-1 EQ-5D data. Treatment is not considered as a covariate but the BoR status is. Given the treatment specific BoR distributions and quality of life values of 0.712 for VGPR+, 0.674 for PR and 0.653 for SD these result in treatment specific quality of life values while remaining in PFS:

- For the 1 prior subgroup of:
  - 0.690 for IXA+LEN+DEX
  - 0.689 for LEN+DEX
  - 0.674 for BORT+DEX
- For the 2+ prior subgroup of:
  - 0.694 for IXA+LEN+DEX
  - 0.684 for LEN+DEX

The PPS quality of life is estimated to be 0.654 which the company notes is higher than the value for SD, arguing that this is due to subsequent treatments among the 24% who received active treatment after progression during TMM-1 follow-up.

Serious adverse events (SAEs) are also modelled with rates being taken from the TMM-1 trial pooled across arms and subgroups for IXA+LEN+DEX and LEN+DEX, and from PANORAMA-1 for BORT+DEX. The duration of each SAE is estimated from TMM-1 data, with the quality of life regression suggesting a common -0.16 quality of life decrement while they are being experienced. SAEs costs are estimated from NHS reference costs.

Hospitalisation costs are also modelled based upon TMM-1 data, with a mean annualised cost per patient of £317 for those in PFS and £304 for those in PPS.

The 24% who received active treatment after progression are modelled as incurring a one off treatment cost of £70,188.

End of life costs of £10,670 are assumed to be incurred by 20% of patients.

This results in company base case estimates:

- For the 1 prior subgroup a cost effectiveness for IXA+LEN+DEX compared to BORT+DEX of [redacted] per QALY.
- For the 2+ prior subgroup a cost effectiveness for IXA+LEN+DEX compared to LEN+DEX of [redacted] per QALY.

1.5 Summary of the ERG's critique of cost effectiveness evidence

The economics of the company submission is incomplete in 3 main areas:

- Relying upon the 1st interim data cut and providing little to no consideration of the 2nd interim data cut. This seems peculiar given the company assertion that longer trial follow-up is needed to properly judge ixazomib.
- Not considering LEN+DEX as a comparator for the 1 prior subgroup. It is specified in the scope. The company states that it cannot provide this. The available evidence suggests that LEN+DEX dominates IXA+LEN+DEX for the 1 prior subgroup.
- Assuming the 2+ prior subgroup is the best proxy for the 2 prior subgroup and not considering the 2 prior subgroup data. This is complicated by the trial being stratified by 1 prior subgroup and 2+ prior subgroup but the company submission, CSR and clarification response provide forest plots differentiated by 1 prior subgroup, 2 prior subgroup and 3 prior subgroup. The available evidence suggests that the cost effectiveness of IXA+LEN+DEX compared to LEN+DEX is somewhat worse for the 2 prior subgroup than for the 2+ prior subgroup.

The economics of the company submission may be biased in a number of areas:

- The NMA results for BORT+DEX compared to LEN+DEX as reviewed in more detail in the clinical effectiveness section suggest survival for BORT+DEX is much too low.
- The costs of BORT+DEX have been overestimated, with a number of biases being introduced within the modelling.
    - Assuming a maximum of 9 cycles rather than 8 cycles
    - Assuming every three week cycle is completed rather than applying the PFS or Time on Treatment (ToT) curve.

  - Assuming treatment is discontinued at progression when partial response at 4 cycles also results in discontinuation.
  - Assuming those with complete response continue to the maximum number of cycles when they only receive a further 2 cycles
  - Assuming a hazard ratio of 1.00 for ToT compared to LEN+DEX due to a lack of data when a hazard ratio of 1.06 for PFS compared to LEN+DEX has been applied
  - The progression dependent bortezomib refunds may also have been underestimated, though the ERG in conjunction with NICE is exploring whether these refunds would apply in the context of the BORT+DEX doublet
- Most BORT+DEX patients will receive their subcutaneous injections in hospital, though there are some home care facilities available. The OP visits subsequent to the first of each cycle have not been costed.
- For the 1 prior subgroup the company base case delays the OS exponential for IXA+LEN+DEX by 5 months but does not do so for LEN+DEX, which by the application of the NMA HR flows through to BORT+DEX. The company accepts that this results in bias against BORT+DEX and that the LEN+DEX OS exponential should also be delayed by 5 months.
- The distribution of Best overall Response (BoR) for BORT+DEX is drawn from a study of monotherapy bortezomib against monotherapy dexamethasone. The company has inadvertently used the dexamethasone values. The ERG is of the opinion that a study of BORT+DEX is more appropriate and that the ENDEAVOR study provides data in the required format.
- The disutility for subcutaneous injection seems too large and for a frail population may, as argued by the company, be related more to the inconvenience of hospital visits than the 3-5 seconds subcutaneous injection. If so, the disutility should be attached to the number of hospital visits and not being on a treatment that involves a small number of subcutaneous injections.
- The quality of life as patients relapse and cycle through treatments seems likely to decline. It will also decline with age.
- The proportion of patients receiving active treatment in PPS is based upon using the number in the trial as the denominator rather than the number who had progressed at the 1st interim data cut. This underestimates the treatment proportion.

- The cost of treatment among those who have progressed and receive another active treatment is modelled as a one off incident cost so may unreasonably tend to cancel out between arms, much like end of life costs. It may be more accurate to model this as an ongoing cost among those in PPS.

1.6 Summary of the ERG's critique of submitted evidence

1.6.1 Strengths

The CS had several strengths.

- Overall, quality of the systematic review was deemed to be reasonable, and assessment of risk of bias of the pivotal RCT was generally appropriate.
- The quality of the included trial was good with a low risk of bias.
- Results for the trial were accurately presented and showed the risks and benefits from the addition of ixazomib to lenalidomide+dexamethasone, one of the scoped comparators.
- The submission provides a relatively clear account of the cost effectiveness modelling that has been submitted. The TMM-1 trial provides a reasonable basis for the comparison of IXA+LEN+DEX with LEN+DEX.

1.6.2 Weaknesses and areas of uncertainty

Clinical Effectiveness

The CS excluded several scoped comparators from their decision problem. The ERG accepts the exclusion of bortezomib retreatment at first relapse, however, does not believe that the exclusion of lenalidomide + dexamethasone for 1 relapse and panobinostat +bortezomib+dexamethasone at second relapse are justified.

There is only one comparative study of ixazomib, therefore, the assessment of the treatment effects of ixazomib compared with bortezomib + dexamethasone relied on indirect comparisons via a NMA. There are a number of major flaws with the NMA which lead to the ERG having concerns over the results of the Company's NMA, and to recommend an alternative analysis (see exploratory analyses).

Methodological flaws:

The quality of reporting of the company's NMAs was disappointing. The NMA details lacked clarity, were dispersed confusingly between clinical effectiveness and cost effectiveness sections and the appendices, and were incomplete lacking NMA input values, NMA codes and much output. Many deficiencies were remedied in clarification but this was late in the assessment timetable.

The ERG has identified several methodological flaws of the NMA, in particular focusing on the assumptions of homogeneity, similarity, and consistency.

- The transitivity assumption does not hold, since the distribution of population characteristics that are effect modifiers differ across the treatment comparisons of the network. One such treatment effect modifier in the Company's NMA is the number of prior therapies. While the TMM-1 trial included around 60% patients at the first relapse, the MM-09 and 10 studies included around 60-65% of patients with 2 prior therapies. The Dimopoulos 2015 study selected patients from 3 RCTs selecting only (100%) those with 1 prior therapy. Another threat to transitivity is the difference in doses for DEX 40 (different scheduling) in MM-1 vs. 009/010 trials.
- The indirect comparison (for OS, HR for risk of death) ixazomib + lenalidomide+dexamethasone with bortezomib + dexamethasone has no common first-order comparator and therefore was based on the second-order indirect comparison which was achieved through comparing the HR estimates for two indirect comparisons. A longer pathway of multiple intermediate indirect comparison steps used to derive the main indirect comparison leads to even greater uncertainties in the estimates. The more intermediate links which separate the indirectly compared treatments, the more unreliable this comparison becomes, through increasing the standard error of the effect estimate. Therefore, the validity of the OS-HR estimate for the indirect comparison IXA + LEN + DEX vs. BORT + DEX is questionable.
- The NMA did not form any closed loops including mixed treatment comparison. Understandably, consistency between indirect and direct comparisons was not assessed. Indeed, this is one of the main limitations of the evidence provided in the NMAs of the manufacturer's submission owing to the inability to judge to what degree the transitivity assumption was violated.

The ERG has also critiqued the assumptions applied in the NMA results. The company applied the NMA hazard ratio (HR) outputs for the development of estimates of mean life years spent

in health states in their economic model. The ERG has several reservations regarding how this was undertaken; several underlying assumptions were not tested and there were some inconsistencies of approach:

- The procedure assumed that proportional hazards hold between treatments compared in the NMA included studies, and in the indirect comparisons between intervention and comparator; no evidence was produced to support these assumptions.
- The application of NMA output HRs to selected parametric baseline models (LEN + DEX arm from Tourmaline) imposes (assumes) the same model shape for all compared treatments; there is no *a piori* reason that this holds and no evidence was submitted in justification.
- It was unclear if HR input values for the NMAs were unadjusted or adjusted, and if they were adjusted what covariates were used in adjustment. No information on this was provided in the CS. Since in the base case economic model the NMA HRs are applied to adjusted parametric baseline models there is the possibility of double counting of adjusting covariates and of application of differing covariates for compared treatments.
- In the main comparison of overall survival for the 1 prior population, the NMA outputs were only used for the BORT + DEX model and not for the IXA + LEN + DEX model; this inconsistency of approach as insufficiently justified.

CS NMA results:

The ERG has identified several flaws in the NMA presented by the company, this includes an unfortunate error on the OS NMA that lead to implausible results. This has been described previously and will be presented in detail in the relevant section of the report.

Cost effectiveness

The use of the 2nd interim analysis within the company modelling appears to somewhat worsen the cost effectiveness estimate for the 1 prior subgroup, but to improve it to a degree for the 2+ prior subgroup. But the ERG has not parsed this modelling, it is a mix of elements from the 1st interim analysis and the 2nd interim analysis, there are a number of uncertainties around it and the curves chosen by the company may not be reasonable either in terms of their AIC and BIC or in terms of their clinical plausibility.

For overall survival among the 1 prior subgroup, due to proportionate hazards being questionable over the first 5 months, the company chooses to use the Kaplan Meier data for the first 5 months and estimate an exponential curve from the post 5 months trial data. No other curves are presented for this post 5 month data set which is not in keeping with the rest of the submission. This reduces the confidence that can be placed in the delayed exponential of the 1 prior subgroup.

Extrapolation that maintains the relative treatment effect of the trials over the 25 year time horizon may exaggerate the differences. The analysis should explore reducing the extrapolated clinical effectiveness. This will probably worsen the company cost effectiveness estimates and the ERG 2 prior subgroup cost effectiveness estimates, and reduce but not eliminate the ERG 1 prior subgroup estimated dominance of BORT+DEX and LEN+DEX over IXA+LEN+DEX.

Addressing the costing issues around BORT+DEX will worsen the cost effectiveness of IXA+LEN+DEX for this comparison. The implementation of the complex progression based PAS for bortezomib if applicable also underestimates the probable refunds. But the complex progression based PAS for bortezomib may not apply to the BORT+DEX doublet. Removing this from the modelling has minimal impact upon the cost effectiveness estimates for IXA+LEN+DEX compared to BORT+DEX.

The treatment effect in the quality of life regression is not reported, and the 1 prior / 2+ prior split is not explored at all. The direction of effect of these is not known by the ERG.

If quality of life declines with each relapse and with age as seems likely this will probably worsen the cost effectiveness of the treatment with the greater overall survival, though this will also be determined by the balance between PPS and PFS which may differ between treatments.

The baseline quality of life was higher in the IXA+LEN+DEX arm than the LEN+DEX arm. There is the suggestion that a better baseline quality of life increases the likelihood of a good response, particularly among the 1 prior subgroup. The company adjusted the parameterised curves for a number of factors, but the baseline quality of life does not appear to have been explored. The company does not perform any adjustment to the BoR data when it might be anticipated that a similar range of covariates including the baseline quality of life, which differed between the arms, might be factors.

Modelling PPS costs as a function of PPS duration rather than a one off incident cost appears to worsen the cost effectiveness of the more effective treatment, though this will depend upon the balance between PFS and PPS which may differ by treatment.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Exploratory analyses related to the clinical effectiveness

First, the ERG made a number of exploratory analyses on the clinical effectiveness estimates for the indirect comparison of ixazomib+lenalidomide+dexamethasone with bortezomib + dexamethasone focusing on PFS (1+ and 1 prior therapy group), OS (1+ and 1 prior therapy group) and ORR (1 prior therapy group).

In the 1+ prior therapy group the ERG found:

- The HR for progression or death of ixazomib+lenalidomide+dexamethasone relative to bortezomib + dexamethasone is 0.75 (95%CI 0.41, 1.38)
- The HR for death for ixazomib+lenalidomide+dexamethasone relative to bortezomib + dexamethasone is 0.91 (95%CI 0.43-1.92)

In the 1 prior therapy group we found:

- The HR for progression or death of ixazomib+lenalidomide+dexamethasone relative to bortezomib + dexamethasone is 0.90 (95%CI 0.41-1.96)
- The HR for death of ixazomib+lenalidomide+dexamethasone relative to bortezomib + dexamethasone is 2.16 (95%CI 0.74, 6.36)
- The OR for ORR of ixazomib+lenalidomide+dexamethasone relative to bortezomib + dexamethasone is 0.77 (95%CI 0.27-2.23)

The ERG would like to insist on the exploratory character of these analyses since no proper systematic review was conducted to search for additional of information. Secondly, the same methodological critiques as those emphasized in the report of the CS NMA apply here. However, since relevant studies from additional literature searches were used, the ERG believes that these exploratory analyses on PFS are more robust than those produced by the company. The ERG's NMA on OS in the 1+ prior therapy group gives a considerably different, but more plausible, estimate for the HR of IXA-LEN-DEX relative to BORT-DEX.

The ERG undertook additional analyses including:

- A comparison of the CS modelled OS and PFS for the BORT + DEX comparator in the 1 prior population and the OS and PFS observed for these outcomes in the studies that the company included in its NMA for these outcomes
- A comparison of the CS NMA HR results for OS and PFS with those reported in multiple studies comparing treatments for MM

These analyses indicated that the CS model of OS for BORT + DEX was likely a considerable underestimate and was largely influenced by NMA studies that did not actually report on this intervention. The analyses also indicated that the CS model of PFS for BORT + DEX was a considerable overestimate and was also largely influenced by NMA studies that did not report on this intervention. Both these indications pointed to possible errors in the NMAs undertaken by the CS. Plots of pairs of HRs for OS and PFS strongly inferred that the CS HR pair for OS for BORT + DEX was an extreme outlier.

The company did not undertake clinical effectiveness analysis of IXA + LEN +DEX versus LEN + DEX for the 2 prior population, even though this was specified by the company as the likely position for their drug in the treatment pathway (as third line therapy). Therefore in further analysis the ERG used survival data provided by the company in clarification to develop Kaplan-Meier estimates and parametric models for OS, PFS and ToT that were used in cost effectiveness analysis. The results indicate that the relatively favourable results seen for IXA + LEN +DEX versus LEN + DEX in the 2+ prior population are not reflected in results for the two prior population and that a small subgroup of 3 prior patients are highly influential in driving the comparison of treatments in the 2+ prior population.

Exploratory analyses related to the cost-effectiveness

The ERG amends the company modelling of the 1 prior subgroup and the 2+ prior subgroup in a number of ways. This mainly affects the 1 prior subgroup modelling that uses the company NMA, with the revisions causing the cost effectiveness estimate for IXA+LEN+DEX compared to BORT+DEX worsening from [redacted] per QALY to [redacted] per QALY. The cost effectiveness estimate in the 2+ prior subgroup for IXA+LEN+DEX compared to LEN+DEX only worsens from £[redacted] to £[redacted] per QALY.

The main additional analyses of the ERG modelling:

- Compare IXA+LEN+DEX with LEN+DEX for the 1 prior subgroup using the company TMM-1 curves for the 1 prior group. This suggests that IXA+LEN+DEX is dominated by LEN+DEX.
- Apply the ERG NMA results for the 1+ prior subgroup rather than the company NMA results for the 1+ prior group to the 1 prior subgroup. This suggests that IXA+LEN+DEX is dominated by BORT+DEX.
- Apply the unadjusted curves derived by the ERG from the 2 prior patient subgroup Kaplan Meier data supplied at clarification. This suggests a cost effectiveness of [redacted] per QALY for IXA+LEN+DEX compared to LEN+DEX for the 2 prior subgroup

For the 1 prior subgroup estimating the IXA+LEN+DEX curves by applying the 1+ prior NMA estimates to the 1 prior LEN+DEX TMM-1 curves, rather than simply using the 1 prior IXA+LEN+DEX TMM-1 curves, improves the cost effectiveness estimate based upon the company NMA from [redacted]k per QALY to [redacted] per QALY. IXA+LEN+DEX also ceases to be dominated by LEN+DEX, and has a cost effectiveness estimate of [redacted]k per QALY. Similarly, when using the ERG NMA IXA+LEN+DEX ceases to be dominated by BORT+DEX, and has a cost effectiveness estimate of [redacted]k per QALY.

There is uncertainty about the reasonableness of the time on treatment curves. These are better labelled time to complete cessation of treatment curves and are used to estimate the treatment costs. They suggest that perhaps as little as the first 65% of IXA+LEN+DEX PFS is spent receiving treatment with the remaining 35% of IXA+LEN+DEX PFS being spent off treatment. Costing treatment using the PFS curves:

- For the 1 prior subgroup using the company NMA worsens the cost effectiveness estimate for IXA+LEN+DEX compared to BORT+DEX from [redacted] per QALY to [redacted] per QALY.
- For the 2+ prior subgroup using the company TMM-1 curves worsens the cost effectiveness estimate for IXA+LEN+DEX compared to LEN+DEX from [redacted] per QALY to [redacted]per QALY.
- For the 1 prior modelling using the company TMM-1 curves still suggests IXA+LEN+DEX is dominated by LEN+DEX.
- For the 1 prior modelling using the ERG NMA still suggests IXA+LEN+DEX is dominated by BORT+DEX.

- For the 2 prior subgroup modelling using the ERG TMM-1 curves worsens the cost effectiveness estimate for IXA+LEN+DEX compared to LEN+DEX from [redacted] per QALY to [redacted] per QALY.

The main sensitivity of results in terms of the curves functional forms, restricting attention to those that may be reasonable to apply for overall survival is:

- For the 1 prior subgroup using the company NMA the cost effectiveness estimate for IXA+LEN+DEX compared to BORT+DEX worsens from [redacted] per QALY to [redacted] per QALY if the Weibull is used for overall survival.
- For the 2+ prior subgroup using the company TMM-1 curves the cost effectiveness estimate for IXA+LEN+DEX compared to LEN+DEX improves from [redacted] per QALY to [redacted] per QALY if the exponential is used for overall survival. But there is uncertainty about the AIC and BIC values for the exponential. It also suggests a fair proportion of patients remain alive after 25 years: over 6% for IXA+LEN+DEX and 1% for LEN+DEX.
- For the 2 prior subgroup modelling using the ERG TMM-1 curves the cost effectiveness estimate for IXA+LEN+DEX compared to LEN+DEX worsens quite considerably from [redacted] per QALY if anything other than the exponential is used for overall survival.

The parallel for the ToT curves is:

- For the 2+ prior subgroup using the company TMM-1 curves the base case ToT curve provides the best cost effectiveness estimates, the Weibull worsening the cost effectiveness estimate from [redacted] per QALY to [redacted] per QALY.
- For the 2 prior subgroup modelling using the ERG TMM-1 curves the cost effectiveness estimate for IXA+LEN+DEX compared to LEN+DEX worsens quite considerable from [redacted] per QALY if anything other than the exponential is used for overall survival. The Weibull is the least worst of the alternatives, only worsening it to [redacted] per QALY.

The 1 prior modelling using the company TMM-1 curves and the ERG NMA suggests that IXA+LEN+DEX remains dominated by LEN+DEX and by BORT+DEX regardless of the functional forms that are chosen.

The modelling of treatment costs after progression is questionable and may unreasonably cancel out between arms. Revising the proportion that receives post progression treatment and exploring an ongoing weekly cost for this:

- For the 1 prior subgroup using the company NMA worsens the cost effectiveness estimate for IXA+LEN+DEX compared to BORT+DEX from [redacted] per QALY to [redacted] per QALY.
- For the 2+ prior subgroup using the company TMM-1 curves worsens the cost effectiveness estimate for IXA+LEN+DEX compared to LEN+DEX from [redacted] per QALY to [redacted] per QALY.
- For the 1 prior modelling using the company TMM-1 curves still suggests IXA+LEN+DEX is dominated by LEN+DEX.
- For the 1 prior modelling using the ERG NMA still suggests IXA+LEN+DEX is dominated by BORT+DEX.
- For the 2 prior subgroup modelling using the ERG TMM-1 curves worsens the cost effectiveness estimate for IXA+LEN+DEX compared to LEN+DEX from [redacted] per QALY to [redacted] per QALY.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem.

The company states that Multiple Myeloma accounts for 1.6% of all neoplasms and 16.6 % of haematologic malignancies (CS, 46) referring to data collected in the USA. In the UK, multiple myeloma accounts for 2% of all newly diagnosed cancers. [1] According to the HMRN, Myeloma accounts for 10.5% of all haematological malignancies in the UK.[2]

Multiple Myeloma (MM) is a rare progressive neoplastic disorder of unknown etiology characterized by accumulation of a plasma cell clone in the bone marrow. The diagnosis of MM is mainly based on plasma cells infiltration in the bone marrow (more than 10% of nuclear cells), osteolytic lesions and the presence of monoclonal immunoglobulin (IgG most commonly) in serum or urine.[3, 4] The overproduction of the immoglobin leads to increased proteasome activity in MM cells, as the ubiquitin-proteasome pathway plays an essential role in regulating the turnover of specific proteins, thereby maintaining homeostasis within cells. [5] The identification of this pathway was used as a target for a class of drugs called proteasome inhibitors (PI) that are currently represented by the proposed drug ixazomib (CS, 46, 31f.) but also by other existing agents like bortezomib and carfilzomib.

At the moment MM remains an incurable disease despite the use of intensive therapy with autologous stem cell transplantation (ASCT) from the 1990s.[6] In most cases, patients will eventually relapse after initial therapy and will require further treatment. The company explains that clonal heterogeneity, that is the presence of several different clones of malignant plasma cells, and shifting clonal dominance can be causally connected to drug resistance and repeated relapses after treatment (CS, 47). The heterogeneity and varying clonal dominance can be explained by the effects of different treatments and shifts in the bone marrow microenvironment.

The choices for subsequent treatments at the stage of relapsed or refractory MM (RRMM) depend on several factors such as the type of previous treatment, its capacity to induce a good response in patients, its tolerance, along with the delay before relapse after initial therapy. Targeting several sub-clones at once is the rationale for using a combination therapy in MM, which is frequent and regarded as successful as stated in the CS. The potential interest of combination therapies has been confirmed by the ERG's clinical experts and is illustrated by a growing number of clinical trials where 2 or more drugs are combined. To date, the therapies combining novel drugs with different mechanisms of action that are used within the UK are mainly limited to the first line treatment of MM and consist of bortezomib-thalidomide,

combined with dexamethasone. Other combination types include the use of a novel drug (IMIDs or bortezomib) mainly with a steroid (prednisone, dexamethasone) +/- an alkylating agent (cyclophosphamide, melphalan). On page 47, the company states that the heterogeneity of MM clones also justifies the need for a variety of treatment options (CS, 47). While this is true, a significant number of novel agents have been available in recent years, like proteasome inhibitors (bortezomib, carfilzomib), and IMIDs (thalidomide, lenalidomide, pomalidomide) although we appreciate that not all these options are currently recommended within the NHS.

The fact that the heterogeneity of clones and the unpredictable shifts in sub-clones must be risk-adjusted by a variety of drugs, that patients respond differently to various treatment options, and that their medical history requires alternative treatments requires a variety of comparators. This greatly contrasts with the exclusion, by the company, of most of the comparators that NICE scoped (see critique of the decision problem). The fact that clinical practice responds to this need of variety is supported by the market share figures that the company provides (CS, 57).

The main symptoms and biological features observed in people with MM are bone lesions (pain, fractions, swelling and degradation), hypercalcemia, renal impairment, anaemia and. neurological complications (CS, 50f.). Patients with MM have limited Quality of Life (QoL). The company describes that, as patients experience pain, MM patients have limited mobility which makes routine activities difficult. Patients also feel more fatigued than the general population, caused by both a lack of sleep due to pain, and anaemia (CS, 52).

The company uses the restricted mobility and independence and the increased fatigue of the patients as an argument for the benefits of the all-oral treatment with IXA-LEN-DEX (CS,52). The company underlines the patient's issue with mobility and getting to the clinics with a study by Baz et al., [7] The study interviewed 20 patients from the USA. The company reports that one patient had a 80-mile journey to the hospital and that the most inconvenient treatment for patients, with the greatest impact on QoL, were intravenous treatments (CS, 53). The study reports the following typical responses:

Table 1: Summary of typical responses as reported in Baz et. al. and quoted in CS, p. 53

Impact on HRQoL	Summary of example participant comments
Travel inconvenience	Long journeys to clinic (up to 2 hour drive each way) Long waiting times at the clinic High number and high frequency of journeys, regularity of journeys Process of treatment itself is time consuming
IV inconvenience	Administration of IV treatment is painful and uncomfortable (more than 1 attempt may be necessary) Marks left by IV treatment are embarrassing

Pain, decreased mobility, fatigue and other symptoms of MM and its treatments present a great burden on patients. However, the study the company presents was done in the USA which make the findings not necessarily transposable to the context of England and Wales. One of the main burdens identified in the study were IV administrations of treatments which is not applicable to the scope of ixazomib as the relevant comparators identified by the company are not IV drugs but treatments given either orally or subcutaneously.

Another burden emphasized in the Baz study[7] was the repeated and long journeys to hospitals to receive treatments, the longest journey being 80 miles. Patients may have shorter journeys to hospitals as suggested by a report on the availability of emergency care indicating that the journey between home and emergency care is rarely more than 30 miles in England.[8] It may be suggested that where emergency care is available, other treatment facilities may be available.

If one assumes that journeys to hospital appointments are of a similar length and burden as suggested by the company, the company suggests that this issue can be remedied by oral administration of ixazomib. The company names this as one of the main benefits of ixazomib, since patients will not have to come to the hospital and can take the medication at home (e.g. CS, 16,18). Whether oral administration would be able to lift the burden of travel requires further discussion, as it is not clear whether the treatment would only be available in hospital pharmacies, patients would be able to receive it in home care, or be able to pick it up from their local pharmacy. The high costs per tablet raise the issue of whether patients should be burdened with the responsibility of looking after and administering this very high-cost treatment, and how the costs would be covered in case of loss of a tablet. It also remains a question whether patients would have to come in to hospital to receive additional infusions for co-morbidities or toxicities.

On page 18, the company states that several reports have shown that many patients with cancer prefer oral to parenteral therapy. While this statement is clearly reported in the listed

references, none of the corresponding studies (references 30-34 [9-13] in the CS) were mainly related to MM but breast and colo-rectal cancer, these 2 cancer types being predominantly treated with IV therapies which is not the case for MM.

The statement related to the more convenient use of an orally administered drug applies for people that would otherwise be treated by an injectable treatment. However, as stated by the company, ixazomib would be mainly used in combination with lenalidomide-dexamethasone as third line, replacing an existing oral combination (lenalidomide-dexamethasone alone). This contradicts all the advantages advocated by the company in relation with an orally administered drug.

The company reports that the average life years lost with MM ranges from 36 months to 5 years, depending on the age of the patient (CS, 55). The company applies a "commonly applied standard value of $150,000" per life year and quotes a calculation by Ludwig et al.[14] that the total value of life years lost for a patient diagnosed at the age of 50 would be $4,035,000 or £2,835,700. The company goes on to say that this "highlights the significant economic burden that MM places on society" (CS, 55). To understand the value of $4,035,000 correctly, the origin of the value of $150,000 has to be explained. This value is not the economic or social value of a persons life-year, that is, it is not the value that is based on calculations that take the contribution of a person to society into account. Instead, $150,000 is the average value that a person would pay for an extra life year gained, or, as defined by the WHO, what a cost-effective treatment might be based on the per capita gross domestic product (GDP) (although these figures would suggest that a life year in a low-income country is worth less than in a high-income country).[14, 15] The figure Ludwig et al[14] presents, and the figure that the company quotes, is therefore not a reflection of the economic burden on society, but of an emotional value that people on average attached to one life-year. There are other methods that would also give an insight to the truly economic value of a life year of a person.

The final figure the company quotes from Ludwig et al.[14] must further be called into question as patients with MM are not usually first diagnosed at the age of 50. According to Cancer Research UK[1], 45% of newly diagnosed patients were 75 and over. The Office for National Statistics estimate the life expectancy of a 65 year old person to be between 18.2 and 21.2 years in 2012 to 2014.[16] If one choses to express the value of a life year in monetary value, if one agreed with $150,000, and if one assumed that the average life expectancy is 85 years for 75 year old patients, the total value of life years lost would be $1,500,000. This calculation can be called into question at any point.

The company argues that high-risk subgroups should be identified according to NICE guidelines (CS, 48; NG35[17]), and states that IXA+LEN+DEX have demonstrated a consistently good performance in pre-specified subgroups, including patients with high-risk cytogenetic abnormalities (CS, 49). The EMA however disagrees and states that "[i]t is not possible to identify a higher-risk subgroup that could benefit from treatment with ixazomib, especially based on post-hoc analysis and in view of non-compelling overall results. In addition, the results for the primary analysis and for sub-groups worsen from the first interim analysis to the second interim analysis and where the better results seen in high-risk patients appeared to be driven by patients with del(17) in the first interim analysis, but seemed driven by those with t(4;14) in the second interim analysis". [18] The EMA states that no benefit can be observed for high-risk patients. This conclusion has not been revoked in the final decision by the EMA in November, in which they agree to grant marketing authorisation on the basis of the good toxicity profile but in expectation of more clinical data to support a positive benefit-risk balance.

2.2 Critique of company's overview of current service provision

The CS presents a treatment pathway for MM on page 56 and corresponding text on pages 56-57. The treatment pathway for first line is presented depending on patients are eligible or not for ASCT, and this is in line with current standards. In the pathway suggested by company, the importance of bortezomib for first line is highlighted and in text the company states that bortezomib retreatement is not recommended for second line. This apparently contradicts the postioning by the company of bortezomib-dexamethasone for second line. By definition, the use of bortezomib-dexamethasone for second line should only pertain to patients who did not receive bortezomib at first line. The ERG considers that the pathway should have better differentiated first line treatment depending on whether patients received bortezomib.

The company correctly reports that "lenalidomide plus dexamethasone doublet combination is currently being appraised by NICE for adults with MM for whom thalidomide is contraindicated and whose disease has progressed after at least 1 prior treatment with bortezomib." (CS, 17). Despite still being under review, the company argues that Len+Dex is not a valid comparator for IXA+LEN+DEX as NICE has "issued a negative Appraisal Consultation Document (ACD) for lenalidomide plus dexamethasone in this setting" (CS, 17).

However, Final Guidance has not been published for lenalidomide plus dexamethasone for second line treatment.

Moreover, the ERG believes the exclusion of lenalidomide-dexamethasone in second line to be contradictory to the positioning of ixazomib itself in second line. Indeed, ixazomib is only indicated in combination with lenalidomide-dexamethasone and not as single agent. This implies that, if ixazomib was to be recommended at first relapse, it would necessarily be in combination with lenalidomide-dexamethasone. Lenalidomide-dexamethasone would de facto become available too which means that lenalidomide-dexamethasone should be considered as a relevant comparator at first relapse too. Indeed, it is highly unlikely that lenalidomide-dexamethasone would be recommended only in patients receiving ixazomib and be non-recommended in patients not receiving ixazomib. This will be discussed further in our critique of the decision problem.

The company claims that Panobinostat in combination with Bortezomib and Dexametasone is recommended as 3rd line treatment, but not often used in clinical practice. The company concludes that Panobinostat is not a relevant comparator for 3rd line treatment. However, Panobinostat is recommended by NICE and is therefore one treatment option.[19] The company argues that clinical practice does require the option of a variety of different treatment options and flexibility in the treatment approach (CS, 17). In addition the company states that the triplet of panobinostat-bortezomib-dexamethasone and lenalidomide with dexamethasone are the only treatment options recommended by NICE for MM patients who had 2 or more prior therapies (CS 18).

The company claims that this is a pathway that was formerly accepted by the Appraisal Committee for Carfilzomib. The company suggests to use IXA + LEN+DEX where Carfilzomib is used. Together with the help of our clinical advisors, the ERG has drafted the following pathway for the treatment of MM in clinical practice. This pathway indicates that there is a gap in 2nd line treatment for people who have received bortezomib at first line and would therefore be ineligible for retreatment with Bortezomib or lenalidomide-dexamethasone:

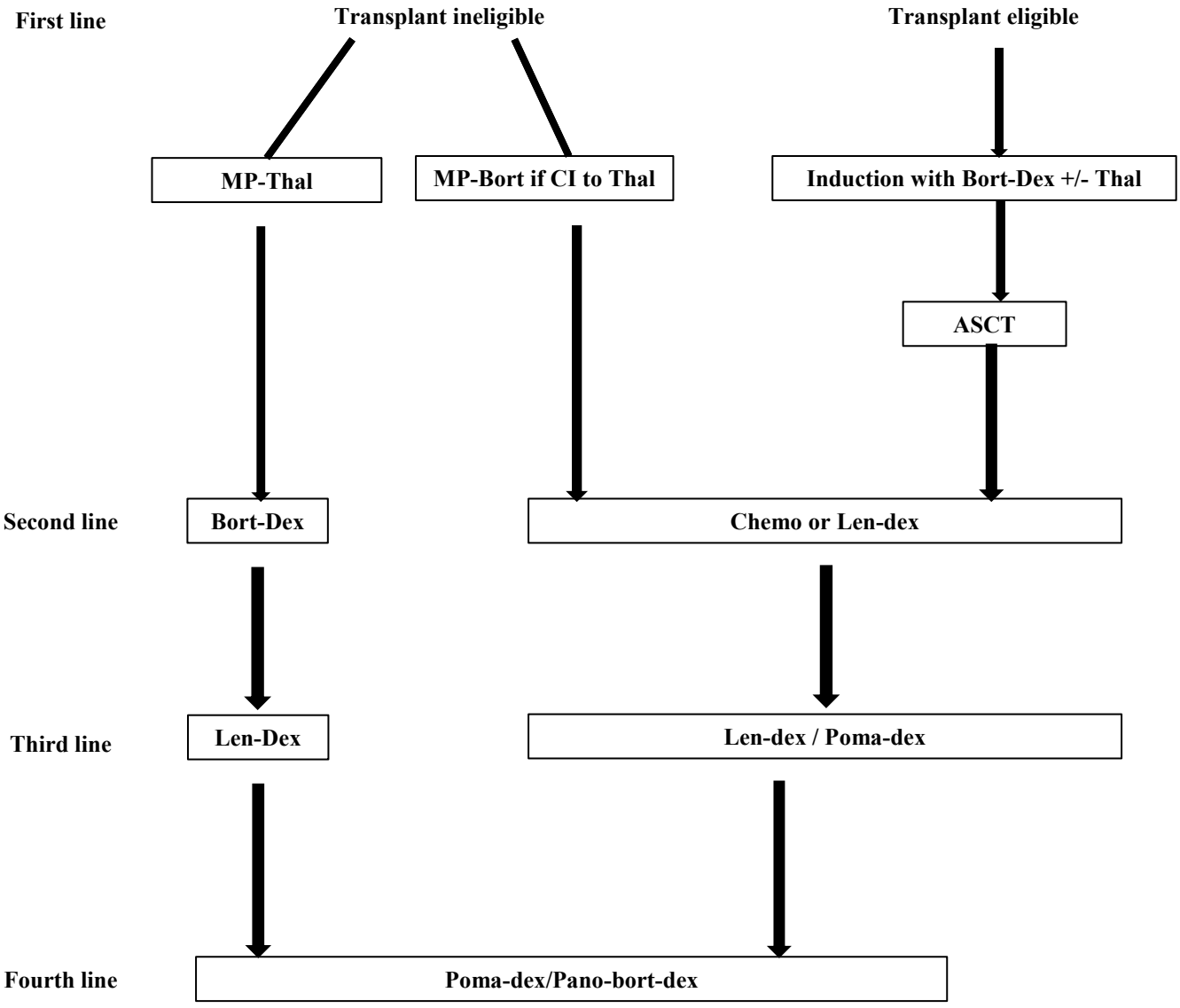


Figure 1: Pathway as suggested by the ERG clinical experts in reference to NICE guidelines and clinical practice (excluding ASCT as a potentially relevant second line option).

The clinical experts suggested to the ERG that the gap in second line treatment is bridged by using treatments that are mainly recommended for first line.

The company suggests that LEN + DEX is not recommended for patients who had 1 prior therapy with bortezomib, whereas the ACD has not been published yet and the appraisal (GID –TAG452) is still in progress.[20] Appraisal GID –TA10005 for Carfilzomib is also still in progress,[21] (CS, 65). However, the company is correct in stating that both drugs are not currently funded by the NHS.

Following the same reasoning, the ERG would like to highlight that the pathway would change if IXA+LEN+DEX was offered as a 2nd line treatment. Whilst LEN+DEX is a treatment option

for patients that have received a BORT- combination as a 2nd line treatment, re-treatment with LEN+DEX after IXA+LEN+DEX is most likely not to be effective. Patients who receive IXA+LEN+DEX in second line would receive POM + DEX in 3rd line and PANO + DEX in 4th line. Patients who received POM+DEX in 4th line have the option to receive PANO + DEX in 5th line.

The introduction of the triplet IXA-LEN-DEX in 2nd or 3rd line would therefore lead to the near exclusion of LEN-DEX in 2nd or 3rd line.

Our clinical advisors agreed with the potential positioning of ixazomib in second and third line which corresponds to the existing positioning of lenalidomide-dexamethasone. The positioning would therefore be slightly reduced compared to the NICE scope that indicated the population of patients with at least 1 prior therapy, which includes line 4 and beyond. However, the ERG agrees with the company's proposed positioning although we disagree with considered comparators. This will be discussed further in the critique of the decision problem.

2.3 Critique of changes to service provision

The company states that no additional tests or investigations will be required when ixazomib is given in addition to lenalidomide-dexamethasone. The ERG agrees with this statement although there is very limited data available on the occurrence of adverse events caused by ixazomib that might need further investigations or concomitant treatment. This is the case for peripheral neuropathy. On page 42, the company indicates that the triple oral combination is expected to have a beneficial impact on healthcare resource within the NHS. This statement is supported by data suggesting that healthcare resource utilisation was lower with the IXA-LEN-DEX relative to LEN-DEX in terms of rates of hospitalisation, acute care unit stays, outpatient stays. However, it is stated that the 95%CI for these estimates overlapped. Most importantly, the company did not account for the use of ixazomib itself among healthcare resource, which is an omission given the cost of one tablet of ixazomib and the total incremental costs.

Again, the ERG disagrees with the simplified view from the company that bortezomib-dexamethasone is the most relevant comparator for ixazomib in second line, given that ixazomib must be combined with lenalidomide and dexamethasone. Therefore, we believe that, if ixazomib was to be recommended, the drug would be implicitly used in the situations where lenalidomide-dexamethasone is already used within the UK. Assuming bortezomib-dexamethasone to be the most relevant comparator for second line, a lenalidomide-dexamethasone based combination (used alone or with ixazomib) would have some advantages

over bortezomib in terms in ease of use or better acceptance, but these would rely on the lenalidomide-dexamethasone based regimen, with or without ixazomib, which means that the advantages of an oral treatement advocated by the company do not come from ixazomib itself but from lenalidomide-dexamethasone.

3 Critique of company's definition of decision problem

3.1 Population

The population in the decision problem, and subsequent clinical evidence matches the population described in the final scope. The population of relevance includes patients with relapsed or refractory multiple myeloma (RRMM) who have had at least one prior therapy.

Our understanding is that the company has proposed the positioning of ixazomib as a second and third line treatment, which would exclude subsequent lines. Despite the exclusion of subsequent lines, the company has conducted clinical and cost-effectiveness analyses considering RRMM patients with at least one prior treatment (i.e. including 4th line and beyond). Although these analyses match the population described in the final scope, it does not exactly correspond to the population targeted by the company to benefit from ixazomib (i.e. second and third line).

Since we assume that the proposed positioning of ixazomib by the company is relevant to the current practice, we believe that the company would have better stated that the population in the decision problem is restricted to RRMM patients at second and third line. This would have been consistent to the choice of comparators in the decision problem where the company better differentiated between patients who have had 1 prior therapy to those who had 2 prior therapies.

3.2 Intervention

The intervention in the decision problem is ixazomib in combination with lenalidomide-dexamethasone and this matches the final scope.

The company provides a description of the technology and the mechanism of action of ixazomib (CS, 31ff.) which the ERG's clinical advisor has confirmed is accurate. Ixazomib is an orally administered medication that was not authorised for use in any other indication than

that of the current appraisal. On 15 September 2016, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the marketing authorisation of ixazomib in combination with lenalidomide and dexamethasone. It is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. The European Commission granted a marketing authorisation valid throughout the European Union for Ninlaro on 21 November 2016.[18]

Of note, the positive opinion from the CHMP follows an initial negative opinion that was initially issued in this indication on May 2016. The reason for the refusal was the CHMP considered that the data from the main study were insufficient to demonstrate a benefit of ixazomib in the treatment of multiple myeloma. Indeed, the results for PFS from the second interim analysis (23 months of follow-up) showed that the risk for progression was not statistically reduced with ixazomib in combination with lenalidomide-dexamethasone compared to lenalidomide-dexamethasone (HR: 0.82, 95% CI 0.67, 1.0; p=0.054) while those for the first interim analysis (15 months of follow-up) showed a statistically significant reduction (HR=0.742; 95% CI 0.59 to 0.94, p=0.012).

After the company submitted an appeal for a re-examination, the CHMP concluded that, according to the pre-specified analysis plan of the main trial, the company could claim a benefit on PFS for ixazomib based on the positive first-interim analysis.

The indication of ixazomib in multiple myeloma, which is the target of NICE scope, has already been approved by the U.S. Food and Drug Administration (FDA) (gained on November 2015). The conclusions of the FDA was that ixazomib given in combination with lenalidomide and dexamethasone had a benefit risk balance supporting traditional approval for the indication.[22]

Ixazomib will be assessed by the Scottish Medicines Consortium in Q1 2017.

Ixazomib is an oral, highly selective and reversible proteasome inhibitor. According to the summary of product characteristics of ixazomib, ixazomib citrate, a prodrug, is a substance that rapidly hydrolyses under physiological conditions to its biologically active form, ixazomib.

Ixazomib preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome.

Ixazomib belongs to the class of proteasome inhibitors like other existing drugs, such as bortezomib and carfilzomib, that are also approved in people with relapsed or refractory multiple myeloma. Ixazomib is owned by Takeda pharmaceutical which also owns bortezomib (Velcade) after the buyout of Millennium Pharmaceuticals in 2008. It is the understanding of the ERG that the patent of bortezomib is now expired allowing the launch of generic versions

of this drug. The ERG has checked that, as of February 2017, three generic versions of bortezomib have been approved by the EMA[23-25] although these may not be yet available within the NHS. The availability of generic versions of bortezomib should contribute to drop the prices of this drug in the near future.

Table 8 in the CS (page 41) summarises administration and costs of ixazomib, and information provided in this table regarding the treatment administration concur with those in the TMM-1 trial.

3.3 Comparators

The comparators described in the decision problem are bortezomib with dexamethasone (BORT+DEX) for people who have had 1 prior therapy and lenalidomide with dexamethasone (LEN+DEX) for people who have had at least 2 therapies. This differs substantially compared to the NICE final scope as follows:

- While the NICE final scope suggested a first group of patients who had at least 1 therapy, the company restricted this group to patients with 1 prior therapy in order to be consistent with the current treatment pathway. The ERG considers this interpretation to be valid.
- The NICE final scope suggested a second group of patients who have had at least 2 therapies which seem to match with the decision problem addressed in the CS (table 1, column "decision problem addressed in the CS", CS). However, it is unclear if the company considers a group of patients with at least 2 prior therapies or with 2 prior therapy only. Indeed, in the column labelled " rationale if different from the final NICE scope" in Table 1 on the CS, it is stated that, in addition to second line, the Company proposes to position IXA+LEN+DEX as a third line treatment. In other words, compared to the NICE scope, the population of RRMM patients with at least 2 prior therapies is restricted to those with two prior therapies. The ERG agrees with the Company's positioning of IXA.

Given this, one of the ERG's critiques of the CS is that one might have expected the clinical and cost-effectiveness analyses of ixazomib to be conducted in these specific subgroups of patients (second line and third line). The 1 prior group modelling could have explored results from a 1 prior specific NMA, though the ERG is of the opinion that of its analyses the 1+ prior group NMA results are more robust than the 1 prior group NMA. Results for the 2 prior group

could have been presented, adjusted for baseline covariates if required, rather than the 2+ prior therapy group.

- For patients who have received 1 prior therapy, the company has excluded lenalidomide-dexamethasone, bortezomib monotherapy, and bortezomib retreatment.

The reason for excluding lenalidomide-dexamethasone is that it is not approved by NICE, is not funded by the CDF, and has recently issued a negative ACD from NICE.

The ERG notes that the comparator LEN-DEX in 2nd line treatment, which is excluded by the company, has a non-negligible market share of 26%, as reported by the CS. Our clinical advisors indicated that lenalidomide-dexamethasone can be used in practice within the NHS in particular among patients who have received bortezomib at first line and who had an inadequate response or experienced toxicity.

Secondly, it makes little sense to consider ixazomib combined with lenalidomide-dexamethasone as a second line agent if the lenalidomide-dexamethasone combination itself is not considered.

Ixazomib is, thirdly, not currently available within the NHS but its clinical effectiveness is being reviewed.

Lastly, we believe that one cannot justify the exclusion of lenalidomide-dexamethasone based on the proposed recommendation as stated in the ACD from NICE given that in this ACD, it is clearly stated that "Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation." [20].

Consequently, the ERG considers that the exclusion of lenalidomide-dexamethasone is not justified and that lenalidomide-dexamethasone should be included as a comparator.

This is why the ERG asked the company in the clarification questions to include the lenalidomide-dexamethasone evidence for patients with 1 prior regimen and to add lenalidomide-dexamethasone to the cost-effectiveness analysis for 1 prior regimen, however the company did not choose to do this. A major advantage of the inclusion of LEN+DEX would have been the benefit of direct evidence (TMM-1 trial)[26], as the company does have estimates for overall survival in patients with only one prior regimen, and also compliance with the NICE scope. Most importantly, the consistent use of the different subgroups would have avoided the confusion that is caused by the use of clinical effectiveness evidence from patients with at least 1 prior regimen within a cost-effectiveness model that focuses on RRMM patients with only one prior regimen.

The ERG considers that the exclusion of bortozemib monotherapy is reasonable because, as stated by the company and confirmed by the ERG's clinical experts, this agent is very rarely used as single agent. However, the inclusion of bortezomib in combination with dexamethasone meant that only an indirect comparison of BORT+DEX to IXA+LEN+DEX has been possible, which necessitated the use of evidence from non-randomised studies within the network meta-analysis. This has been critiqued in the relevant section.

The ERG is concerned by the company's exclusion of bortezomib-retreatment. The company states that this is not funded by NHS England. The exclusion raises some issues about the treatment of RRMM patients at first relapse within the NHS. According to our clinical advisors, there seem to be different interpretations of the current possibility within the NHS to retreat patients with bortezomib at second line. In practice, some centres undertake it while others do not. Assuming that bortezomib retreatment is not funded by the NHS for this indication and knowing that there seems to be a growing number of patients receiving a bortezomib-based regimen as first-line (either in combination with thalidomide-dexamethasone prior to intensive therapy, or melphalan-prednisone in patients ineligible for intensive therapy), the ERG has asked the company in the clarification questions to consider the case of RRMM patients at first relapse who have previously received bortezomib.

According to our clinical advisors, one of the potential comparators here could have been a thalidomide-based regimen.

For people who have received 2 prior therapies, the company has excluded panobinostat-bortezomib-dexamethasone, stating that this option is predominantly used as 4th line. According to the data on market share trends provided by the company, panobinostat only represents 7% of 3rd line in the UK (19% in 4th line), which corroborates the company's statement. However, our clinical advisors confirmed that this regimen, which is currently recommended by NICE in this situation, is an option in patients at third line. Moreover, the guidance recommending this regimen was published in January 2016, which is very recent, which means that the current market share of panobinostat is not yet mature compared to that of lenalidomide-dexamethasone (made available for several years) and might increase in the future.

Consequently, the ERG considers that the exclusion of panobinostat- bortezomib-dexamethasone is not entirely justified and that this regimen should be included.

3.4 Outcomes

Most of the outcomes measures to be considered in the NICE scope have been reported in the decision problem. They are overall survival (OS), progression-free survival (PFS), response rates (RR), adverse effects and health-related quality of life (HRQoL).

The company was unable to report *time-to-next treatment* as this outcome was not measured in the ixazomib main trial but proposed *time-to-progression*, *time-to-response*, and *duration of response* as surrogate outcomes for *time-to-next treatment*. The ERG considers this approach to be valid.

3.5 Other relevant factors

On page 29, the company considered that ixazomib could be a potential candidate to be recommended for use within the CDF for two years. This could offer the opportunity to collect clinical data such as more mature survival data. The ERG appreciates the interest of collecting data to provide real-world evidence on drugs that have only been evaluated through rigorous clinical trials. However, such a short period of data collection (2 years) is likely to be irrelevant with the scope of MM even at the stage of relapsed or refractory disease. Looking at the data from the TMM-1 trial[26], although we acknowledge that a RCT may not exactly represent real-word practice, the median overall survival has not been reached for any of the included population (1 prior line and 2-3 prior lines) in either the IXA-LEN-DEX or LEN-DEX arms after a median follow-up of 23 months (second interim analysis). Consequently, the ERG considers that the inclusion of ixazomib within the CDF for 24 months would not enable the collection of mature overall survival data, unless the effectiveness of ixazomib in real-word setting is reduced compared to what was observed in the TMM-1 trial. A reduced effectiveness of ixazomib in real-life conditions cannot be excluded, given that the compliance of patients with their treatment might not be as good as that observed in the main RCT. On this basis, the ERG believes that mature overall survival data should be obtained from the TMM-1 trial once it becomes available.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the company's approach to systematic review

The CS undertook a systematic review for evidence of clinical effectiveness of relevance to the decision problem. The review included a search for studies on the intervention and separate searches for any comparator studies for a network meta-analysis (NMA).

The ERG's quality assessment of the CS, based on CRD quality assessment questions for systematic reviews,[27] is summarised below. The quality of the company's systematic review is reasonable, although the ERG has noted that there was no reporting of studies excluded at full-text level in the CS. This has provided by the Company following the clarification questions from the ERG and NICE. The ERG has also highlighted severe limitations in the quality of reporting of studies in the NMA.

The submitted evidence generally reflects the decision problem, although summary baseline characteristics and data from the comparator trials were not consistently reported.

Overall, the chance of systematic error in the systematic review is uncertain owing to limited details of the primary studies being reported for the NMA.

Table 2: Quality assessment of the CS systematic review of clinical effectiveness

CRD Quality Item	Yes/No/Uncertain with comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all relevant research?	Yes although the ERG has highlighted that the Company did not search for additional information from HTA reports (see Celgene Submission)
3. Is the validity of included studies adequately assessed?	No, this concerns the quality assessment of non-RCTs
4. Is sufficient detail of the individual studies presented?	No, very limited information is provided
5. Are the primary studies summarised appropriately?	No, see previous comment

4.2 Description of company's search strategy

A systematic literature review was undertaken to identify data on the clinical efficacy and safety of ixazomib and relevant comparators, and to provide evidence for the network meta-analysis (NMA). Searches were performed to identify published research articles and

conference abstracts and were supplemented by unpublished trial data for ixazomib supplied by Takeda UK. The search strategy was last updated on the 7th October 2016.

The databases searched were MEDLINE, Embase, Cochrane library, the Centre for Reviews and Dissemination Databases and PubMed. In addition, conference abstracts of the American Society of Haematology (ASH), American Society of Clinical Oncology (ASCO), European Haematology Association (EHA) and European Society for Medical Oncology (ESMO) were manually checked. The Clinicaltrials.gov database was searched to identify ongoing studies, and references from systematic reviews, indirect comparisons, and network meta-analyses were searched. Each abstract was assessed for inclusion by two independent reviewers. The search strategy for the NMA included both RCT and observational studies.

The searches identified 7833 unique records. After screening of the titles and abstract, 41 full text articles were further assessed for eligibility. This resulted in 14 studies (from 21 publications) for inclusion in the NMA network. The searches were well described, apart from the reasons given for the exclusion of the 20 studies excluded after screening for full text. The list of reasons given were supplied in the company's clarification response.

Critique of Clinical Effectiveness Searches

The ERG considers that the very sensitive searches undertaken in Section 4.1 of the CS included the appropriate search terms and sources that would result in capturing the relevant published evidence and conference abstracts. Any omissions would have resulted from studies being missed at the screening of the 7,833 studies. The ERG feels that a search of the NICE web site to check submissions for comparator drugs should also have been undertaken.

4.3 Statement of the inclusion / exclusion criteria used in the study selection

The eligibility criteria are listed in CS Table 26, CS page 73. The eligible population includes adults with diagnosed relapsed or refractory multiple myeloma who previously received at least one therapy. While the intervention of interest for this STA is ixazomib, the company has listed ten different interventions. Ixazomib is not mentioned in the list, but we understand that it was included in the "lenalidomide containing regimens". The company indicated that their comparators were placebo or dexamethasone along with studies without a control group but with two interventions of interest. It would have been clearer to list only ixazomib-based regimen as the intervention and to list all the other interventions as comparators. Although ixazomib is not clearly mentioned, our interpretation of the table matches the decision problem,

the NICE scope and the licensed indication. The comparators listed in the NICE scope, bortezomib, lenalidomide and panobinostat, are stated among the 10 listed interventions. The company's eligibility criteria for the systematic review state that trials with outcome measures of either progression free survival (PFS), overall survival (OS), overall response rate (ORR), treatment discontinuation, Adverse events, Time to Progression (TTP), Duration of response (DoR), Time to next treatment (TTNT), Duration of treatment, Health-related quality of life (HRQoL) are included regardless of these were primary or secondary outcomes. These match the decision problem and the NICE scope. In terms of study design, the company included Randomised-controlled trials (RCTs), observational studies, and conference abstracts of both RCTs and observational studies. The inclusion of non-randomised studies, including not only observational studies but also prospective interventional studies, has been justified by the limited availability of RCTs for some of the comparators of interest. This is the case for the comparison of bortezomib-dexamethasone to bortezomib. However, the company has not assessed whether this could lead to inadequate control of biases that could threaten the validity of the NMA findings.[28] Moreover, the inclusion of conference abstracts is questionable, given the limited avaibility of information that can be used for quality assessment.

In the section pertaining to the study selection, the company indicated that, as agreed by the NICE appraisal committee following the publication of the carfilzomib ACD, they only reported the following "studies": ixazomib-lenalidomide-dexamethasone vs bortezomib-dexamethasone and ixazomib-lenalidomide-dexamethasone vs lenalidomide-dexamethasone. It is unclear why the company refers to the carfilzomib ACD which is unrelated to the ixazomib submission. Similarly, whilst we are aware of the TMM-1 trial comparing ixazomib-lenalidomide-dexamethasone with lenalidomide-dexamethasone, there is, as far as we know, no study that directly compares ixazomib-lenalidomide-dexamethasone and bortezomib-dexamethasone. We assume that what was meant here is an indirect comparison between ixazomib-lenalidomide-dexamethasone and bortezomib-dexamethasone rather than a study in the strict sense of term.

4.4 Identified Studies

The main trial of the CS is the Tourmaline MM-1 study (1 publication from the main trial, [26] 1 publication from the China study,[29] plus unpublished data from the 2nd data cut IA2 (12th July 2015). The company also included this trial in their NMA (for discussion of the NMA see relevant section). The trial was funded by the Millennium Pharmaceuticals subsidiary of Takeda Pharmaceuticals.

The details of the trial were summarised and discussed in the CS on pp.81-110. The trial design was reported on p.81f. of the CS. The trial was an international, Phase III, randomised, double blind trial comparing IXA+LEN+DEX (4mg IXA on days 1, 8, 15 plus 25mg LEN on days 1-21, plus 40 DEX on days 1, 8, 15, 22) with LEN+DEX (placebo plus 25mg LEN on days 1-21, plus 40 DEX on days 1, 8, 15, 22) in 28 days cycles. 360 patients were randomly assigned to the IXA+LEN+DEX group, and 362 to the Placebo +LEN+DEX group. Randomisation was stratified by number of prior therapies (1 vs. 2 or 3), previous proteasome inhibitor treatment (naïve vs. exposed), and International Staging System disease stage (ISS I, II or III). Treatment continued until disease progression or unacceptable toxicity. Permitted concomitant medications were thromboprophylaxis according to American Society of Clinical Oncology (ASCO) guidelines, aspirin (81-325mg orally once daily), low-molecular weight heparin, prophylactic antiviral therapy as clinically indicated, myeloid growth factors, erythropoietin, red blood cells and platelet transfusions, standard anti-emetics as clinically indicated and prophylactic, topical, intravenous or oral antihistamines or steroids, bisphosphonates, CYP1A2 inhibitors. Strong CYP3A inducers were to be avoided and radiation therapy or anti-neoplastic treatment was not permitted (CS, 85).

Eligibility criteria were reported on p.82f. and in table 30 on p.83. The trial was designed to select patients with RRMM based on standard criteria and with measurable disease and an Eastern Cooperative oncology Group (ECOG) performance status between 0-2 (on a scale from 0-5), whilst excluding patients who were refractory to lenalidomide or proteasome inhibitor-based therapy. The trial included male and female patients who had 1-3 prior therapies and relapsed after previous treatment, both refractory and not refractory, and who had never responded to previous treatment. Patients were recruited in 147 centres in 26 countries, including 9 centres in the UK, which included 21 patients (CS, 84, table 31).

The median age of patients in both the IXA+LEN+DEX and the placebo group was 66 years, (38-91 in the IXA group and 30-89 in the placebo group). 53% of patients in the IXA group and 51% in the placebo group were over 65 years old. For both groups, the time since diagnosis was similar (median 44.2 months IXA vs. 42.2 months placebo). The number of prior therapies between the groups was also similar: The company states that 224 (62%) patients in the IXA group and 217 (60%) patients in the placebo group had 1 prior therapy, 97 (27%) vs. 111 (31%) had 2, and 39 (11%) vs. 34 (9%) had 3 prior therapies. The company summarises that 425 (59%) patients had received 1 prior therapy and 297 (41%) had received 2 to 3 prior therapies (CS, 94). In terms of stratification factors, 212 (59%) of the IXA group and

213 (59%) in the placebo group had 1 therapy, and 149 (41%) vs. 148 (41%) had 2 or 3 therapies.

Patients' ISS Stage evaluation between both groups was also similar: At ISS Stage I, there were 226 (63%) patients in the IXA vs. 233 (64%) placebo group, Stage II had 89 (25%) IXA vs. 87 (24%) placebo and Stage III had 45 (13%) IXA vs. 42 (12%) placebo patients (total 12 %, 87 patients, CS, 94). The values of the ECOG performance were also similar: 180 (50%) patients in the IXA group vs. 170 (47%) in the placebo group were status 0, 156 (43%) vs. 164 (45%) were status 1, and 18 (5%) vs. 24 (7%) were status 2.

The most common reason for patients to discontinue treatment were progressive disease (34% and 40% in the IXA vs. placebo group), and adverse events (17% and 14% in the IXA vs. placebo group).

The primary and key secondary outcomes are described in the CS p.86 table 32. Reported outcomes included overall survival (OS), progression free survival (PFS), response rates, time to next treatment, adverse effects of treatment and health-related quality of life. Not reported is time to next treatment (TNT), but the company suggests to use *time to progression (TTP)*, *time to response* and *duration of response* as surrogates for TNT (CS, 85). The ERG's clinical advisors have agreed that TTP can be used as an approximation for TNT. The results are reported in the CS section 4.7, adverse events in section 4.12 (p.141f.). The results from the trial are discussed in section 4.2.1.

4.5 Relevant studies not included in the submission

Our independent searches of the NICE web site for relevant multiple myeloma comparator drugs identified relevant evidence from a Company Submission by Celgene[20] and NICE committee papers for carfilzomib.[21]

4.6 Description and critique of the approach to validity assessment

For RCTs, the company used specific criteria as described in the CRD's guidance for undertaking reviews in health care[27], which the ERG considers to be appropriate. However, the assessment undertaken by the company is inadequate because the ratings are study-specific but not outcome-specific. Ideally, one should be able to differentiate between the risk of bias (RoB) of PFS and OS if for example, the outcome data completeness for these outcomes differs. The per study rather than per outcome RoB ratings conceal this distinction.

4.6.1 Quality assessment of the Tourmaline MM1 trial

CS Table 38 provides a quality assessment of the Tourmaline MM1 study[26] using criteria recommended by NICE. The table below summarises the ERG's check on this QA.

Table 3: Company and ERG assessment of trial quality

		Tourmaline MM1 (Moreau 2016)[26]
1. Was randomisation carried out appropriately?	CS	Yes, randomisation of patients in a 1:1 ratio to study interventions was carried out using an IVRS
	ERG	YES
Comment: the CS states "*randomisation scheme generated by an independent statistician at the sponsor, who was not on the study team. Patients were randomised strictly sequentially at each study centre as they became available for randomisation.*		
2. Was concealment of treatment allocation adequate?	CS	Yes, allocation was concealed by using an IVRS for randomisation
	ERG	YES
3. Were groups similar at outset in terms of prognostic factors?	CS	Yes, baseline characteristics were well balanced between treatment groups for the ITT population and for the pre-specified subgroups
	ERG	YES (refer to CS Table 37)
4. Were care providers, participants and outcome assessors blind to treatment allocation?	CS	Yes, in this double-blind study, all study personnel, including the investigators, site personnel, study clinicians, sponsor, and participants, were blinded to treatment assignments. Only the independent statistical centre and Independent Data Monitoring Committee had, at prespecified interim analysis and interim safety review time points, access to un-blinded individual patient data.
	ERG	YES
5. Were there any unexpected imbalances in drop-outs between groups?	CS	No, there were no unexpected imbalances in drop-outs between treatment groups: at data cut-off for the second interim analysis (~23-months), 136 (38%) and 133 (37%) patients in the IXA+LEN+DEX and LEN+DEX arms, respectively, remained on treatment, and 222 (62%) and 229 (63%), respectively had discontinued
	ERG	NO. Early withdrawal from the study appears to be 6 and 8 in the two arms respectively. Reasons included transfer to another therapy, transfer to stem cell transplantation patient decision or patient and physician decision.
Comment: The CS here refers to patients not retained on treatment rather than to those not retained in the study.		
6. Is there any evidence that authors measured more outcomes than reported?	CS	No, there is no evidence that suggests that authors measured more outcomes than they reported.
	ERG	NO
Comment: Three sequential interim analyses and a final analysis were planned. The primary outcome of PFS was implicitly referenced to the first interim analysis, data for the additional outcomes listed in CS Table 32 were available for various interim analyses.		

7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	CS	Yes, an ITT analysis (all randomised patients) was used for analyses of efficacy The safety population, which included all patients who received ≥ 1 dose of study drug, was used for analyses of safety and tolerability.
	ERG	YES

The ERG QA mostly agrees with the company assessment of study quality for TMM; the study was judged to be at low risk of bias. Approximately equal numbers discontinued in both arms of the trial (CS Table 52) with limited loss to follow up (~2%).

No comparator trials of relevance to the decision problem were available for quality assessment.

4.6.2 Quality assessment of the RCT evidence used in the NMA

The CS assessed and tabulated the quality of studies that were included in the CS NMAs (CS Appendix 5 Table 3). Some of these studies had multiple Table entries, e.g. referring to main study publication and subgroup or extension publications. Unfortunately the listed studies in Appendix 5 Table 3 were not readily identifiable since references were not included; instead the Appendix suggested the reader "*See table 43 in the main body of the submission for details of references"*. The ERG did not find this helpful when cross checking the submission.

The CS quality assessment was conducted using guidance from 'Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).[27] The ERG consider this to be an appropriate tool.

The ERG has applied the same assessment tool as the company and has attempted to identify the appropriate publications for quality assessment. The results are summarised in Table 4 in which the ERG assessment is appended in the row below that reporting the CS assessment. The ERG has not quality assessed publications that describe extension or subgroup analyses of RCTs already assessed for quality.

In a several instances the ERG found the CS quality assessment unsatisfactory. In particular a Phase I study (Richardson et al., 2014[30]) appears to have been assessed as though it were an RCT, and some studies that are published only as abstracts / conference proceedings have been assessed as if they were full peer reviewed publications.

Table 4: Quality assessment of studies listed in CS Appendix 5 Table 3 (references added by ERG)

Study	Randomisation appropriate?	Allocation concealment adequate?	BlindΦ to treatment allocation?	Groups similar at the outset?	Imbalances in drop-outs ? (YES=no unexpected imbalances)	Evidence that all key outcomes reported?	ITT analysis: conducted and appropriate? ?	Overall quality assessment = Good, Moderate or Poor*
Tourmaline-MM1 (Data cuts IA1 and IA2)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
ERG Moreau et al., 2016[26] CSR ixazomib2015[31]	Yes	NC	Yes	Yes	Yes	Yes	Yes	Good
Tourmaline-MM1 (Chinese continuation study)	Yes	Yes	Yes	Yes	NC	Yes	NC	Moderate
ERG Hou et al., 2016[29]	This publication is an Abstract; it contains insufficient information for quality assessment; CS Appendix 4 contains further details but this has not been peer reviewed.							
Montefusco et al., 2015	NC	NC	NC	NC	NC	Yes	NC	Poor
ERG Montefusco et al., 2015[32]	NC	NC	NC	NC	NC	Yes	NC	Poor
APEX	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
ERG Richardson et al., 2005[33]	NC method not reported	NC	No	Yes	Yes	Yes	Yes	Good
APEX (Extended follow-up)	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
ERG Richardson et al., 2007a[34]	As above **ERG** Richardson et al., 2005 [136]							
ENDEAVOR	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
ERG Dimopoulos et al., 2016[35]	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
ENDEAVOR (subgroup analysis)	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
ERG Moreau et al., 2015c[36]	As **ERG** Dimopoulos et al., 2016 [138]							
ASPIRE	Yes	NC	No	Yes	Yes	Yes	Yes	Good

Study	Randomisation appropriate?	Allocation concealment adequate?	BlindΦ to treatment allocation?	Groups similar at the outset?	Imbalances in drop-outs ? (YES=no unexpected imbalances)	Evidence that all key outcomes reported?	ITT analysis: conducted and appropriate? ?	Overall quality assessment = Good, Moderate or Poor*
ERG Stewart et al., 2015a[37]	NC method not reported	NC	No	Yes	Yes	Yes	Yes	Good
ASPIRE (Interim analysis)	Yes	NC	No	Yes	Yes	Yes	No*	Good
ERG Dimopoulos et al., 2015b[38]	This publication is an Abstract; it contains insufficient information for quality assessment;							
MM-010	Yes	NC	No	Yes	Yes	Yes	Yes	Good
ERG Dimopoulos et al., 2007[39]	NC; method not reported	NC; method not reported	No	Yes	Yes	Yes	Yes	Good/ moderate
MM-009	Yes	NC	Yes	Yes	Yes	Yes	Yes	Good
ERG Weber et al., 2007 [40]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
PANORAMA-1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
ERG San-Miguel et al., 2014[41]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
PANORAMA-1	Yes	Yes	Yes	Yes	Yes	Yes	No†	Good
ERG. study identity unclearΨ	San-Miguel et al., 2015c[147] publication is an Abstract; it contains insufficient information for quality assessment;							
MM-002	Yes	NC	No	Yes	Yes	Yes	Yes	Moderate
ERG Richardson et al., 2014[30]	Main Text Table 43 provides Richardson et al., 2014 [149] as the reference for study MM-002; In Table 43 it is listed as an RCT. However reference 149 describes a Phase 1 study. The CS quality assessment inappropriately views the study as an RCT.							
MM-003	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
ERG San-Miguel et al., 2013[42]	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
MM-003	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
ERG San-Miguel et al., 2015d[43]	As **ERG** San-Miguel et al., 2013 [150]							

Study	Randomisation appropriate?	Allocation concealment adequate?	BlindΦ to treatment allocation?	Groups similar at the outset?	Imbalances in drop-outs ? (YES=no unexpected imbalances)	Evidence that all key outcomes reported?	ITT analysis: conducted and appropriate? ?	Overall quality assessment = Good, Moderate or Poor*
Abbreviations: NC = not clear Φ Were care providers, and participants blind to treatment allocation?								
* This interim analysis from the ASPIRE trial was based on patients who had received 1 prior therapy. ITT analysis was categorised for patients who had received 1+ prior therapies								
† This subgroup analysis from the PANORAMA-1 trial was based on patients who had received ≥2 prior regimens. ITT analysis was categorised for patients who had received 1+ prior therapies								
Ψ ERG note that main text Table 43 lists four references to the PANORAMA trial; it is not clear which study the CS has quality assessed.								

4.6.3 Quality assessment of the non-RCT evidence used in the NMAs

The company included three non-RCTs (observational studies) in their NMA submission (Dimopoulos 2010[44], Dimopolous 2015[45], and Zagouri 2016[46]). Among these, we chose to assess the Dimopoulos 2015 study in more detail, since it directly contributes to the main comparison (for OS, ORR). The Dimopoulos 2010 study was not assessed because it was reported as a conference abstract.

Although the manufacturer assessed the risk of bias/quality of this study, the ERG was unable to identify the name of the tool (no reference was provided). The tool used lacks the most important item– an item covering the domain of bias due to confounding. Confounding is the most important threat to the validity of non-randomised evidence. Other important missing domains included bias due to deviations from intended treatments (e.g., performance bias, contamination, co-intervention, adherence to drugs).[47]

The company included an observational (non-randomised) matching-adjusted indirect comparison [MAIC] study (Dimopolous 2015[45]) in their network that compared BORT vs. BORT +DEX. This was done to compare IXA + LEN + DEX to BORT + DEX indirectly. The authors of this study used IPD from two RCTs (APEX[33] and DOXYL-MMY-3001[48]), and a cohort study (MMY-2045[49]) to match the baseline patient characteristics by using propensity score pair-matched adjustment technique to compare PFS and OS between the study arms. The responses to some of the quality assessment tool items in Appendix 6 (Table 5) are inappropriate. The item of selection bias is rated as 'yes - all patients received as many cycles of bortezomib or dexamethasone, as required'. Furthermore, the item asking if the study results are internally valid, the manufacturer's response is 'In the APEX study, bortezomib was considered to be generally well tolerated, with longer overall survival compared to dexamethasone.' The item asking if all participants were accounted for at study conclusion, the manufacturer's response is about patients receiving treatment (and discontinuations) and follow-ups.

The manufacturer instead should have acknowledged the reduction of the analysed sample from 384 (n=142 in BORT + DEX and n=242 in BORT) to 218 (109 in BORT + DEX vs. 109 in BORT) due to adjustment procedures. The excluded outcome data could have resulted in bias if the excluded patients' baseline characteristics, i.e., important predictors of the outcome, and the proportions of patients differed across the compared arms. For the item asking if outcome

measures were reliable, the manufacturer should have clarified whether the outcomes across the three studies had the same or similar definitions. In contrast, the company's responses to the above mentioned domains were 'Yes', meaning that the domain was addressed adequately by the study.

There is considerable potential of bias and uncertainty in the reported estimates for this study since it was based on non-randomised evidence. First of all, there was no common comparator to connect and indirectly compare BORT + DEX to BORT. The success of matching process cannot be validated since there is no common comparator. Although the authors used IPD and adjusted baseline patient characteristics using propensity score matching (adjusted on 13 baseline covariates), there is still some potential that unknown confounders could have biased the outcomes measures and effect estimates. The three studies (APEX[33], DOXYL,[48] and MMY-2045[49]) from which the data was taken were conducted about 7 years apart, which would introduce additional differences in the drug management, trial conduct, or study populations, and other unaccounted factors between the studies. It is not clear if the study authors applied the same inclusion and exclusion criteria to the populations across the three studies.

Another observational study[46] did not contribute to the network's main comparison (IXA + LEN + DEX vs. BORT + DEX (=>1 prior therapy, ITT population). The risk of bias for PFS in this study was high, given a severe imbalance of important risk factors between the study groups, with more heavily pre-treated patients in the LEN + intermediate dose DEX vs. LEN + low dose DEX group (e.g., number of prior treatments, proportion of refractory disease, prior exposure to BORT/THAL, resistance to BORT). The favourable PFS result for LEN + low dose DEX vs. LEN + intermediate dose DEX group (median PFS: 26 months vs. 10 months) could have been simply due to the less severe disease distribution in the former study group. However the company's responses to the quality assessment tool's domains were 'Yes', meaning that they considered the domain to be addressed adequately by the study.

4.7 Description and critique of company's outcome selection

The NICE scope lists the specified the outcomes as:

- progression-free survival (PFS)
- overall survival (OS)
- response rates
- time to next treatment
- adverse effects of treatment
- health-related quality of life.

The CS states that "all of the outcomes in the NICE scope have been reported in the TMM-1 Phase III study, except for time to next treatment". The CS suggests that time to progression; time to response; and duration of response (each of which were collected in the MM1 trial) may be useful surrogates for time to next treatment.

The primary outcome in the TMM-1 trial was PFS estimated at the first interim analysis (IA1, 262 PFS events, October 2014) when median follow-up was 14.6 and 14.8 months respectively in the two arms. PFS was defined as the time from the date of randomisation to the date of first documentation of disease progression based on central laboratory results and IMWG criteria as evaluated by an IRC, or death due to any cause, whichever occurred first.

Several interim analyses and a final analysis of outcomes were planned; a second interim analysis (IA2; 365 PFS events) was conducted after a median follow-up of ~ 23 months. The CS states "*TMM1 trial follow-up is ongoing with a further interim analysis planned for 2017 (IA3, 322 deaths), and final OS analysis (486 deaths) planned for 2019";* and *"At the decision problem meeting with NICE for this submission, it was agreed the primary data cut IA1 was appropriate for the base case of the economic analysis. Therefore, a scenario analysis has been performed which considers the impact on results using the IA2 data cut."* The ERG considers that the use of data with a median follow-up of only 15 months for the base-case economic analysis would result in some uncertainty of results that might be avoidable.

Pre-specified secondary endpoints included OS and health related quality of life. OS was defined as the time from randomisation to death from any cause. To monitor health related quality of life,

the company used the EORTC QLQ-C30 and MY-20 questionnaires (i.e. *the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 [EORTC QLQ-C30] and the Quality of Life Questionnaire MM Module 20 [MY-20]*). Questionnaires were obtained every 2 cycles until disease progression.

Other secondary endpoints not listed as pre-specified in Moreau et al. 2016[26] included response rates based on central laboratory results and International Myeloma Working Group 2011 criteria. Response rates were monitored every cycle until disease progression. Various response categories and response sub-categories of response (e.g. complete response and stringent complete response) were included in the CS.

The CS provides adverse events data for the second interim analysis. Adverse events were graded per National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.

With the exception of time to next treatment the outcomes selected in the CS conform to those identified by NICE as relevant to the decision problem.

4.8 Description and critique of the company's approach to trial statistics

The main objective of the TMM-1 trial was to determine if the addition of IXA to LEN-DEX improves PFS. The sample size of approximately 703 patients was calculated so that the study was adequately powered to detect a treatment difference for PFS but also for OS which was a secondary outcome measure. Three interim analyses were planned, the first being when approximately 36% experienced a PFS event (either progression or death whichever occurred first). According to the statistical analysis plan (SAP), if the first interim analysis showed a statistically significant difference on PFS, the Company could claim a benefit for PFS. At the second interim analysis, the SAP indicates that if a statistically significant difference on OS was observed, the Company could claim a benefit on OS. If not, results from the third and final analysis would determine if a benefit on OS could be claimed for IXA.

The data presented in the submission correspond to the first and second interim analysis. Therefore, these are not final data.

The FDA requested the evaluation of a non-inferential PFS in the second interim analysis, which the Company added as part of the amendment 3 of the protocol.

The Company undertook intention-to-treat analyses (ITT) for the efficacy outcomes.

Two of the 360 patients in the IXA arm did not receive any study treatment while three if the 362 patients in the Placebo group accidentally received limited dosing of IXA.

The CS states the methods to handle missing data and withdrawal in table 35 of the main submission.

Overall, the ERG considers the trial statistics to be appropriate.

Pre-specified subgroup analyses were conducted and are reported in the CS: these are relative to baseline stratification factors, demographics, disease characteristics and number and types of prior therapy. The subgroup analysis by prior line of therapy (1 versus 2-3 prior therapy) is of relevance to the NICE scope. However, this does not exactly match with the anticipated positioning of IXA which is, according to the Company, second and third line.

4.9 Description and critique of the company's approach to the evidence synthesis

The evidence synthesis presented in the CS focussed on a narrative review of the TMM-1 trial, the only study found that compared IXA + LEN + DEX versus placebo + LEN + DEX, plus a number of NMAs that primarily aimed to synthesise evidence bearing on the relative effectiveness of treatments in the 1+ prior population, particularly with respect to of BORT + DEX versus IXA + LEN + DEX.

4.9.1 Critique of the reporting of the direct evidence (based on the CS)

The reporting of the TMM-1 trial was generally clear and comprehensive. The ERG did not find significant discrepancies between the CS and the published account of the trial.[26] In clarification the company was invited to expand its explanation for the selection of BORT + DEX as the only comparator to IXA + LEN + DEX for the 1+ prior population, even though LEN + DEX was identified as such in the NICE scope and within the NHS this combination is used for this

population, while many patients will already have received BORT + DEX and therefore may be unlikely to receive the same therapy second line or later. The company response reasons that LEN + DEX is not currently funded by NHS (England), that it has received a draft negative ACD from NICE and that there has been no date set for the FAD, and that the current NICE pathway identifies BORT + DEX as the only recommended second line treatment; the response further points out that "up front" BORT + DEX is probably be used for selected groups of patients. The ERG find these explanations unsatisfactory and suggest that the appraisal committee would prefer to view evidence bearing on both potential comparators.

4.9.2 Critique of the reporting of the NMA (based on the CS)

The company submitted eight NMAs; two of these concerned the 2+ prior population and were not used in cost effectiveness analysis. The quality of reporting of the company's NMAs was disappointing. Although the CS of 332 pages + 104 page appendix was received on time (19/12/2016) this was superseded by an amended text with different pagination received 10/01/2017; the appendix remained unchanged and un-paginated; NMA information was scattered between main text and appendix with frequent cross referencing. As a consequence the ERG encountered difficulties in finding the NMA information and undertaking a systematic assessment of their quality and reliability within the remaining time frame, thus an evaluation of the NMAs was restricted by late arrival of critical information. The ERG has focussed on those NMAs critical to the base case economic analysis.

Table 5: Appraisal of methodological reporting of the NMA (based on the CS)

Rationale and searches	
1. Is the rationale for the NMAs and the study objectives clearly stated?	The NMAs were based on a previous undertaking by the company that included a large number of irrelevant comparators. Some of these appear to have been retained in the CS NMAs.
2. Are searches stated and do they appear appropriate?	Yes; it is not clear if the search presented is that ofr the previous NMA or for the ones submitted.
3. Are inclusion/exclusion criteria adequately reported?	Yes (CS 4.10.2.2). Both observational studies and RCTs were to be included
4. Is the quality of the included studies assessed?	Yes; but this has not been well undertaken (see relevant section).
Model methods	
1. Is the statistical model described?	Yes; but software codes were only provided in clarification

2. Is there a justification for the choice of outcome measure provided?	Yes
4. Has a structure of the networks been provided?	Yes; the contributing studies to the networks were difficult to identify
3. Has the choice of fixed or random effects model been justified?	Yes
5. Is any of the programming code used in the statistical programme provided?	No; software codes were only provided in clarification
6. Is a sensitivity analysis presented, is this appropriate?	Yes; sensitivity analyses were undertaken according to DEX dose, and according study design.
Results	
1. Are the results of the NMA presented?	Only selected results presented; others provided on clarification.
2. Does the study describe an assessment of the model fit?	Yes. Also DIC's are presented in leverage plots for overall response rate.
3. Is the evidence combined and the results presented?	Partially.
4. Has there been any discussion around the model uncertainty?	Yes
5. Are the point estimates of the relative treatment effects accompanied by some measure of variance?	Yes

Despite the submission's large size, relatively meagre information was provided for important aspects of the NMAs. In particular the input values and software codes were missing as were most NMA outputs; those outputs that were reported were confusingly distributed between clinical and cost effectiveness sections of the submission. Details of studies included in the NMAs were listed in single tables with no indication which studies referred to which networks. The supplied network diagrams were accompanied by a list of bibliography reference numbers so that again it was cumbersome to determine which studies contributed to which network. Most deficiencies were remedied in clarification response received 04/02/2014.

In summary the quality of NMA reporting in the submission was confusing, lacked clarity and was incomplete.

4.9.3 Methodology of the NMA

The ERG has critically appraised the methodology of the NMA, in particular focusing on the assumptions of homogeneity, similarity, and consistency.

The ERG has presented in Table 6 the baseline characteristics of studies that have been included in the Company's NMAs. For simplicity, we only reported those directly contributing to the comparison of the main interventions of interest (IXA+LEN+DEX versus BORT-DEX) for the NMA in the 1+ prior therapy group that were conducted for the two main outcomes, PFS and OS. The ERG did not report the baseline characteristics on the Montefusco study[50] because the latter has been considered as irrelevant. Lastly, the ERG was unable to report the baseline characteristics from the eVOBS study since very limited information was provided (conference abstract only). The baseline characteristics were not homogeneously reported across studies, which means that many data are not listed in Table 6.

There is considerable heterogeneity in the baseline characteristics across studies that were included in the NMA. First, these studies were conducted over very different time periods. While the TMM-1 study recruited patients in the 2010's, the MM-09 and MM-010 study, along with the APEX trial recruited patients in the early to mid 2000's. Over the last decade, there have been major changes in the first-line treatment of MM. Indeed, thalidomide or bortezomib have been incorporated into the treatment pathway. For instance, MP-THAL or MP-BORT have become gold standard treatment for patients ineligible for ASCT while BORT combined with DEX +/- THAL has become increasingly used for induction therapy before ASCT. These new regimens have contributed to improve overall survival. The ERG also noted that the proportion of patients with prior stem-cell transplantation differ across studies. Overall, the history of treatment of patients from the studies included in the NMA strongly differ which is a problem as the first-line treatment is an effect modifier.

Secondly, the ERG noted that the proportion of patients with 1 or 2 prior-therapies is not well balanced across studies. While the TMM-1 trial included around 60% patients at the first relapse, the MM-09 and 10 studies included around 60-65% of patients with 2 prior therapies. The Dimopoulos 2015 study gathered patients from 3 RCTs selecting only (100%) those with 1 prior therapy. The number of prior-line is an effect modifier for several major clinical outcomes (PFS, OS).

Lastly, the ERG has noted that the Company included within the NMA IXA+LEN+DEX using the information provided by the TMM-1 trial where 69% of patients previously received BORT.

This greatly contrasts with the rest of studies (MM-09, MM-010, APEX, Matched pair RCTs) since the range of patients with a prior BORT treatment was 0-11.4%.

Table 6: Compared baseline characteristics of studies included in the NMA and directly contributing the estimation of the comparison of interest

	Tourmaline MM 1[26]		MM – 010[39]		MM – 09[40]		APEX[33]		Matched pairs RCTs [45]	
	IXA-LEN-DEX (N=360)	LEN-DEX (N=362)	LEN-DEX (N=176)	DEX (N=175)	LEN-DEX (N=177)	DEX (N=176)	BORT (N=333)	DEX (N=336)	BORT-DEX (N=109)	BORT (N=109)
Age, years, median (range) - yr	66 (38-91)	66(30-89)	63 (33-84)	64 (40-82)	64 (36-86)	62 (37-85)	62	61	62 (42-86)	64 (38-84)
Male sex - no (%)	207 (58)	202 (56)	59.10%	58.90%	59.9	59.1	118(56%)	200 (60%)		
White race - no (%)	310 (86)	301 (83)								
ECOG PS 0 no/total no (%)	180/354 (51)	170/358 (47)	78 (44.3)	65 (37.1)	74 (41.8)	83 (47.2)			26 (24)	25(23)
ECOG PS 1 no/total no (%)	156/354 (44)	164/358 (46)	72 (40.9)	79 (45.1)	83 (46.9)	80 (45.5)			71 (65)	73 (67)
ISS disease stage I no. (%)	226 (63)	233 (64)								
ISS disease stage II no. (%)	89 (25)	87 (24)								
ISS disease stage III no. (%)	45 (12)	42 (12)								
Durie-Samon stage I -no. (%)			11 (6.2)	8 (4.6)	6 (3.4)	5 (2.8)				
Durie-Samon stage II -no. (%)			50 (28.4)	57 (32.6)	56 (31.6)	55 (31.2)				
Durie-Samon stage III -no. (%)			115 (65.3)	110 (62.9)	114 (64.4)	116 (65.9)				
Cytogenetic features - no of patients (%)										
Standard risk cytogenetic abnormalities	199 (55)	216 (60)								
High-risk cytogenetic abnormalities	75 (21)	62 (17)								
Patients with 1 prior therapy -no. (%)	224(62)	217 (60)	56 (31.8)	57 (32.6)	68 (38.4)	67 (38.1)	132 (40)	119 (35)	109 (100%)	109 (100%)
Patients with 2 prior therapies -no. (%)	97 (27)	111(31)	120 (68.2)	118 (67.4)	109 (61.6)	109 (61.9)	186 (56)	194 (58)	0	0
Prior stem-cell transplantation	212 (59)	199 (55)	97 (55.1)	95 (54.3)	109 (61.6)	108 (61.4)	222/332 (67)	229/336 (68)	44 (40%)	51 (57%)
Prior bortezomib - no. (%)	248(69)	250 (69)	8 (4.5)	7 (4)	19 (10.7)	20 (11.4)	0%	0%	0%	0%
Prior IMID therapy - no./ total no. (%)	193 / 360 (54)	204/362 (56)							45 (41%)	38 (35%)
Lenalidomide	44/360 (12)	44 /362 (12)	0%	0%	0%	0%	0%	0%		
Thalidomide	157/ 360 (44)	170/362 (47)	53 (30.1)	67 (38.3)	74 (41.8)	80 (45.5)	160/332 (48)	168/336 (50)		

Transitivity assumption

The authors do not discuss whether or not they assessed the transitivity assumption and whether it was violated. If the transitivity assumption is compromised or does not hold, the consistency assumption is also violated, leading to biased estimates in the network meta-analysis. The ERG examined the transitivity assumptions applicable to the NMAs included in the manufacturer's submission. A more detailed account of the transitivity assumptions is provided below.

The transitivity assumption does not hold if the distribution of population characteristics that are effect modifiers differ across the treatment comparisons of a network. One such treatment effect modifier in the Company's NMA is the number of prior therapies. For example, the RCT (TMM) data in Table 41 have indicated the IXA + LEN + DEX's favourable effect on PFS, OS, TTP, and OR tended to be similar to LEN + DEX in the 1 prior therapy subgroup (e.g., at 23 months, PFS-HR=0.99, 95% CI: 0.76, 1.29), whereas in the 2 + prior therapy subgroup, the IXA+ LEN + DEX's favourable effect was more pronounced relative to LEN + DEX (e.g., at 23 months, PFS-HR=0.62, 95% CI: 0.45, 0.86). The networks for PFS (1+ prior population) and OS (1+ prior population) include trials of clinically diverse populations (1 prior and 2+prior therapy), rendering the compared treatments in these networks not jointly randomizable. In the OS network, the matched-pairs study[45] which directly contributed to the main comparison between IXA and LEN + DEX included only the 1 prior therapy population subgroup, whereas other trials of the same network included 1 and 2+ prior therapy subgroup populations. The uneven distribution of this effect modifier across the network comparisons violates the transitivity assumption. In four studies (APEX, MM010, MM009, and the matched-pairs study), all or most patients included were BORT naïve (89-100%), whereas in other studies (TMM[26] and PANORAMA[51]) 40%-70% of the sample was comprised of patients with prior BORT. Another threat to transitivity is the difference in doses for DEX 40 (different scheduling) in TMM[26] vs. MM09/010 trials [39, 40], therefore these interventions cannot be considered as one node of LEN + DEX.

The study (Dimopoulos 2015[44]) uses APEX RCT data[33] which also contributes to the network as the RCT, leading to double counting.

The indirect comparison (for PFS) between IXA + LEN + DEX vs. BORT + DEX was achieved through adding non-RCT data (Montefusco 2015) [although the company stated that it was an RCT] that compared BORT + DEX + CYCLO vs. LEN + DEX + CYCLO to the network. The authors may have assumed that the effects of CYCLO in the two arms would be cancelled out, thereby allowing the comparison between BORT + DEX vs. LEN + DEX. We cannot completely exclude the likelihood of interaction between CYCLO and LEN + DEX that may lead to an estimate of magnitude different from that expected between BORT + DEX vs. LEN + DEX. Also, LEN + DEX (from MM1 RCT) and LEN + DEX + CYCLO (Montefusco 2015 RCT[32]) cannot be considered as one treatment node of the network. These are two different interventions. The dosages of LEN + DEX in TMM-1 RCT (25mg and 40mg) differed from those in the Montefusco 2015 RCT (20mg + LEN 15mg), therefore these interventions cannot be considered as one node of LEN + DEX. These are special cases of the transitivity assumption being violated. Therefore, the validity of HR (PFS) estimate for the indirect comparison between IXA + LEN + DEX vs. BORT + DEX is questionable.

The indirect comparison (for OS, HR for risk of death) between IXA + LEN + DEX vs. BORT + DEX has no common first-order comparator and therefore was based on the second-order indirect comparison which was achieved through comparing the HR estimates for two indirect comparisons IXA + LEN + DEX vs. DEX and DEX vs. BORT + DEX. The first indirect comparison IXA + LEN + DEX vs. DEX was obtained from contrasting the estimates of two direct comparisons IXA + LEN + DEX vs. LEN + DEX reported for one RCT (TMM) and DEX vs. LEN + DEX reported in two other RCTs pooled (MM-09[40] and MM-010[39]). The second indirect comparison DEX vs. BORT + DEX was obtained from comparing the estimates of two direct comparisons DEX vs. BORT reported in APEX-RCT and BORT vs. BORT +DEX reported in one observational study (Matched pairs).[45] A longer pathway of multiple intermediate indirect comparison steps to derive the main indirect comparison leads to even greater uncertainties in the estimates. The more intermediate links separate the indirectly compared treatments, the more unreliable this comparison becomes through increasing

the standard error of the effect estimate.[52, 53] Therefore, the validity of the OS-HR estimate for the indirect comparison IXA + LEN + DEX vs. BORT + DEX is questionable.

Consistency assumption

The NMA did not form any closed loops including mixed treatment comparison (pooled indirect and direct evidence for the same comparison). Understandably, consistency between indirect and direct comparisons was not assessed. Indeed, this is one of the main limitations of the evidence provided in the NMAs of the manufacturer's submission, i.e., the inability to judge to what degree the transitivity assumption was violated, since this reflects statistically on the degree of consistency between direct and indirect comparisons.

4.9.4 Assumptions applied in the development and application of the company's NMA results

The ERG has critically considered the assumptions of the data included in the NMAs and applied for cost effectiveness analysis.

The CS produced NMAs using hazard ratio and count data; an appropriate reference is provided and the submission describes a methodological adjustment described as a "pseudo drop out rate".[50] It appears that the NMAs assume that treatment baselines and treatment effects on the log hazard scale were normally distributed. For the count data, it is presumed a binomial model was used. The CS did not appear to undertake any sensitivity analyses around the priors. Although the CS indicates that convergence was assessed using the Gelman-Rubin diagnostic, iteration plots and frequentist validation models, few specific findings were presented.

The NMA outputs were "pooled" HR estimates (and credible intervals) for paired treatment comparisons in various MM populations. In clarification these were provided more fully than in the CS. The NMA outputs for OS and PFS were used to produce

parametric models that were employed in cost effectiveness analysis so as to develop estimates of mean years spent in health states.

The ERG has the following concerns in regard to the use of the NMA output for estimating life-years gained (LYG) as used in the CS economic evaluation.

A. The NMAs output hazard ratios for OS and PFS are used to modify "baseline" parametric models for LEN + DEX (exponential model for OS and gamma model for PFS). The ERG is concerned that this procedure assumes proportional hazards between LEN + DEX and other treatments and between the arms in the studies used in the NMA; this assumption has not or cannot be tested. In the CS no details are provided regarding this assumption. The ERG considers it is possible the assumption may be violated in a number of studies input for the NMAs. A further concern is that for PFS (1+ prior population) the IXA + LEN + DEX and comparator BORT + DEX arms are not handled equitably since a NMA hazard ratio is only employed for the BORT + DEX arm.

B. Although the NMA used HR inputs from the published survival analyses this does not use considerable survival information embedded in the constituent studies, specifically information embodied in the shape of the survival curves and their disposition along the time axis; factors that will affect the estimate of mean life years gained (LYG). When only HRs are used in this way to estimate LYG they may fail to provide useful information since identical HRs for pairs of survival curves with proportional hazards may deliver different LYG depending on their shape and dispersion on the time axis.[54]

C. The ERG is concerned that the input hazard ratios for the NMAs may or may not be adjusted for covariates; the CS provides no details in this regard. Since in the CS base-case the NMA HRs are applied to parametric models adjusted for several covariates, the use of adjusted HRs for the NMA might result in double counting of some variables in some cases or in adjustment by differing covariates in the compared treatments in other instances.

D. Although the parametric models of OS and PFS developed in the CS may fit reasonably well to the observed data from the TMM-1 trial, their extrapolation in

modelling survival beyond the observed median follow up of about 15 months (IA1) or 20 months (IA2) to the life-time horizon may not be appropriate, since models were developed under a proportional hazards assumption that may not hold. When the data is sparse (as is the case for OS here) a potential consequence of using such modelling is that the estimated proportion of mean survival accumulated in the extrapolation may contribute nearly all of the mean survival, implying there will be great and differing levels of uncertainty in the estimates for different treatments.

In summary: The CS HRs from the NMA are used to generate estimates of LYG under different treatments. To generate the survival curve for comparator treatment 'X' (a treatment other than LEN + DEX) the CS takes the HR estimates from the NMA (e.g. X versus LEN + DEX) and applies this to a multivariate exponential distribution fit for OS of LEN + DEX arm of the TMM-1 trial. The LYG estimate for X is the area under this newly generated survival curve. This procedure: (1) imposes proportional hazards between compared treatments; in the opinion of the ERG there is no a priori reason to expect proportional hazards to hold for two treatment regimens that differ in their mode(s) of action; (2) forces an exponential curve shape on the comparator which may be unlikely to reflect that observed in studies of that treatment (there is no a priori reason to expect that the observed curve will conform to a distribution that happens to fit a treatment regimen with differing mechanisms of action); (3) anchors the generated curve on the time axis according to the position of the TMM-1 LEN + DEX survival curve (again there is no a priori reason that this is appropriate); (4) if the parametric model for the TMM-1 LEN + DEX arm is an erroneous estimate of survival then it follows that all NMA-dependent comparator treatment estimates may also be erroneous. The resulting survival curves from this procedure may be implausible and/or bear little relationship to the observed curves found in published studies.

4.10 Summary of submitted evidence

The evidence submitted by the company comes from the results from a single pivotal trial along with the results from network meta-analyses.

4.10.1 Results from the pivotal trial

The primary outcome of TMM-1 trial was progression free survival (PFS), defined as time from date of randomisation to the date of first documentation of disease progression or death from any cause, whichever comes first. It was evaluated based on central laboratory results and IMWG criteria as evaluated by an independent research commission. Secondary outcomes included overall survival, response rates (overall, complete, very good partial and partial), duration of response, time to progression and safety. Overall survival was also evaluated for high-risk patients carrying del(17) (CS, p.86, table 32).

The company reports results for two data cuts, one published data cut at a median follow-up of 15 months (corresponding to the first interim analysis) and a second unpublished data cut at a median follow-up of 23 months (corresponding to the second interim analysis). In the following we will present the results for primary and secondary outcomes for both data cuts, and the results of their subgroup analysis for patients with 1 prior and 2 + 3 prior therapies. The results from the third interim analysis are not yet available and are expected in Q2 2017.

4.10.1.1 Progression-free survival (PFS)

Median PFS was 20.6 months in the IXA+LEN+DEX group and 14.7 months in the placebo group in the first data cut (hazard ratio (HR) for progression or death 0.74 ; 95% CI 0.59-0.94; p=0.012). The company claims that this constitutes a significant 35% and meaningful ~6 months' improvement on median PFS (CS, 97).

At the second interim analysis, PFS for the IXA group was 20 months, for the placebo group 15.9 months (HR 0.82, 95% CI 0.67-1.0). The initially observed benefit in the 1st interim analysis therefore did not persist throughout the 2nd interim analysis. This was

one of the reasons for the negative initial opinion provided by the CHMP for the marketing authorisation. However, the company argued that this corresponded to a non-inferential PFS analysis added in the latest amendment of the study protocol, and that according to the statistical analysis plan, the company was therefore able to demonstrate PFS benefit. Although the CHMP revised their initial opinion, acknowledging this second analysis was non-inferential, the presence of a statistically significant difference on PFS with very immature data (15 months of median follow-up) and the absence of statistically significant difference on PFS with less immature data (23 months of median follow-up) is questionable. Interestingly, some members of the CHMP expressed divergent position on the positive opinion for marketing authorisation[18] saying that the second analysis provides enhanced information for quantification of the treatment effect.

In the discussion on clinical efficacy within the EPAR, it is stated that if this second analysis had been the primary analysis for PFS the study would have failed. Also, the report states that a p-value of 0.054 clearly does not represent the level of evidence that would be expected from a single pivotal trial.

Table 7: Tourmaline trial entire ITT population PFS results (HR <1 favours IXA+LEN+DEX)

	IXA-LEN-DEX	LEN-DEX
Number of patients	360	362
1st interim analysis (median FUP 15 months)		
Number of progressions or deaths	129	157
Median PFS (months)	20.6	14.7
HR for progression of death (95%CI)	0.74 (0.5, 0.94)	
P value	0.012	
2nd interim analysis (median FUP 23 months)		
Number of progressions or deaths	177	195
Median PFS (months)	20	15.9
HR for progression or death (95%CI)	0.82 (0.67, 1.0)	
P value	0.054	

In the study protocol for the TMM-1 trial (amendement 3), it was stated that sensitivity analyses for PFS would include: 1). PFS assessed by investigator will be analyzed in the ITT population, 2)- PFS assessed by IRC will be analyzed in the per protocol population. The ERG was not able to find these sensitivity analyses in the CS.

4.10.1.2 Overall Survival (OS)

The company also reports the results on OS from both first and second interim analysis (Table 8). The company indicated that OS data are not yet mature which is true given that the median OS is not reached in the 2 analyses. The company states that early data show a survival trend in favour of IXA-LEN-DEX relative to LEN-DEX but the upper confidence interval of the HR for death greatly exceeds 1. According to their statistical analysis plan, the company cannot claim OS benefit and given the immaturity of data, no conclusion, either positive or negative, can be drawn on OS.

Table 8: Tourmaline trial entire ITT population OS results (HR <1 favours IXA+LEN+DEX)

	IXA-LEN-DEX	LEN-DEX
Number of patients	360	362
1st interim analysis (median FUP 15 months)		
Number of deaths	51	56
Median OS (months)	NE	NE
HR for death (95%CI)	0.90 (0.62,1.32)	
P value	0.586*	
2nd interim analysis (median FUP 23 months)		
Number of deaths	81	90
Median OS (months)	NE	NE
HR for death (95%CI)	0.87 (0.64, 1.18)	
P value	0.359	

* p-value found in the EPAR and not reported in the main CS

The results for OS were also presented in the high-risk del(17p) group corresponding to a total of 69, of which 36 received IXA and 33 placebo. Four (11%) of the IXA group had died at first interim analysis, and 9 (27%) in the placebo group. We report here a summary of these analyses (Table 9).

Table 9: Tourmaline trial high-risk del (17p) population OS results (HR <1 favours IXA+LEN+DEX)

	IXA-LEN-DEX	LEN-DEX
Number of patients	36	33
1st interim analysis (median FUP 15 months)		
Number of deaths	4	9
Median OS (months)	NE	NE
HR for death (95%CI)	0.506 (0.144, 1.777)*	
P value	0.280*	

2nd interim analysis (median FUP 23 months)		
Number of deaths	9	15
Median OS (months)	NE	30.9
HR for death (95%CI)	0.487**	
P value		

* CI extracted from the complete study report but not from the main CS

** no 95%CI reported

With an HR of 0.506, the company concludes a 49% reduction in risk of death with IXA compared to placebo. This statement is misleading as the company did not report here the 95%CI for the HR for OS which indicates that the result is not statistically significant. In the complete study report, it is stated that the HR for death is 0.506 (0.144, 1.777).

At the second interim analysis, 9 (25%) of the high-risk IXA patients and 15 (45%) of the high-risk placebo patients had died. The company concludes that this shows a 51% reduction of risk of death for patients with del(17) (HR=0.487). Again, this statement is misleading in the absence of 95% CI around the HR. We were not able to identify this 95% CI but it is likely that the upper CI would exceed 1 rendering the result inconclusive given the small sample size.

In the complete study report, the ERG identified additional data on the OS in patients with no evidence of del(17) and considered these of interest. The results are presented in Table 10.

Table 10: Tourmaline trial patients with no evidence of Del (17p) population OS results (HR <1 favours IXA+LEN+DEX)

	IXA-LEN-DEX	LEN-DEX
Number of patients	324	329
1st interim analysis (median FUP 15 months)		
Number of deaths	47	47
Median OS (months)	NE	NE
HR for death (95%CI)	0.990 (0.659, 1.486)*	
P value	0.960*	

* extracted from the complete study report but not from the main CS

Although we acknowledge these data are immature, these results suggest that IXA has no impact on OS compared to placebo in people with no evidence of del(17).

Overall, the company concludes a survival trend in favour of IXA+LEN+DEX for both ITT and the high-risk population. However, the EMA did not agree with the company's conclusion for both ITT and for the high-risk population. On the contrary, the EMA argues that the evidence the company provided is not substantial enough to draw conclusions for high-risk groups (EMA, 124).

4.10.1.3 Time to progression

In the 1st interim analysis, the median TTP for the IXA+LEN+DEX group is 21.4 months, for the LEN+DEX group 15.7 (HR 0.71, 95%CI 0.56-0.91;p=0.007). The 2nd interim analysis the results for IXA+LEN+DEX was 22 .4 months and 17.6 months (Table 11). The ERG regrets that the company presented the HR for progression (0.79) without its 95%CI.

These results indicate that, like for PFS, the benefit of IXA on the risk of progression is reduced between the first and second interim analysis. The comparable HR for TTP and PFS from both first and second interim analysis confirm our statement that TTP can be considered as a good proxy for PFS (see section on NMA critique).

Table 11: Tourmaline entire ITT population Time to progression results (HR <1 favours IXA+LEN+DEX)

	IXA-LEN-DEX	LEN-DEX
Number of patients	360	362
1st interim analysis (median FUP 15 months)		
Number of progressions	114	145
Median TTP (months)	21.4	15.7
HR for progression (95%CI)	0.71 (0.56, 0.91)	
P value	0.007	
2nd interim analysis (median FUP 23 months)		
Number of progression	158	180
Median TTP (months)	22.4	17.6
HR for progression (95%CI)	0.79 (0.64, 0.98)	
P value	*	

* P value not reported in the main CS

4.10.1.4 Response rates and duration of response

The company reports overall response, very good and complete response, and complete response as presented in Table 12 of the CS. IXA+LEN+DEX had a significantly higher overall response rate (78.3% vs. 71.5%; p=0.04) compared to LEN-DEX at the first interim analysis (CS, 98). The company also reports that the time to response is significantly shorter (1.1 vs. 1.9 months) and that the duration of response is longer (20.5 vs. 15 months) (CS, 98, table 39).

Table 12: Tourmaline entire ITT population Response rates (OR >1 favours IXA+LEN+DEX)

	IXA-LEN-DEX	LEN-DEX
Number of patients	360	362
1st interim analysis (median follow up 15 months)		
Overall response rate, n (%)†	282 (78.3)	259 (71.5)
OR for OR rate (95% CI)	1.44 (1.03, 2.03)	
P value	0.04	
Very good response and complete response, n (%)	173 (48.1)	141 (39.0)
OR for VGPR+CR (95% CI)	1.45 (1.08, 1.95)	
P value	0.014	
Complete response or better, n (%)	42 (11.7)	24 (6.6)
OR for CR or better (95% CI)	1.87 (1.10, 3.16)	
P value	0.019	
2nd interim analysis (median follow up 23 months)		
Overall response rate, n (%)†	283 (78.6)	265 (73.2)
OR for OR rate (95% CI)	1.35 (0.96, 1.91)	
P value	NR	
Very good response and complete response, n (%)	185 (51.4)	159 (43.9)
OR for VGPR+CR (95% CI)	1.35 (1.01, 1.81)	
P value	NR	
Complete response or better,n (%)	53 (14.7)	37 (10.2)
OR for CR or better (95% CI)	1.52 (0.97, 2.38)	
P value	NR	

For the second interim analysis, the company claims that response rates were improved consistently with the first interim analysis, that the time to response was shorter and the duration of response longer (CS, 100). The ERG has noted that no CI was provided for any of the treatment effect estimates presented in Table 40 of the CS, which means that no formal conclusion could be drawn from these results. This is why the ERG asked the company to provide these CIs as part as clarifications. Interestingly, the response provided by the Company indicated that the overall response rate behaves in line with the previously presented PFS and TTP and shows that the initial benefit of IXA+LEN+DEX is not sustained to the same degree during the second interim analysis. The overall response rate (ORR) is now 78.6% vs. 73.2% but the lower CI falls below 1 (OR 1.35 (95%CI 0.96, 1.31) indicating a lack of statistical significance. Similar results were observed for the rate of CR or better. For VPGR+CR, the benefit of IXA-LEN-DEX over LEN-DEX remains statistically significant between the two analyses but the OR in the second interim analysis is numerically lower compared to that of the first interim analysis (1.45 vs 1.35 respectively).

4.10.1.5 Health-related quality of life (HRQoL)

Quality of life was assessed by EORTC-QLQ-C30 and MY-20 questionnaires at every two cycles (CS, 101). The results indicated similar quality of life for both treatments both at first and second data cut (CS, 101). The company argued that quality of life was maintained despite the addition of a third agent. The company concludes that IXA does not have a negative impact on patients treated with LEN+DEX. (CS, 102).

The company states that “there was a trend for better physical functioning, emotional functioning and fatigue scores” for the IXA+LEN+DEX group at both analysis. Physical functioning improved over the first 6 cycles, emotional functioning over the first 4, after which both stabilised (CS, 102).

The company does not report the data on which the company bases these conclusions so the ERG is unable to verify the conclusions the company has drawn.

4.10.1.6 Subgroup analysis

The company does not expand on the subgroup that received IXA+LEN+DEX after 1 prior therapy. The company argues that, as LEN+DEX is currently not recommended for 2nd line treatment, IXA+LEN+DEX will be more relevant as an alternative to the currently recommended LEN+DEX treatment in 3rd line, that is, after 2 or more prior therapies (CS, 102).

The NICE final scope however requests the assessment of IXA+LEN+DEX for patients with 1 prior therapy. IXA+LEN+DEX does not appear to have a substantial benefit over LEN+DEX as a second line treatment, that is, for patients with 1 prior therapy.

Subgroup 1 prior therapy

The TMM-1 trial shows that the risk of progression or death is not reduced with IXA-LEN-DEX compared to LEN-DEX in both first and second interim analysis (Table 13) : the hazard ratios are 0.88 (95% CI 0.65, 1.20) and 0.99 (95% CI 0.76, 1.29) respectively.

Table 13: Tourmaline 1 prior therapy PFS, OS and TTP results (HR <1 favours IXA+LEN+DEX)

	IXA-LEN-DEX	LEN-DEX
Number of patients	212	213
1st interim analysis (median FUP 15 months)		
Number of progressions or deaths (PFS)	80	88
Median PFS (months)	20.6	16.6
HR for progression or death (95% CI)	0.88 (0.65, 1.20)	
P value	NR	
Number of deaths (OS)	31	26
Median OS (months)	NE	NE
HR for death (95% CI)	1.24 (0.74, 2.10)	
P value		
Number of progression (TTP)	73	84
Median TTP (months)	20.6	16.6
HR for progression (95% CI)	0.84 (0.61, 1.16)	
P value	NR	
2nd interim analysis (median FUP 23 months)		

	IXA-LEN-DEX	LEN-DEX
Number of patients	212	213
Number of progressions or deaths (PFS)	109	112
Median PFS (months)	18.7	17.6
HR for progression or death (95% CI)	0.99 (0.76, 1.29)	
P value	NR	
Number of deaths (OS)	48	45
Median OS (months)	NE	NE
HR for death (95% CI)	1.11 (0.74, 1.66)	
P value	NR	
Number of progressions (TTP)	100	106
Median TTP (months)	19.5	18.7
HR for progression (95% CI)	0.96 (0.73, 1.26)	
P value	NR	

The OS results show similar insignificant changes. The lack of benefit of IXA+LEN+DEX vs. LEN+DEX again becomes obvious: Whilst no median overall survival can be estimated, 31 vs. 26 patients died during the first interval (HR 1.24, 95% CI 0.74- 2.10), and 48 vs. 45 during the second interval (HR 1.11, 95% CI 0.74- 1.66). These numbers show that more people died in the IXA+LEN+DEX group than in the placebo group and that the risk of death in the IXA group may seem numerically higher for patients with one prior therapy. However, the difference between the groups is not statistically significant.

Although these data on PFS and OS in the 1 prior group are still immature, the ERG notes the clear absence of benefit of IXA-LEN-DEX, which questions the statement that the benefits of IXAZOMIB outweighs the risks in the subgroup of patients.

Similar results to PFS are reported for Time to Progression (TTP): In the first interim analysis, TTP for the IXA group is 20.6 months vs. 16.6 months in the placebo group (HR 0.84, 95% CI 0.61- 1.16). The difference between the groups is not significant. At second interim analysis the difference between the groups remains insignificant with 19.5

months for the IXA+LEN+DEX group and 18.7 months for the LEN+DEX group (HR 0.96, 95% CI 0.73- 1.26) (Table 13).

The IXA and placebo group show very similar response rates (**Table 14**). At first interim analysis, the overall response rate in the IXA+LEN+DEX group is 76.9% vs. 74.6% in the LEN-DEX group (OR 1.13, 95% CI 0.72- 1,77). The combined result for very good response and complete response are 44.8% vs. 43.7% with a OR of 1.05 (95% CI 0.71-1.54) and complete response or better are 9% vs. 8% with a OR of 1.13 (95% CI 0.57-2.25).

At second interim analysis, the difference between the two groups remains insignificant.

Table 14: Tourmaline 1 prior therapy Response rates (OR >1 favours IXA+LEN+DEX)

	IXA+LEN+DEX	LEN+DEX
Number of patients	212	213
1st interim analysis (median FUP 15 months)		
Overall response rate, n (%)	163 (76.9)	159 (74.6)
OR for OR rate (95%CI)	1.13 (0.72, 1.77)	
P value	NR	
very good response and complete response, n (%)	95 (44.8)	(43.7)
OR for VGPR + CR (95%CI)	1.05 (0.71, 1.54)	
P value	NR	
Complete response or better,n (%)	19 (9.0)	17 (8.0)
OR for CR or better (95% CI)	1.13 (0.57, 2.25)	
P value	NR	
2nd interim analysis (median FUP 23 months)		
Overall response rate, n (%)	164 (77.4)	166 (77.9)
OR for OR rate (95%CI)	0.97 (0.61, 1.5[illegible])	
P value	NR	
Very good response and complete response, n (%)	105 (49.5)	105 (49.3)
OR for VGPR + CR (95%CI)	-	
P value	NR	
Complete response or better,n (%)	26 (12.3)	27 (12.7)
OR for CR better (95% CI)	-	
P value	NR	

The results of the main trial do not show any benefit of IXA-LEN-DEX over LEN-DEX in terms of response rates. Initial insignificant benefits in PFS, TTP and OS seem to decrease from first to second interim analysis. It may even be argued that the triplet performs worse than the doublet.

Overall, the similarity between the IXA-LEN-DEX and LEN-DEX groups with 1 prior therapy supports the company's request not to place IXA-LEN-DEX at 2nd line within the UK. The company did however provide a cost-effectiveness analysis of IXA-LEN-DEX in the 1 prior therapy group.

Subgroup 2-3 prior therapies

The company claims that IXA+LEN+DEX demonstrates a benefit for patients who received 2-3 prior therapies.

A total of 148 patients with 2-3 prior therapies received IXA-LEN-DEX and 149 received LEN-DEX (as per stratification factor). The company claims that there was an improvement in response rates, TTP and median PFS for both first and second interim analysis (CS, 103). The ERG has argued in the previous section that this is not the case for the subgroup with 1 prior therapy, and that the benefit of IXA+LEN+DEX reduces in the ITT population from the first to the second interim analysis, however the company claims that there is a benefit for IXA+LEN+DEX over LEN+DEX both for the ITT population and the subgroups, and for both first and second interim analysis (CS, 103).

Regarding PFS, the data the company provide for the subgroup of patients with 2-3 prior therapies show a greater benefit of IXA+LEN+DEX compared to LEN+DEX. The company presents an HR of 0.58 (95% CI 0.4, 0.84) for the first and an HR of 0.62 (95% CI 0.45, 0.86) for the second interim analysis (Table 15).

Table 15: Tourmaline 2-3 prior therapies PFS, OS and TTP results (HR>1 favours IXA+LEN+DEX)

	IXA+LEN+DEX	LEN+DEX
Number of patients	148	149
1st interim analysis (median FUP 15 months)		
Number of progressions or deaths (PFS)	49	69
Median PFS (months)	NE	12.9
HR for progression or death (95% CI)	0.58 (0.40, 0.84)	
P value	0.05	
Number of deaths	20	30
Median OS (months)	NE	NE
HR for death (95% CI)	0.62 (0.35, 1.09)	
P value	NR	
Number of progressions	41	61
Median TTP (months)	NE	13.0
HR for progression (95% CI)	0.55 (0.37, 0.82)	

	IXA+LEN+DEX	LEN+DEX
Number of patients	148	149
P value	NR	
2nd interim analysis (median FUP 23 months)		
Number of progressions or deaths	68	83
Median PFS (months)	22.0	13.0
HR for progression or death (95% CI)	0.62 (0.45, 0.86)	
P value		
Number of deaths	33	45
Median OS (months)	NE	NE
HR for death (95% CI)	0.65 (0.41, 1.02)	
P value	NR	
Number of progressions (TTP)	58	74
Median TTP (months)	28.8	14.1
HR for progression (95% CI)	0.58 (0.41, 0.83)	
P value	NR	

The company argues that median PFS were similar for the IXA+LEN+DEX group in this subgroup of patient with 2-3 prior therapies and the ITT population, whereas the LEN+DEX group shows a numerical inferiority in the 2-3 prior therapies subgroup and the ITT group. In other words, the company argues that because IXA works just as well in the ITT population as it does in this subgroup, whereas the LEN+DEX group of the ITT population shows better results than LEN+DEX group of for this subgroup, there must be a benefit of IXA+LEN+DEX (CS, 106).

The company also argues that the OS results show a consistent trend towards an OS benefit with IXA with HRs of 0.62 (95% CI 0.35, 1.09) and 0.65 (95% CI 0.41, 1.02) (CS, 107). In both analyses, the upper CI is above 1 which means that the results are not statistically significant although the study might be underpowered to demonstrate a benefit in this sub-group.

The company states that the TTP of the 2-3 prior therapies subgroup compared to the ITT population supports the claim that PFS is improved in the IXA+LEN+DEX arm compared to the LEN+DEX arm in the subgroups and the ITT population (CS, 108).

The overall response rate given for patients with 2-3 prior therapies also do not show any change between first and second interim analysis, neither in the IXA+LEN+DEX group nor in the placebo group. IXA-LEN-DEX has a better outcome compared to LEN-DEX on overall response, VGPR+CR, and CR (Table 16).

The ERG regrets that no CI was provided for the OR for VGPR+CR and CR in the second interim analysis.

Table 16: Tourmaline 2-3 prior therapies Response Rates (OR >1 favours IXA+LEN+DEX)

	IXA-LEN-DEX	LEN+DEX
Number of patients	148	149
1st interim analysis (median FUP 15 months)		
Overall response rate, n (%)	119 (80.4)	100 (67.1)
OR for ORR (95% CI)	2.03 (1.19, 3.45)	
P value	0.05	
Very good response and complete response, n (%)	78 (52.7)	48 (32.2)
OR for VGPR + CR (95%CI)	2.36 (1.47, 3.79)	
P value	0.05	
Complete response or better,n (%)	23 (15.5)	7 (4.7)
OR for CR (95%CI)	3.85 (1.58, 9.36)	
P value	0.05	
2nd interim analysis (median FUP 23 months)		
Overall response rate, n (%)	119 (80.4)	99 (66.4)
OR for OR (95%CI)	2.09 (1.23, 3.56)	
P value		
Very good response and complete response, n (%)	80 (54.1)	54 (36.2)
OR for VGPR + CR	-	
P value		
Complete response or better,n (%)	27 (18.2)	10 (6.7)
OR for CR or better	-	
P value		

Overall, the ERG has noted that the results for the main outcome of interest, PFS and OS, tend to show a better relative effectiveness for IXA-LEN-DEX in the 2-3 prior therapy group compared to the 1 prior therapy group.

Because the company considers that IXA will be mainly positioned in the third line of treatment, the ERG has been interested in the clinical outcomes of IXA in the subgroup

of patients with 2 prior therapy only and asked the company to provide results accordingly in the clarification responses.

In Table 3 of the clarification document (page 17), the company was able to provide these estimates. The ERG has reported those results in Table 17 for OS and PFS.

Table 17: Tourmaline 2 prior therapies PFS, and OS results (HR>1 favours IXA+LEN+DEX)

	IXA+LEN+DEX	LEN+DEX
Number of patients	97	111
1st interim analysis (median FUP 15 months)		
Number of progressions or deaths (PFS)	36	47
Median PFS (months)	17.5	14.1
HR for progression or death (95% CI)	0.75*	
P value	NR	
Number of deaths	14	18
Median OS (months)	NE	NE
HR for death (95% CI)	0.77 (0.38-1.55)	
P value	NR	
2nd interim analysis (median FUP 23 months)		
Number of progressions or deaths	47	58
Median PFS (months)	19.3	15.6
HR for progression or death (95% CI)	0.749**	
P value	NR	
Number of deaths	23	31
Median OS (months)	NE	NE
HR for death (95% CI)	0.725 (0.42-1.25)	
P value	NR	

*extracted from Figure 19 on the main CS, note that the value mentioned in Table 3 (page 17) on the clarification response is 0.723;

**extracted from Table 4 (page 18) on the clarification response (95%CI not provided)

These results show that, within the group of patients with 2 prior therapy, which corresponds to the main population targeted by the company within the NHS, IXA+LEN+DEX is not statistically significantly beneficial compared to LEN+DEX and the relative clinical effectiveness of the IXA combination appears lower compared to the

2 or 3 prior therapy group in terms of PFS (HR for progression or death 0.75 versus 0.58 respectively in the first interim analysis; HR of 0.749 versus 0.62 respectively in the second interim analysis) and OS (HR for death 0.77 versus 0.62 respectively in the first interim analysis; HR 0.725 versus 0.65 respectively in the second interim analysis). This seems explained by the relative better effectiveness of IXA in the 3 prior therapy group, which does not correspond to a population targeted by the company, compared to the 2 or 3 prior therapy. In other words, the more favourable results observed for IXA in the 2 or 3 prior therapy group seem to be driven by the results in the 3 prior therapy. This has been accounted for in a sensitivity analysis undertaken by the ERG in the cost-effectiveness evaluation.

4.10.1.7 PFS other subgroups

The company presents PFS results for the first interim analysis for pre-specified subgroups. The company highlights the cytogenetic risk factor group that has a high risk factor: The PFS values given for patients carrying del(17) are 21.4 vs. 9.7 months (HR 0.60; 95% CI 0.29, 1.24), and in patients with t(4;14) median PFS was 18.5 vs 12 months (HR 0.65; 95% CI 0.25, 1.66). The company concludes that IXA "may improve or overcome the known traditional poor prognosis in patients with high-risk cytogenetic features" (CS, 109f.). However, the large confidence intervals do not indicate that this conclusion can be drawn with any degree of certainty.

4.10.1.8 Conclusion

The ERG concludes that, although it may be, as the company argues, "commonly accepted that a multidrug combination such as a triplet of drugs, with different mechanisms of action, is required for relapsed or refractory disease" (CS, 109), there is limited evidence to conclude that the IXA+LEN+DEX combination provides a significant benefit over LEN+DEX in the entire population of RRMM. Both drug combinations show similar results in the 1 prior therapy subgroup (with IXA results worsening in second interim analysis). A benefit of using IXA has been identified in the 2-3 prior

therapy subgroup but this needs to be confirmed with more mature data. Moreover, the ERG has highlighted that this benefit seems to be driven by favourable results observed in the subgroup of patients with a very advanced disease stage (3 prior lines).

4.10.1.9 Adverse events

The company reports adverse event data that were collected at the second interim analysis. The safety population included 361 patients in the IXA+LEN+DEX arm and 359 in the LEN+DEX arm with a median of 17 (range 1-34) and 15 (1-34) treatment cycles. The company reports a similar dose intensity for both groups (CS 142, table 53), with a dose intensity of Lenalidomide of 93.8% vs. 96.6% and Dexamethasone of 92.2% vs 94.9 in the two study arms. Ixazomib was dosed with a relative dose intensity of 97.4% vs. placebo of 98.8% (CS, table 53).

Study treatment has been discontinued in 62% vs. 63% of the IXA vs. placebo patients (CS, 141, table 52). The percentages for the reasons for discontinuation of treatment appear to be similar in both groups, as shown in Table 18. Discontinuation due to progressive disease is slightly more common in the LEN+DEX arm with 40% for LEN+DEX vs. 34% for IXA+LEN+DEX. Discontinuation due to adverse events does occur in 17% vs. 14% in the IXA+LEN+DEX group vs. LEN+DEX.

Table 18: Reasons for treatment discontinuation (median follow-up of ~23 months) as presented in table 52 of CS

Reason for treatment discontinuation, n (%)	IXA+LEN+DEX	LEN+DEX
Number of patients	360	362
Any	222 (62)	229 (63)
Progressive disease	124 (34)	146 (40)
Adverse event	60 (17)	50 (14)
Common adverse events resulting in treatment discontinuation		
Diarrhoea	6 (2)	1 (<1)
Peripheral neuropathy NEC	7 (2)	2 (<1)

Reason for treatment discontinuation, n (%)	IXA+LEN+DEX	LEN+DEX
Number of patients	360	362
Fatigue	4 (1)	2 (<1)
Thrombocytopenia	4 (1)	4 (1)
Cardiac failure	1 (<1)	3 (<1)
Neutropenia	3 (<1)	3 (<1)
Decreased platelet count	1 (<1)	3 (<1)
Withdrawal by patient	7 (2)	11 (3)
Protocol violation	0	1 (<1)
Lost to follow-up	1 (<1)	0
Other	30 (9)	21 (6)

Both groups also show similar numbers for occurrence of adverse events. Any adverse events occur in 98% vs. 99% of the IXA vs. the placebo group; serious adverse events in 47% vs. 49%. Adverse events resulting in dose reduction of any drug occur in 56% vs. 50%, and in discontinuation of any drug in 25% vs. 20%. On-study deaths were reported in 4% of the IXA group and 6% of the placebo group (15 cases vs. 23) (CS, 142f., table 54, here Table 19).

Table 19: Overall safety profile at the 23-month analysis (safety population) as reported in CS, table 54

	IXA+LEN+DEX	LEN+DEX
Number of patients	361	359
Median follow-up	23.3 months	22.9 months
Adverse events, n (%)		
Any AE	355 (98)	357 (99)
Any grade ≥3 AE	267 (74)	247 (69)
Any serious AE	168 (47)	177 (49)
AE resulting in dose reduction of any drug	203 (56)	181 (50)
AE resulting in discontinuation of any drug	91 (25)	73 (20)
AE resulting in discontinuation of regimenc	60 (17)	50 (14)
On-study death	15 (4)	23 (6)

The results the company presents show that the overall percentages of adverse events in both arms seem to be very similar. More patients who received IXA experienced grade ≥3

AE compared to those who received placebo (74% versus 69%) but the difference is not statistically significant.

The most common haematologic adverse events were neutropenia (33% vs. 31% for IXA vs. placebo, with grade 3 events at 18% vs. 18% and grade 4 at 5% vs. 6%) and thrombocytopenia (31% vs. 16% for IXA vs. placebo), with grade 3 events at 12% vs. 5% and grade 4 at 7% vs.4% (CS, 143, 144, table 55). Thrombocytopenia is an overlapping AE seen with ixazomib and lenalidomide-dexamethasone, which explains the higher occurrence in the IXA+LEN+DEX group.

The most common non-haematologic adverse events were gastrointestinal events, rash and peripheral neurophathy (CS, 143). Diarroea occurred in 45% vs. 39% of patients, with grade 3 events contributing 6% vs. 3% in the IXA vs. the placebo group. Rash, occurred in 36% vs. 23% of patients in the IXA vs. placebo group, with grade 3 events contributing 5% vs. 2%. Peripheral neuropathy occurred in 27% vs. 22% of the IXA vs. the placebo group, of which 2% vs. 2% were grade 3 adverse events.

The company states that the only ≥5% increase in grade 3 adverse events occurs in Thrombocytopenia. This is where the largest increase of 15% in overall increase of adverse events occurs, which almost doubles the occurrences. Patients in the IXA group also experience 13% more rashes (Table 20). The table below also highlights differences of ≥ 5% in red where one treatment shows an increase of any grade adverse events compared to the other. This also includes grade 1 and 2 adverse events. The company notes that treatment compliance “appeared high and similar between groups” (CS, 146), which suggests, according to the company, that IXA+LEN+DEX “was as simple and convenient for patients” as the LEN+DEX treatment.

Table 20: Common Adverse Events, table adjusted from table 55 CS p.144.

	IXA+LEN+DEX (N=361)			LEN+DEX (N=359)		
	Any-grade	Grade 3	Grade 4	Any-grade	Grade 3	Grade 4
Commona haematologic AEs of any cause, n (%)						
Neutropenia	118 (33)	64 (18)	17 (5)	111 (31)	63 (18)	22 (6)
Thrombocytopenia	**112 (31)**	**43 (12)**	**26 (7)**	**57 (16)**	**19 (5)**	**13 (4)**
Anaemia	103 (29)	34 (9)	0	98 (27)	48 (13)	0
Commona non-haematologic AEs of any cause, n (%)						
Diarrhoea	164 (45)	23 (6)	0	139 (39)	9 (3)	0
Constipation	126 (35)	1 (<1)	0	94 (26)	1 (<1)	0
Nausea	104 (29)	6 (2)	0	79 (22)	0	0
Vomiting	84 (23)	4 (1)	0	42 (12)	2 (<1)	0
Rash SMQ	**131 (36)**	**18 (5)**	**0**	**82 (23)**	**6 (2)**	**0**
Rash HLTc	72 (20)	9 (2)	0	45 (13)	6 (2)	0
Fatigue	106 (29)	13 (4)	0	102 (28)	10 (3)	0
Peripheral oedema	101 (28)	8 (2)	0	73 (20)	4 (1)	0
Peripheral neuropathy	97 (27)	9 (2)	0	78 (22)	6 (2)	0
Back pain	87 (24)	3 (<1)	0	62 (17)	9 (3)	0
Upper respiratory tract infection	83 (23)	2 (<1)	0	70 (19)	3 (<1)	0
Nasopharyngitis	81 (22)	0	0	73 (20)	0	0
Insomnia	73 (20)	7 (2)	0	98 (27)	11 (3)	0
Muscle spasms	66 (18)	0	0	95 (26)	2 (<1)	0

Other adverse events, listed in the CS, do not show significant differences between the treatment groups.

The company states that patients in the subgroup who received 2 or 3 prior therapies did not experience more adverse events than patients in the 1 prior subgroup (CS, 146, table 56). This statement is in line with the data presented in the Table 55 of the CS (not reported in the ERG report).

The company states that the relatively low toxicities is particularly beneficial for RRMM patients (that is, patients who received 2-3 prior therapies) because they are typically older and less fit. The company concludes that the “efficacy”, “convenient oral dosing” and “favourable tolerability profile” contribute to the understanding of ixazomib as a “therapeutic innovation” that offers a “significant benefit for patients with RRMM” (CS, 146f.). The ERG would like to point out that despite the only small increase in toxicity if Ixazomib is added to LEN+DEX, the ERG cannot agree with the company’s conclusion because overall the efficacy data are to date not mature enough to strongly support the effectiveness of IXA even in heavily pretreated patients.

4.10.2 Results from the NMA

The company has undertaken several NMAs for the outcomes of interest and by differentiating by the number of prior lines. While the NICE scope asked to differentiate the 1 prior group and the 2+ prior group, the company included a NMA considering people with at least 1 prior therapy (1+ prior) stating that these networks provide the most robust assessments as they are based on larger number of studies. The company presented results from their basecase network along with various scenario analysis including or excluding studies with specific doses for certain regimen. For simplicity, we will only present the results from their basecase network.

4.10.2.1 1+ prior therapies population

Progression-free survival

The main results of the NMA for PFS are presented in Table 21.

Table 21: PFS NMA – 1+ prior therapies population (HR < 1 favours IXA+LEN+DEX)

PFS NMA – 1+ prior therapies population	Definition	Ixazomib+len+dex vs. len+dex Hazard Ratio (95% CrI)	Ixazomib+len+dex vs. bort+dex Hazard Ratio (95% CrI)
Base case PFS network	RCT and observational studies, combined doses, and primary publications (+ 10% pseudo drop out).*	0.74 (0.59, 0.94)	0.72 (0.41, 1.19)

The company used the Montefusco study[32] to connect the interventions of interest in their network. The Montefusco study does not compare LEN-DEX to BORT-DEX but LEN-DEX-CYCLO to BORT-DEX- CYCLO. As previously indicated in the report, and as stated in our clarification questions, the ERG believes that the use of this study is invalid as no data can validate the absence of effects of cyclophosphamide on the relative effectiveness of these two drugs in this context. In response to that, the company has indicated that there was no a priori reason why LEN-DEX or BORT-DEX would benefit from the addition more than the other, thus they have made the assumption that the addition of cyclophosphamide would increase the efficacy of both regimens by the same

relative amount and therefore leave the relative efficacy unaltered. The ERG does not accept this response as sufficient to judge the use of the study as appropriate.
In addition to the concern that the use of CYCLO affects the relative effectiveness of the drugs in question, the company itself rated the study, which is only available as a conference abstract, to be of poor quality. Lastly, while the company assumed that the Montefusco study design is a RCT, the ERG believes, based on the sole abstract, that this study is not a RCT.
The ERG believes that the company used the Montefusco study because there were not enough published studies available which reported PFS: Recent trials reported both PFS and time to progression (TTP) while less recent trials like APEX[33] and MM-9[40] and 10[39] only report TTP. TTP results only count progression as an event (death are censured), while PFS results count both progressions and deaths as events, whichever occurs first. Based on these definitions, the ERG considered that TTP could be a good proxy for PFS in studies that did not report PFS. The ERG's clinical advisors agreed with the suggestion. This approach was also used in a recently published work conducted by Van Beurden-Tan et al.[55] comparing the different treatment of RRMM, including BORT-DEX, LEN-DEX and IXA-LEN-DEX.

When requested to undertake the NMA for PFS using TTP as a proxy for PFS in the clarification questions, the company responded that they were not able to provide this new analysis given the timeline constraints.

Within the scope of additional searches, the ERG became aware of the CELGENE submission[20] for LEN that reports the results of PFS. The results are presented in Table 22 with the HR for PFS of LEN-DEX compared to DEX. The HRs for PFS can easily be used to calculate the HRs for progression or death.

Table 22: Celgene submission for LEN HR for PFS (HR >1 favours)

	Statistic	Study MM-009		Study MM-010	
		Len/Dex	Dex	Len/Dex	Dex
Overall PFS (wk)	Median [b] [95% CI] [c]	41.1 [29.4, NE]	20.1 [16.7, 24.1]	NE [34.1, NE]	20.1 [19.7, 21.7]
	Mean [d] SD Min, Max	21.2 13.39 0.0, 60.1	15.7 11.17 0.0, 57.0	19.8 10.93 0.0, 44.7	16.4 10.03 0.3, 48.1
Hazard ratio [95% CI] [d]		2.970 [2.089, 4.222]		2.567 [1.834, 3.592]	
Log-rank Test p-value [e]		<0.001		<0.001	

In conclusion, the ERG considers the results of the CS NMA for PFS to be not reliable. The ERG has therefore undertaken additional exploratory analyses to provide a new estimate of the risk of progression or death of IXA-LEN-DEX relative to BORT-DEX.

Overall survival

The results of the company submission NMA for OS are presented in Table 23 for the main comparison of interest.

Table 23: NMA OS for 1+ prior therapies (HR <1 favours IXA+LEN+DEX)

OS NMA – 1+ prior therapies population	Definition	Ixazomib+len+dex vs. len+dex Hazard Ratio (95% CrI)	Ixazomib+len+dex vs. bort + dex Hazard Ratio (95% CrI)
Base case OS network	**RCT and observational studies, specific doses, and primary publications**	**0.90 (0.61, 1.31)**	**0.31 (0.13, 0.65)**

These results indicate that the risk of death is similar between IXA+LEN+DEX and LEN-DEX, which is consistent with the currently available data from the TMM-1 trial.

For the second comparison, the company indicated that patients in the IXA+LEN+DEX group harbour a much lower risk of death compared to those in the BORT+DEX group (HR of death 0.31, 95%CrI 0.13, 0.65). The ERG was surprised by the magnitude of this result suggesting a 69% reduction for the risk of death with IXA+LEN+DEX relative to

BORT+DEX. The magnitude of this benefit is in marked contrast to the CS NMA results for PFS where IXA+LEN+DEX reduces the risk of progression or death by only 28% compared to BORT+DEX (the difference being not statistically significant), as discussed in the previous section.

In the treatment of MM, there is a known good correlation between PFS and OS [56] indicating that a positive benefit in PFS can translate into a positive benefit in OS. However, this previously observed relationship is at odds with the results of the company's NMA, where a moderate (non-significant) reduction of the risk of progression or death (HR 0.72, 95%CrI 0.41 to 1.19) for IXA+LEN+DEX relative to BORT+DEX translates into a very high reduction for the risk of death (HR 0.31, 95%CrI 0.13, 0.65). A similar relationship has previously not been observed.

In clarification the ERG requested the full results of the CS NMA which had not been included in the original submission. The company provided a pairwise hazard ratio comparisons matrix for OS for the 1+ prior therapy population (ITT population) as used in their basecase network (reproduced in Figure 2).

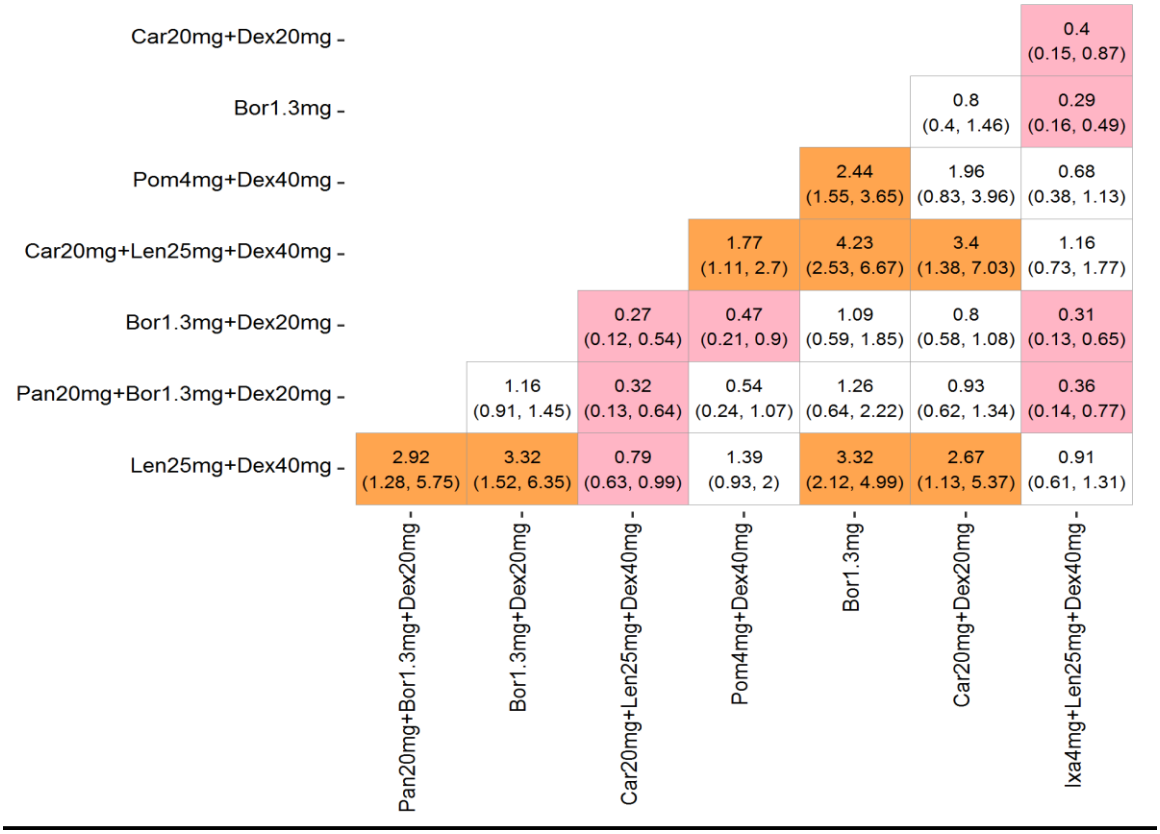


Figure 2: Pairwise hazard ratio comparison matrix for OS within 1+ prior therapies as basecase network

In Figure 2, in line with the fact that, in the TMM-1 trial, IXA+LEN+DEX has similar survival performance as LEN-DEX, the HR for death of BORT-DEX relative to LEN+DEX is 3.32 (95%CrI, 1.52 to 6.35). The ERG is unaware of any trials that compare LEN+DEX to BORT+DEX.

In their CS NMA for OS in the 2+ prior group, the pairwise HR comparisons matrix (received by the ERG in clarification responses) indicates the HR of IXA+LEN+DEX is 0.64 (95% CrI 0.35 , 1.09) relative to LEN-DEX, and 0.61 (95%CrI 0.25, 1.25) relative to BORT+DEX. The implied HR of BORT-DEX relative to LEN-DEX is 0.61/0.64=0.95 suggesting a similar effectiveness between LEN+DEX and BORT+DEX for this population. There is no a priori reason why the two drug regimen would have a similar effectiveness in patients with 2+ prior line but show a large difference in effectiveness for patients with 1+ prior line.

Further surprising results in the hazard ratio comparisons matrix are the following:

- The HR for death of 2.92 (95% CrI 1.28 to 5.75) for PANO-BORT-DEX relative to LEN-DEX indicates a much worse outcome for this triplet combination relative to LEN-DEX.
- The HR for death of 3.4 (95%CrI 1.38 to 7.03) for CARFIL-DEX relative to CARFIL-LEN-DEX suggests that the addition of lenalidomide to CARFIL-DEX greatly reduces the risk of death by 70%.

In the clarification responses, the company provided data for the relative effectiveness of all interventions that were included in the NMA (Table 24).

Table 24: Relative effectiveness of all interventions compared to LEN-DEX as provided by company (clarification response)

	Mean	Median	95CI Lower	95CI Upper
hr(Lenalidomide 25mg Dex 40mg)	1.0000	1.0000	1.0000	1.0000
hr(Panobinostat 20mg Bortezomib 1.3mg Dex 20mg)	2.9183	2.7076	1.2765	5.7548
hr(Bortezomib 1.3mg Dex 20mg)	3.3249	3.1152	1.5193	6.3506
hr(Carfilzomib 20mg Lenalidomide 25mg Dex 40mg)	0.7950	0.7898	0.6289	0.9882
hr(Pomalidomide 4mg Dex 40mg)	1.3895	1.3622	0.9279	2.0006
hr(Ixazomib 4mg Lenalidomide 25mg Dex 40mg)	0.9128	0.8949	0.6111	1.3126
hr(Bortezomib 1.3mg)	3.3213	3.2414	2.1152	4.9906
hr(Carfilzomib 20mg Dex 20mg)	2.6657	2.4647	1.1263	5.3700
hr(Dex 40mg)	1.8662	1.8472	1.4114	2.4226
hr(Lenalidomide 25mg Dex 20mg)	0.6045	0.5798	0.3289	1.0214
hr(Pomalidomide 4mg)	1.4853	1.4412	0.8792	2.3548

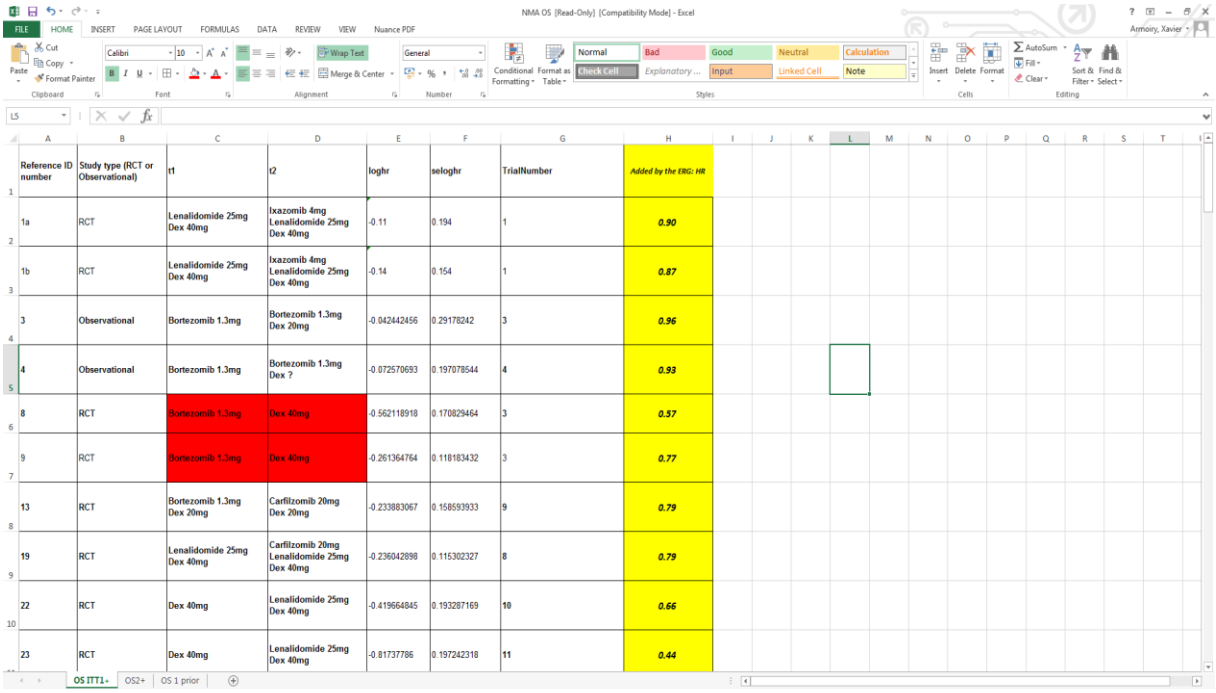
The ERG's understanding is that this table presents the HR for death of all interventions relative to LEN-DEX. This is confirmed by the given HR of IXA-LEN-DEX of 0.89 which is consistent with the results relative to LEN-DEX as it is reported in the TMM-1 trial. Also, the HR of DEX relative to LEN-DEX is 1.8662 (mean), 0.535 for the reciprocal, and 1.8472 (median), 0.54 for the reciprocal, which is consistent with the pooled analysis of the MM9 and 10 trials.

The company reports that the mortality HR of DEX relative to LEN+DEX is lower than the HR of BORT relative to LEN+DEX (3.2414). This implies the surprising result that the HR of DEX relative to BORT is 1.8472/3.2414=0.569 suggesting that DEX reduces the risk of death compared to BORT. This strongly contradicts (i.e. reverses) the results of the APEX trial comparing BORT to DEX, which reported that the HR of BORT relative to DEX was 0.57.[33]

Based on the non-plausibility of these results, the ERG considers that the NMA findings are invalid. Upon receipt in clarification of all inputs and all codes in R used to perform the CS NMAs the ERG attempted to identify a potential source of error in the inputs within the NMA. In response to the clarification questions, the company provided all inputs and all codes in R used to perform the NMAs.

One of the received excel file documents, named "NMA.OS", contained a separate sheet for the 1+ prior group called "OS ITT1+". This sheet contains the trial output values (with study reference row numbering identification) that are the input sources for the R code. These files were created from the data extraction sheet.

On the Excel sheet (see print screen copy Figure 3), the company had listed the treatment arms (labelled t1 and t2) for each included study. After the ERG back-calculated the HRs for death (see column highlighted in yellow), the ERG concluded that the HR that was used to calculate the logHR corresponded to that of the intervention in the t2 column relative to that of the t1 column. In fact, for the trial identified as number 3 (the APEX trial), the HR of 0.57 and 0.77 are reported (in the clarification sheet Figure 3) as the risk of death for DEX relative to BORT while the HR of 0.57 and 0.77, presented in the Richardson 2005[33] and 2007[34] papers, actually correspond to the risk of death for BORT compared to DEX. Consequently, the label of the interventions for this trial have been flipped (cells highlighted in red).



Reference ID number	Study type (RCT or Observational)	t1	t2	loghr	seloghr	TrialNumber	Added by the ERG: HR
1a	RCT	Lenalidomide 25mg Dex 40mg	Ixazomib 4mg Lenalidomide 25mg Dex 40mg	-0.11	0.194	1	0.90
1b	RCT	Lenalidomide 25mg Dex 40mg	Ixazomib 4mg Lenalidomide 25mg Dex 40mg	-0.14	0.154	1	0.87
3	Observational	Bortezomib 1.3mg	Bortezomib 1.3mg Dex 20mg	-0.042442456	0.29178242	3	0.96
4	Observational	Bortezomib 1.3mg	Bortezomib 1.3mg Dex ?	-0.072570693	0.197078544	4	0.93
8	RCT	Bortezomib 1.3mg	Dex 40mg	-0.562118918	0.170829464	3	0.57
9	RCT	Bortezomib 1.3mg	Dex 40mg	-0.261364764	0.118183432	3	0.77
13	RCT	Bortezomib 1.3mg Dex 20mg	Carfilzomib 20mg Dex 20mg	-0.233883067	0.168593933	9	0.79
19	RCT	Lenalidomide 25mg Dex 40mg	Carfilzomib 20mg Lenalidomide 25mg Dex 40mg	-0.236042898	0.115302327	8	0.79
22	RCT	Dex 40mg	Lenalidomide 25mg Dex 40mg	-0.419664845	0.193287169	10	0.66
23	RCT	Dex 40mg	Lenalidomide 25mg Dex 40mg	-0.81737786	0.197242318	11	0.44

Figure 3: Excel sheet of treatment arms (labelled t1 and t2) for each included studies as provided by company

With these inputs, BORT has a worse outcome for OS compared to DEX. Since the OS results are fairly similar for BORT+DEX and BORT, and LEN+DEX is superior to DEX, this explains why BORT+DEX appears in the CS NMA output with a much worse outcome compared to LEN+DEX and consequently to IXA+LEN+DEX.

In conclusion, the results from this NMA on OS in the 1+ prior therapy group are erroneous.

Other outcomes

Overall response rate

The results of the NMA for ORR are presented in Table 25 for the main comparison of interest.

Table 25: NMA results for ORR

ORR NMA – 1+ prior therapies population	Definition	Ixazomib+len+dex vs. len+dex Odds Ratio (95% CrI)	Ixazomib+len+dex vs. bort + dex Odds Ratio (95% CrI)
Base case ORR network	RCT and observational studies, specific doses, and primary publications	1.44 (1.03, 2.03)	0.88 (0.35, 1.85)

These results suggest a better outcome for IXA-LEN-DEX relative to LEN-DEX, which is in line with the TMM-1 results, but a slightly worse outcome for IXA-LEN-DEX compared to BORT-DEX (sucra score of 0.487 versus 0.530 respectively), which is not intuitive.

Looking at the full results from the NMA provided by the company following the clarifications questions, the ERG has also noticed other unexpected results such as:

- The OR for ORR of 0.44 (95%CrI 0.16 to 0.96) for IXA-LEN-DEX relative to CARFIL-DEX
- The OR for ORR of 1.94 (95%CrI 0.84 to 3.84) for BORT-DEX relative to LEN-DEX

However, the ERG was able to verify that the NMA inputs were correct.

Best overall response (BoR)

The results of the NMA for BoR are presented in Table 26 for the main comparison of interest.

Table 26: NMA results for 1+ prior therapy for BoR

BoR NMA – 1+ prior therapies population	Definition	Ixazomib+len+dex vs. len+dex Odds Ratio (95% CrI)	Ixazomib+len+dex vs. bort + dex Odds Ratio (95% CrI)
Base case BoR network	RCTs, combined doses, and primary publications	1.47 (1.08, 1.95)	3.82 (1.32, 8.93)

The ERG is unable to provide comments on the validity of these estimates as the company again used the Montefusco study to connect BORT-DEX to LEN-DEX. The ERG's arguments outlined above regarding the inclusion of the study for the NMA on

PFS also apply here. The company does not provide any justification for the use of the Montefusco study in the NMA for BoR. The ERG assumes that the reason is the absence of reporting of BoR in other trials that could have connected BORT-DEX to LEN-DEX. While BoR results are reported in the MM9 and 10 trials [20], the ERG has verified that neither the APEX trial nor the Dimopoulos study presented results on VGPR or better.

Although BoR and ORR have different definitions, one can expect that a drug that has a better ORR result would also have a better BoR outcome. This was observed in the direct comparison of IXA-LEN-DEX to LEN-DEX. The OR for ORR of IXA-LEN-DEX relative to LEN-DEX is 1.44 (95%CrI 1.03, 2.03) and the OR for BoR of IXA-LEN-DEX relative to LEN-DEX is 1.47 (95%CrI 1.08, 1.95). The ERG has observed discrepancies in the indirect comparison of IXA-LEN-DEX to BORT-DEX between the OR for ORR and BoR (0.88 (95%CrI 0.35, 1.85) versus 3.82 (95%CrI 1.32, 8.93)).

In conclusion, the ERG considers that the results of the NMA for BoR including the Montefusco study in the network are not reliable.

Discontinuation due to AEs

The most interesting results of the NMA for discontinuation due to AEs are presented in Table 27.

Table 27: NMA results for discontinuation due to adverse events

Discontinuation due to AE's NMA – 1+ prior therapies population	Definition	Ixazomib+len+dex vs. len+dex Odds Ratio (95% CrI)	Ixazomib+len+dex vs. bort + dex Odds Ratio (95% CrI)
Base case AE discontinuation network	RCT and observational studies, specific doses, and primary publications	1.25 (0.77, 1.92)	2.58 (0.81, 6.32)

Although the difference between the interventions is not statistically significant, the results suggest that the risk of discontinuation due to AEs is higher with IXA-LEN-DEX compared to LEN-DEX and BORT-DEX. The company also reports that the SUCRA score was 0.271 for IXA-LEN-DEX, 0.140 for LEN-DEX and 0.689 for BORT-DEX. The company concludes that IXA-LEN-DEX results in a better outcome compared to BORT-DEX. However, the ERG must stress that this conclusion is incorrect. Instead, the

SUCRA scores conversely indicate a worse outcome for IXA-LEN-DEX relative to BORT-DEX. Moreover, the ERG has noted a discrepancy between the SUCRA scores provided in the main text of the company submission and the SUCRA scores provided in the clarifications (Table 14 page 46). The clarification response reports a SUCRA score of 0.271 for LEN-DEX and 0.140 for IXA-LEN-DEX.

The ERG has checked the company's data extraction for discontinuation due to AEs using the excel file provided by the company that was used in their NMA. We noted a discrepancy between this excel file and the company submission with regards to the number of events in the TMM-1 trial:In the excel file, 46 events / 360 patients were counted for the IXA-LEN-DEX and 39 events /362 patients were counted for the LEN-DEX, while in the CS, the number of reported events are 60 and 50 respectively. The number of events reported in the CS are the same as those presented in the main paper by Moreau et al. [26] The ERG has investigated the reason for this discrepancy and was eventually able to confirm that the Ixazomib clinical study report C16010, reports 46 for IXA+LEN+DEX vs. 39 for LEN+DEX adverse event which were a primary reason for study treatment discontinuation (Table 10 b, page 99). As previously stated, the latter were used in the company's NMA for discontinuation due to AEs. The ERG would welcome a clarification from the company on this point. However, a change in the number of events accounted in the NMA would only have a minor impact. Using the values of 39 and 46 discontinuations due to AEs leads to an OR for IXA-LEN-DEX of 1.213. Applying the values of 50 and 60 discontinuations due AEs for LEN-DEX and IXA-LEN-DEX respectively, the OR would be 1.248.

4.10.2.2 1 prior therapy population

In their submission, the company indicated that there was an insufficient number of studies with the relevant data available to construct networks to compare IXA-LEN-DEX to BORT-DEX. The ERG could not confirm this and requested clarification from the company. The company provided a table with relevant studies that reported PFS and ORR data (clarification response, p.53-56). The company indicated that there were no results in the 1 prior group for a BORT-DEX arm in any study for OS and BoR.

Following additional searches, the ERG disagrees with the company's statement on OS and suggests that the table the company provided (table 21, clarification document) is not comprehensive.

For both outcomes (PFS and OS), the company could have included the results from:

- the Dimopoulos 2015[45] study comparing BORT-DEX to BORT. This study only selected RRMM patients at second line, which corresponds by definition to people with only one prior therapy.
- the APEX trial [33] comparing BORT to DEX. This study presented a subgroup analysis for OS and TTP, which can be used as a proxy for PFS, in the 1 prior group only.
- the MM9 et MM10 (Celgene submission[20]) comparing LEN-DEX to DEX. In this submission, the results of OS and PFS are reported for the 1 prior group only.

The ERG has not searched for relevant data for other outcomes (ORR, BoR, discontinuation due to AEs), but the tables presented above suggests that an NMA could have been conducted within the 1 prior therapy group for the two main outcomes of interest. that is PFS and OS.

The lack of these estimates for the 1-prior population is a serious limitation of the CS as it jeopardizes the subsequent cost-effectiveness analyses for this subgroup of patients although it corresponds to the NICE scope.

4.10.2.3 2+ prior therapies population

The company indicated that the only available comparison for IXA-LEN-DEX to the main comparator of interest, LEN-DEX, comes from the direct comparison of these two regimens (TMM-1 trial). The results of these analyses have been presented for completeness. As these results corresponds to those from TMM-1 trial, the ERG has not reported further on the corresponding tables in the section. For completeness, the ERG has examined if the error in the excel file that was identified for the NMA on OS in the 1+ prior therapy group (flipped interventions for BORT and DEX) was also present in the excel file that the Company used in the NMA on OS for the 2+ prior therapy group. The

ERG has been able to identify that the same error was reproduced in the excel document. Indeed, the Company reported that the LogHR of DEX relative to BORT was -0.46, which corresponds to an HR 0.63. Again, this is erroneous since 0.63 corresponds to the HR of BORT relative to DEX. Luckily, the error had no consequence since BORT-DEX and LEN-DEX (and therefore IXA+LEN+DEX) were indirectly compared using the PANO-BORT-DEX intervention. In other words, the NMA ignored the BORT versus DEX comparison. Consequently, the results of this NMA for OS in the 2+ prior population, indicating that the HR for OS of IXA+LEN+DEX is 0.64 (95% CrI 0.35 , 1.09) relative to LEN-DEX, and 0.61 (95%CrI 0.25, 1.25) relative to BORT+DEX, which suggests a similar effectiveness between LEN+DEX and BORT+DEX in this population, seem to be credible.

4.11 Additional work on clinical effectiveness undertaken by the ERG

4.11.1 Exploratory NMA

4.11.1.1 General statements and methods

In previous sections, the ERG has emphasized that the NMAs provided in the CS had some serious flaws. Moreover, several outputs from these NMAs were included in the cost-effectiveness analysis. Therefore, the ERG undertook a series of additional exploratory NMAs to provide more robust estimates for the key clinical effectiveness outcome measures. Given the timeline constraints, the ERG has limited the analyses to the outcomes used in the cost-effectiveness analyses (i.e., PFS, OS, and ORR).

For the 1 prior therapy group, the ERG has conducted analyses for PFS, OS, and ORR as the company did not provide an NMA.

For the 1+ prior therapy group, the ERG conducted an NMA for PFS (the company's NMA was invalid because they included Montefusco study[32] into the network) and for OS (the company made an error on the inputs for the APEX study[33]). Since we have already validated the results of the company's NMA for ORR, no additional analyses for

this outcome will be presented. The ERG has not undertaken an NMA for the 2+ prior therapies group because the evidence for the comparison of interest (IXA-LEN-DEX versus LEN-DEX) comes directly from the TMM-1 trial.

As the Zagouri study[46] was not contributing to the treatment effect estimate of interest and it was of very poor methodological quality, we excluded it from the analyses. We also excluded the data provided by the Richardson 2014 study[57] that compared pomalidomide-dexamethasone to pomalidomide. Likewise, this study had no contribution to the treatment effect estimate for the comparison between IXA-LEN-DEX and BORT-DEX. Besides, we judged pomalidomide alone to be an irrelevant intervention, as this drug is licensed only in combination with dexamethasone.

We compared hazard ratio (95% CI) estimates for PFS, ORR, and OS across studies.

If P values were reported instead of 95% CIs, we determined a Z value corresponding to P value (assuming the normal distribution) and calculated the SElog(HR) as log(HR)/Z. Then the 95% CIs around log(HR) were derived as log(HR) ± (1.96 * SElog(HR)). We derived HR and 95% CIs by exponentiation of log(HR) and log of upper and lower limits of the 95% CI, respectively.

We used the package -network- in Stata [58] to conduct network meta-analyses. Because -network- operates in a frequentist paradigm, there was no need to perform sensitivity analysis on prior distributions. Where possible, we based our meta-analyses on using random-effects model; however, when the networks were too sparse (i.e., only few studies available for each contrast between two treatments), we used a fixed-effect model. We used a common heterogeneity model, where the between-studies variance is assumed equal across comparisons. Since there was no mixed (direct + indirect) comparisons between interventions, there was no need to check networks for inconsistency.

By simplification, we only presented the results for the interventions contributing to the treatment effect estimate for the comparison between IXA-LEN-DEX and BORT-DEX, that is LEN-DEX, DEX, and BORT. We did not present any rankograms or SUCRA scores for these interventions.

4.11.1.2 Progression-free- survival

1+ prior group

The data we used for the NMA for PFS in the 1+ prior group are presented in Table 28.

For the results from the APEX study, we used the HR for TTP as a proxy for the HR for PFS as this study did not report results on PFS. While the MM-009[40] and MM-010 [39] studies, comparing LEN-DEX to DEX, reported results on TTP in the main papers, we have been able to ascertain the results for PFS from the Celgene submission that was presented to NICE in 2013.[20] In this submission, PFS was evaluated as part of the supportive analysis for the primary outcome, TTP. On pages 70-71 (Table 17) of this document, we used time-to- progression-free survival to calculate the HR for progression or death. Again, these results show a great similarity between the HR for TTP and PFS (MM-009: 0.35 vs 0.34 respectively; MM-010: 0.35 vs 0.39 respectively), which supports the use of TTP as an acceptable proxy for PFS in the APEX study.

Table 28: Data used in the NMA for PFS in the 1+-prior therapy group

Study	trt1	trt2	$HR_{1 vs 2}$	95%CI for the HR
eVOBS 2010[44]	bortdex	Bort	0.73	0.306-1.060*
Matched pairs from RCTs (Dimopoulos 2015)[45]	bortdex	bort	0.595	0.351-1.008
Apex 2005[33]	bort	dex	0.55**	0.410-0.740
MM-009 2007[40]	lendex	dex	0.34	0.24-0.48
MM-010 2007[39]	lendex	dex	0.39	0.28-0.55
Tourmaline 2016[26]	Ixalendex	lendex	0.74	0.59-0.94
PANORAMA[51]	panbortdex	bortdex	0.63	0.52-0.76
ASPIRE 2015[37]	carlendex	lendex	0.69	0.57-0.83
ENDEAVOR 2016[35]	carfildex	bortdex	0.53	0.44-0.65
MM-003 2013[42]	pomdex	dex	0.48	0.39-0.60

**back-calcultated from the p-value* ***uses TTP as a proxy for PFS*

Using these data, a summary of the direct pairwise comparisons from studies is presented in Figure 4. The treatment effect is measured as HR for progression or death. An HR <1 denotes a better outcome while an HR >1 denotes a worse outcome.

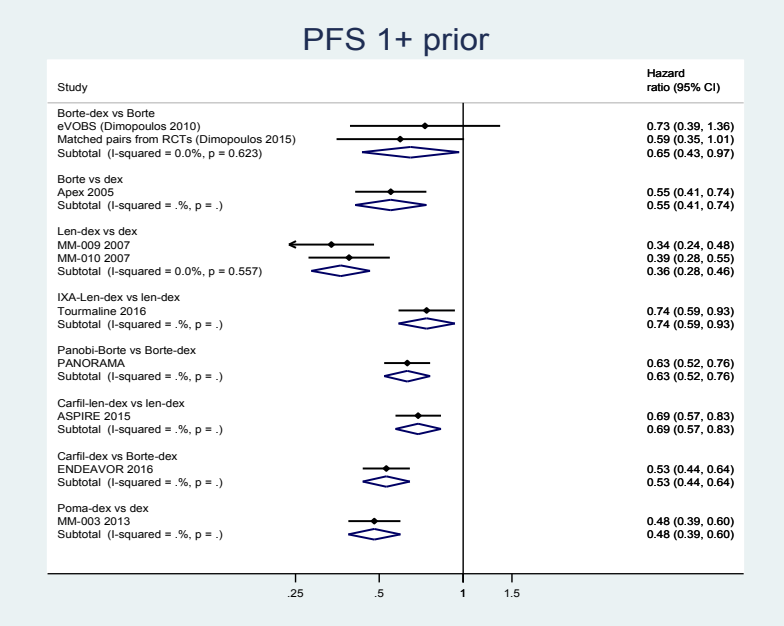


Figure 4: Pairwise meta-analyses: PFS in the 1+ prior group

The network of interventions is presented in Figure 5. The structure of the network differs considerably from that of the Company since we have omitted the Montefusco study (as described previously).

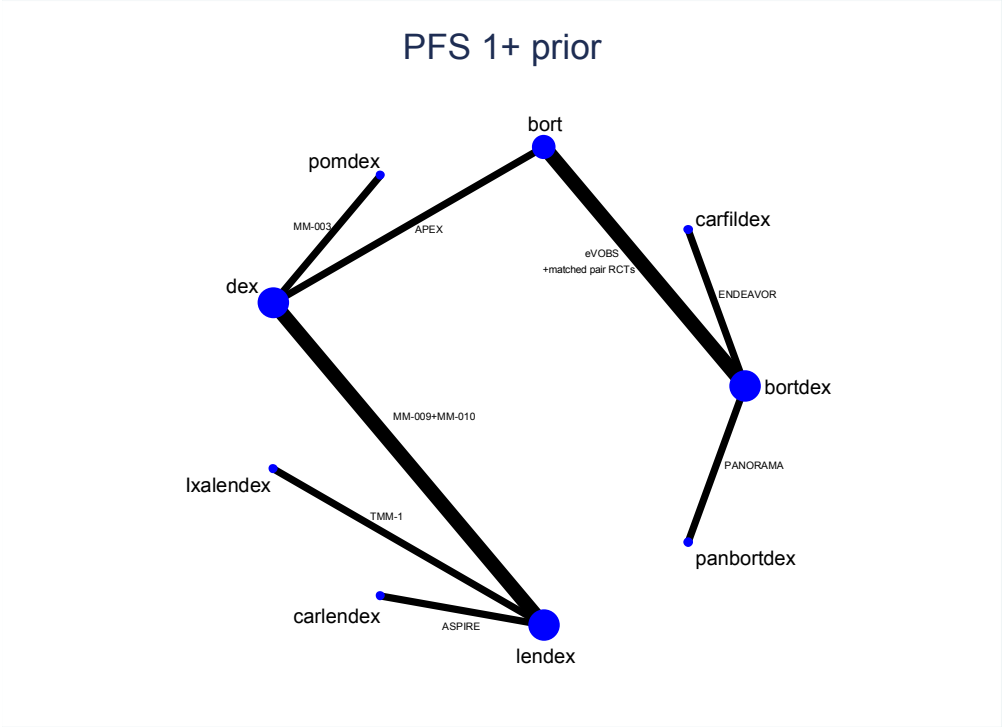


Figure 5: network of interventions: PFS in the 1+prior group

The results of pairwise comparisons from the NMA using either BORT-DEX or LEN-DEX as reference treatment are presented in Table 29. For the main comparison of interest, the HR for progression or death of IXA-LEN-DEX relative to BORT-DEX is 0.75 (95%CI 0.41, 1.38). This result is similar compared to that in the CS (0.72 (95%CrI 0.41-1.19)) but we consider is more robust since the ERG used a more appropriate network.

Table 29: Network meta-analysis: PFS in the 1+ prior therapy group

Risk for progression or death	HR	95%CI
Relative to BORT-DEX		
DEX	2.8	1.70-4.62
BORT	1.54	1.03-2.31
LEN-DEX	1.02	0.58-1.77
IXA-LEN-DEX	0.75	0.41-1.38
Relative to LEN-DEX		
DEX	2.75	2.16-3.51
BORT	1.51	1.03-2.22

BORT-DEX	0.98	0.56-1.71
IXA-LEN-DEX	0.74	0.59-0.93

1 prior group

The data we used for the NMA for PFS in the 1 prior group are presented in Table 30.

For the results from the APEX study, we used the HR for TTP as a proxy for the HR for PFS as this study did not report results for PFS. As in the analysis for the 1+ prior therapy group, we have been able to identify results for the MM-009 and MM-010 studies on PFS from the Celgene submission that was presented to NICE in 2013[20] on page 82 (table 22).

For the comparison of BORT-DEX to BORT, we used the results from the Dimopoulos 2015 paper[45] that evaluated these two interventions in the specific group of people treated as second line. The eVOBS study[44] was not used here because the number of prior lines was not reported.

Table 30: Data used in the NMA for PFS in the 1 prior therapy group

Study	trt1	trt2	$HR_{1 \text{ vs } 2}$	95%CI for the HR	LogHR	SE_{logHR}
Matched pairs from RCTs (Dimopoulos 2015)[45]	bortdex	bort	0.595	0.351-1.008	-0.519	0.269
Apex 2005[33]	bort	dex	0.56*	0.387-0.808**	-0.580	0.188
MM-009 2007[40]	lendex	dex	0.30	0.19-0.47	-1.204	0.231
MM-010 2007[39]	lendex	dex	0.39	0.24-0.62	-0.942	0.242
Tourmaline 2016[26]	Ixalendex	lendex	0.88	0.65-1.2	-0.128	0.156
PANORAMA[51]	panbortdex	bortdex	0.66	0.50-0.86	-0.420[#]	0.140[#]
ASPIRE 2015[37]	carlendex	lendex	0.69	0.52-0.91	-0.370[#]	0.140[#]
ENDEAVOR 2016[35]	carfildex	bortdex	0.45	0.33-0.61	-0.800[#]	0.160[#]

**uses TTP as a proxy for PFS **back-calculated from the p-value [#]values directly taken from the CS clarification response (page 53, table 21)*

Using these data, a summary of the direct pairwise comparisons from studies is presented in Figure 6. Again, the treatment effect is measured as HR for progression or death.

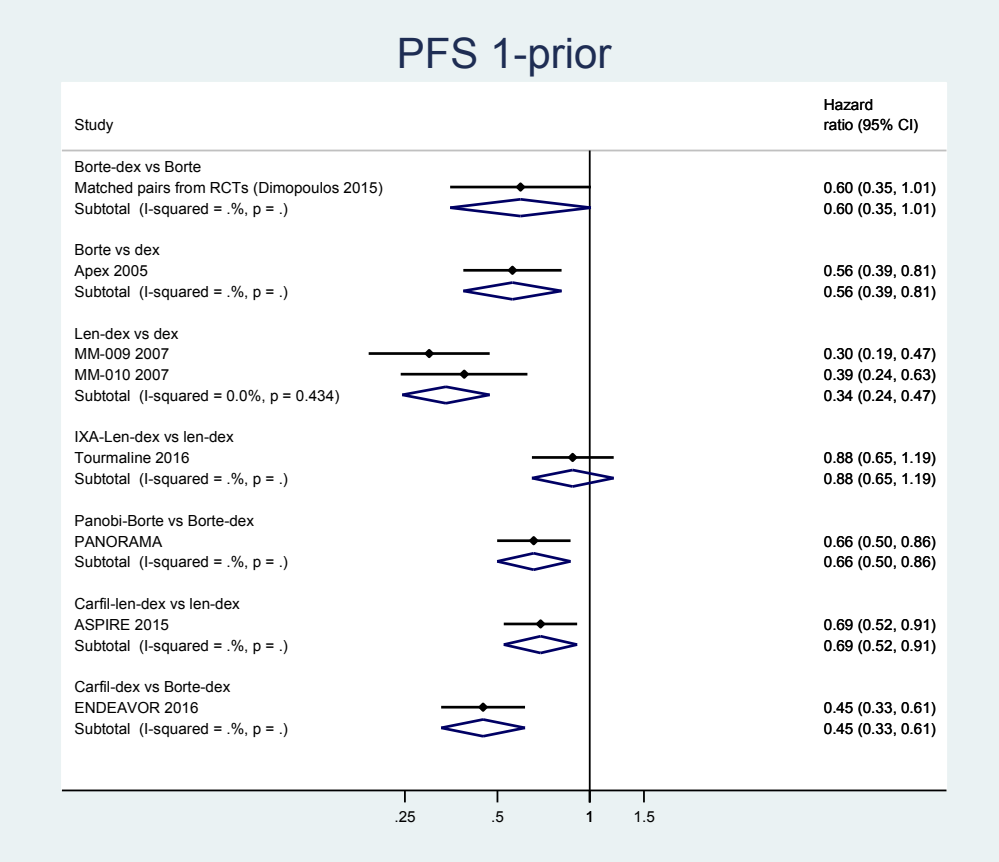


Figure 6: Pairwise meta-analyses: PFS in the 1prior group

The network of interventions is presented in Figure 7. The structure of the network is very similar to that of the analysis in the 1+ prior therapy group.

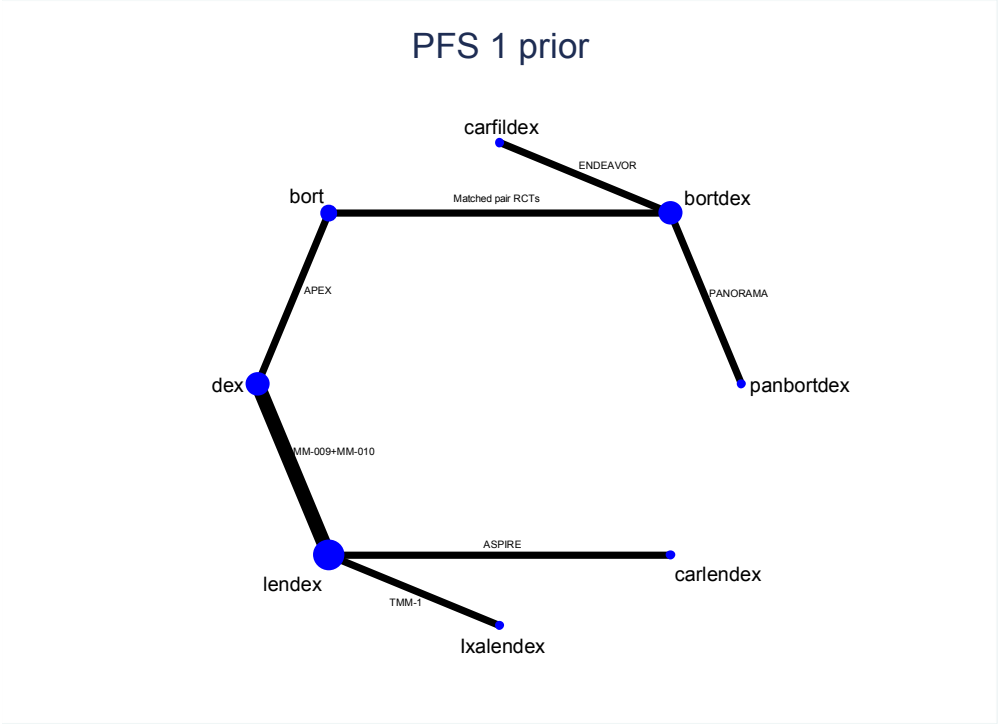


Figure 7: network of interventions: PFS in the 1prior group

The results of pairwise comparisons from the NMA using either BORT-DEX or LEN-DEX as reference treatment are presented in Table 31. The HR for progression or death of IXA-LEN-DEX relative to BORT-DEX is 0.90 (95%CI 0.41-1.96) in the 1 prior therapy group. These results, despite being obtained through an indirect comparison, are consistent with those from the TMM-1 trial which showed a reduced effectiveness of IXA-LEN-DEX in the subgroup of patients treated at second line as compared to that in 1 + prior subgroup.

Table 31: Network meta-analysis: PFS in the 1 prior therapy group

Risk for progression or death	HR	95%CI of the HR
Relative to BORT-DEX		
DEX	3.00	1.57-5.71
BORT	1.68	0.99-2.84
LEN-DEX	1.02	0.49-2.10
IXA-LEN-DEX	0.90	0.41-1.96
Relative to LEN-DEX		
DEX	2.94	2.12-4.08
BORT	1.64	1.006-2.696

BORT-DEX	0.98	0.476-2.017
IXA-LEN-DEX	0.879	0.648-1.194

4.11.1.3 Overall survival

1+ prior group

The data we used for the NMA for OS in the 1+ prior group are presented in Table 32. The data were provided by the company, except that we present the correct HR of 0.57 for death for BORT vs DEX. The other difference with the inputs from the CS is that we used the results from the eVOBS study (Dimopoulos 2010) which was excluded in the base case OS NMA in the CS. The ERG found no a-priori reason not to use this study in this NMA, although we acknowledge the eVOBS study was a non-RCT reported as a conference abstract. The ERG considered this study to be worth inclusion in the NMA by pooling it together with Dimopolous 2015 study. The eVOBS study contributed to the main comparison of interest (BORT-DEX vs BORT) and stabilised the network by providing narrower 95% CIs. We also presented an alternative analysis excluding the eVOBS study.

Table 32: Data used in the NMA for OS in the 1+ prior therapy group (including the eVOBs)

Study	trt1	trt2	$HR_{1 \text{ vs } 2}$	95%CI for the HR
eVOBS[44]	bortdex	bort	0.93	0.632-1.368*
Matched pairs from RCTs (Dimopoulos 2015) [45]	bortdex	bort	0.958	0.541-1.698
Apex 2005[33]	bort	Dex	0.57	0.408-0.797
MM-009 2007[40]	lendex	Dex	0.44	0.3-0.65
MM-010 2007[39]	lendex	Dex	0.66	0.45-0.96
Tourmaline 2016[26]	Ixalendex	lendex	0.90	0.62-1.32
PANORAMA[51]	panbortdex	bortdex	0.87	0.69-1.1

ASPIRE 2015[37]	carlendex	lendex	0.79	0.63-0.99
ENDEAVOR 2016[35]	carfildex	bortdex	0.79	0.58-1.08
MM-003 2013[42]	pomdex	Dex	0.74	0.56-0.97

* CI back-calculated from the HR and the p-value.

Using these data, a summary of the direct pairwise comparisons for each study is presented in Figure 8. The treatment effect is measured as HR for death which means that an HR <1 denotes a reduced probability of death, while an HR>1 denotes a greater probability of death.

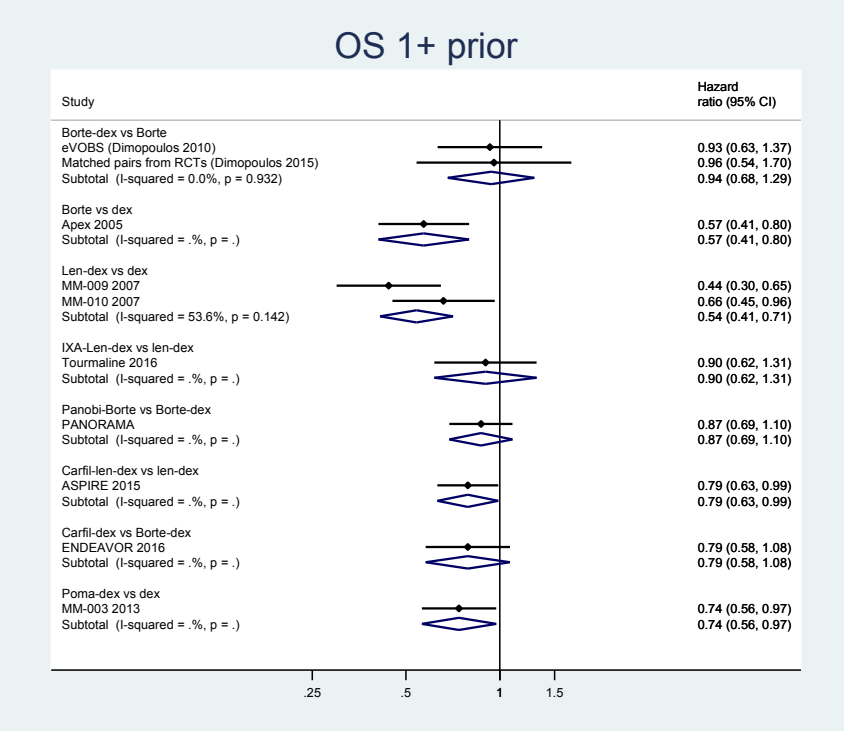


Figure 8: Pairwise meta-analyses: OS in the 1+ prior group (including the eVOBs study)

The network of interventions is presented in figure 9. The structure of the network is very similar compared to that of the PFS analysis in the 1+ prior therapy group.

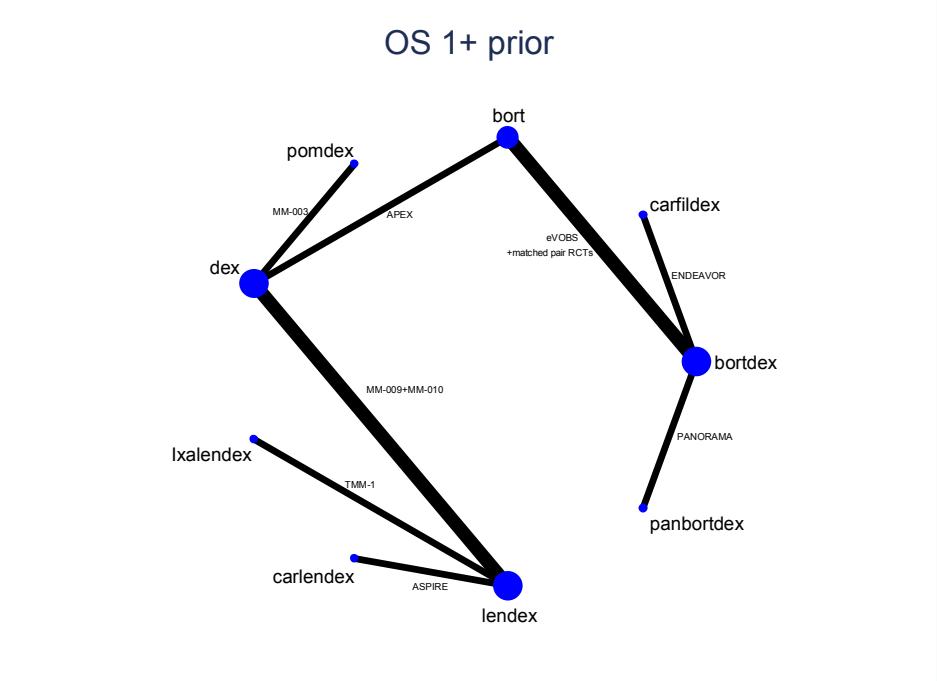


Figure 9: network of interventions: OS in the 1+prior group (including the eVOBs study)

The results of pairwise comparisons from the NMA using either BORT-DEX or LEN-DEX as the reference treatment are presented in Table 33. The HR for death for IXA-LEN-DEX vs BORT-DEX is 0.91 (95%CI 0.43-1.92). The implied HR for death of BORT relative to DEX is 1.06/1.86 =0.569 which is the same as the HR reported in the APEX trial.[33]

Table 33: Network meta-analysis: OS in the 1+ prior therapy group (including the eVOBs study)

Risk of death	HR	95%CI of the HR
Relative to BORT-DEX		
DEX	1.86	1.1-3.17
BORT	1.06	0.75-1.52
LEN-DEX	1.01	0.55-1.86
IXA-LEN-DEX	0.91	0.43-1.92
Relative to LEN-DEX		
DEX	1.85	1.36-2.51
BORT	1.05	0.64-1.74
BORT-DEX	0.99	0.54-1.83
IXA-LEN-DEX	0.90	0.6-1.4

As indicated in previous section, the ERG has also presented results excluding the eVOBs study (Table 34). With this scenario, the HR for death of IXA-LEN-DEX relative

to BORT-DEX is 0.89 (95%CI 0.29-2.72). Although the HR is rather similar compared to the previous analysis (0.91 vs 0.89 respectively), the CI is much wider with this alternative analysis.

Table 34: Network meta-analysis: OS in the 1+ prior therapy group (excluding the eVOBs study)

Risk of death	HR	95%CI of the HR
Relative to BORT-DEX		
DEX	1.83	0.76-4.42
BORT	1.04	0.57-2.11
LEN-DEX	0.99	0.37-2.6
IXA-LEN-DEX	0.89	0.29-2.72
RELATIVE TO LEN-DEX		
DEX	1.85	1.24-2.75
BORT	1.05	0.54-2.05
BORT-DEX	1.01	0.38-2.66
IXA-LEN-DEX	0.90	0.51-1.57

1 prior group

The data we used for the NMA for OS in the 1-prior group are presented in Table 35.

As for the analyses on PFS, we extracted the data related to MM-009 and MM-010 studies from the Celgene submission that was presented to NICE in 2013[20] in Table 23 (page 84). Those from the ASPIRE[37]and ENDEAVOR[35] studies were extracted from the committee papers of the Carfilzomib STA (ID934).[21]

Table 35: Data used in the NMA for OS in the 1 prior therapy group

Study	trt1	trt2	HR 1 vs 2	95%CI for the HR
Matched pairs from RCTs (Dimopoulos 2015) [45]	bortdex	bort	0.958	0.54-1.70
Apex 2005[33]	bort	dex	0.42	0.22-0.82*
MM-009 2007[40]	lendex	dex	0.7	0.44-1.1
MM-010 2007[39]	lendex	dex	0.71	0.41-1.23

Tourmaline 2016[26]	Ixalendex	lendex	1.24	0.74-2.1
ASPIRE 2015[37]	carlendex	lendex	0.68	0.43-1.07
ENDEAVOR 2016[35]	carfildex	bortdex	0.56	0.3-1.02

* CI back-calculated from the HR and the p-value

Using these data, a summary of the direct pairwise comparisons from studies is presented in Figure 10. The treatment effect is measured as HR for death.

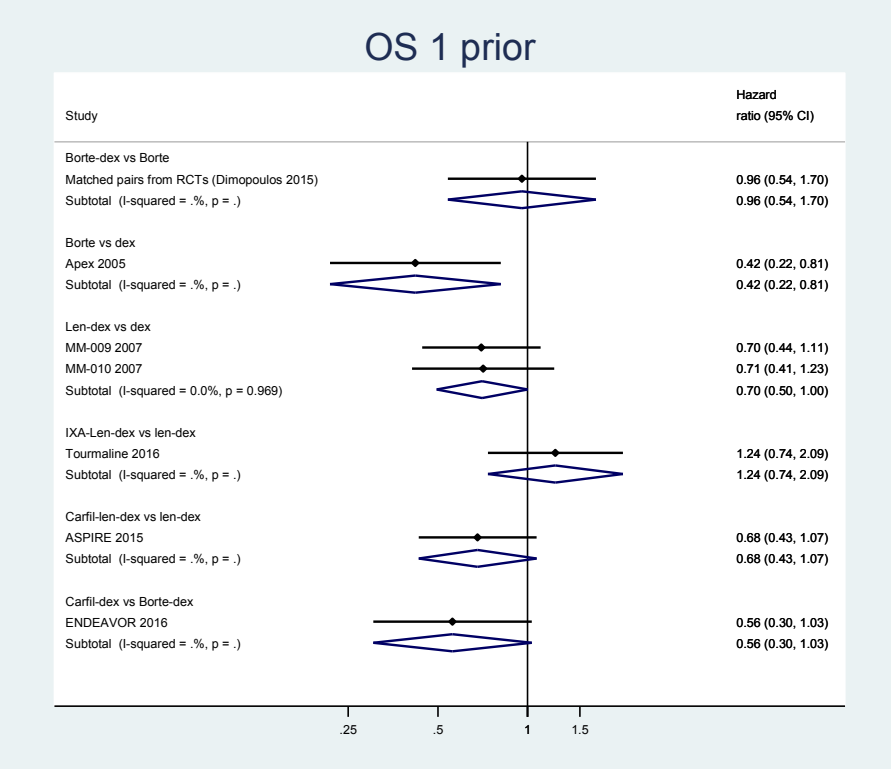


Figure 10: Pairwise meta-analyses: OS in the 1 prior group.

The network of interventions is presented in Figure 11.

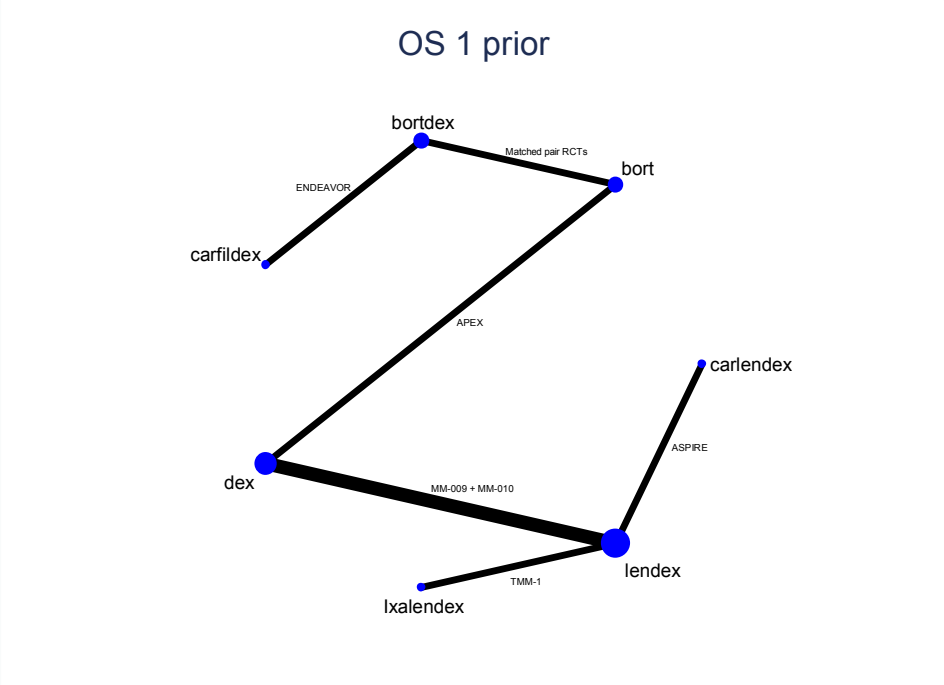


Figure 11: network of interventions: OS in the 1prior group

The results of pairwise comparisons from the NMA using either BORT-DEX or LEN-DEX as reference treatment are presented in Table 36. The HR for death of IXA-LEN-DEX relative to BORT-DEX is 2.16 (95%CI 0.74, 6.36). The limited number of small studies providing estimates with wide CIs within each study led to very wide CIs for the interventions that have been indirectly compared. Also, the ERG considers the results from this exploratory NMA to be questionable. For instance, the results of the HR of CARFIL-DEX relative to BORT-DEX (not shown in the table) is 0.56 (95%CI 0.3, 1.03) consistently with the results from ENDEAVOR while the HR of CARFIL-LEN-DEX relative to BORT-DEX (not shown in the table) is 1.19 (95%CI 0.42, 3.39). This implies the HR of CARFIL-DEX relative to CARFIL-LEN-DEX is 0.48 which makes very little sense.

Table 36: Network meta-analysis: OS in the 1+ prior therapy group

Risk for death	HR	95%CI
Relative to BORT-DEX		
DEX	2.48	1.03-5.95
BORT	1.04	0.59-1.85
LEN-DEX	1.74	0.68-4.48
IXA-LEN-DEX	2.16	0.74-6.36
RELATIVE TO LEN-DEX		
DEX	1.42	0.99-2.02
BORT	0.596	0.28-1.26
BORT-DEX	0.57	0.22-1.46
IXA-LEN-DEX	1.24	0.74-2.09

4.11.1.4 Overall-response rate

As previously stated, the ERG has undertaken a last exploratory NMA for ORR only for the one-prior therapy group. The data used were those reported by the company in their clarification response in table 22 (page 54-55). The ERG also incorporated the results for the comparison of BORT-DEX to BORT, which enables connection to the network, obtained from the Dimopoulos 2015 paper evaluating these two interventions in the specific group of people treated as second line.

Table 37: Data used in the NMA for ORR in the 1 prior therapy group

Study	trt2	trt1	OR $_{1 \text{ vs } 2}$	95%CI of the OR	LnOR	SelnOR
Tourmaline 2016[26]	Len-dex	Ixa-Len-Dex	1.13	0.7-1.77	0.12	0.23
Apex 2005[33]	Bort	Dex	0.44	0.26-0.74	-0.83	0.27
ENDEAVOR 2016[35]	Len-dex	Carfil-Len-dex	2.86	1.65-4.95	1.05	0.28
ASPIRE 2015[33]	Bort-dex	Carfil-dex	2.39	1.55-3.67	0.87	0.22

MM-009 2007[40]	Dex	Len-dex	4.57	2.09-10.01	1.52	0.40
MM-010 2007[39]	Dex	Len-dex	6.36	2.96-13.66	1.85	0.39
Matched pairs from RCTs (Dimopoulos 2015)[45]	Bort	Bort-dex	3.46	1.92-6.22	1.24	0.30

Using these data, a summary of the direct pairwise comparisons from studies is presented in Figure 12. The treatment effect is measured as Odds ratio (OR) for ORR. An OR<1 denotes a worse outcome while an OR>1 denotes a better outcome.

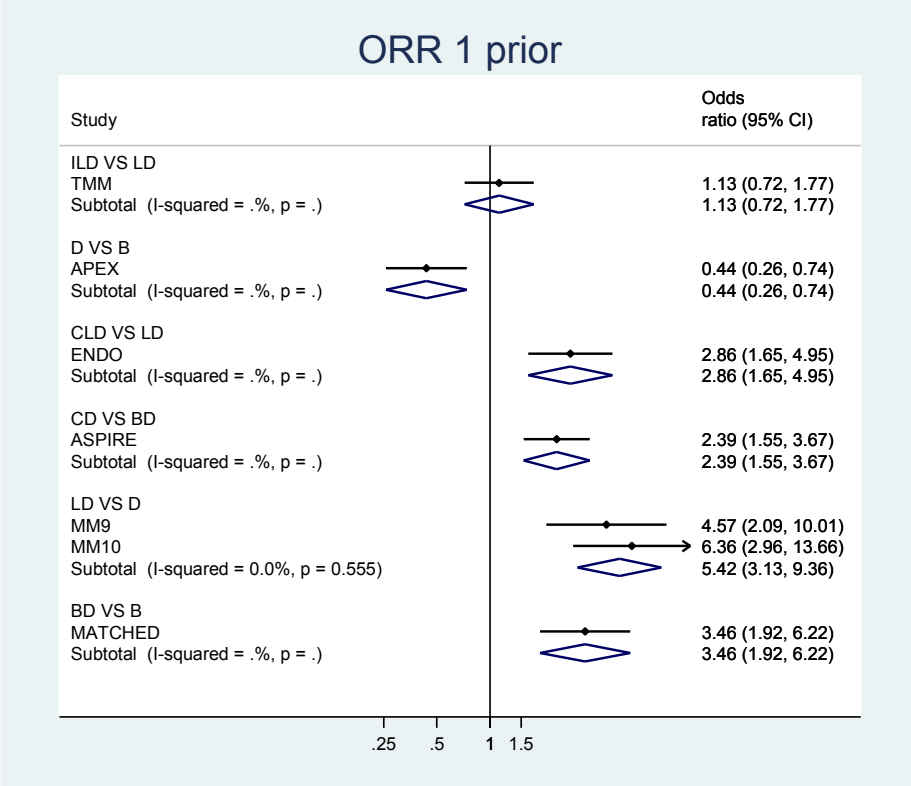


Figure 12: Pairwise meta-analyses: ORR in the 1prior therapy group

The network of interventions is presented in Figure 13.

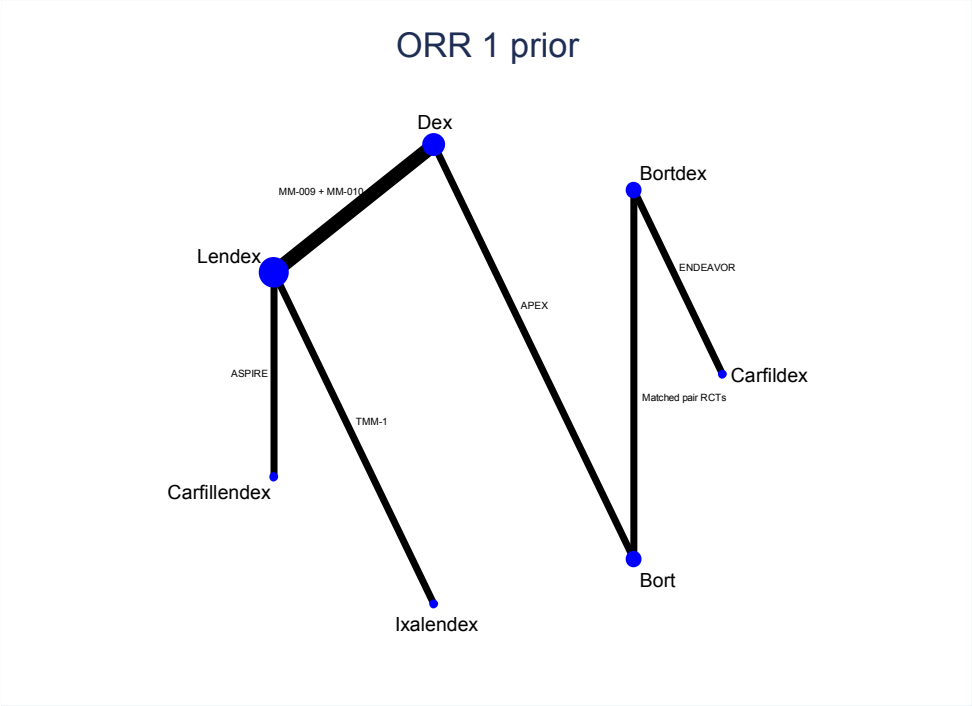


Figure 13: network of interventions: ORR in the 1prior group

The results of pairwise comparisons from the NMA using either BORT-DEX or LEN-DEX as reference treatment are presented in Table 38. The OR for ORR of IXA-LEN-DEX relative to BORT-DEX is 0.77 (95%CI 0.27-2.23) in the 1 prior therapy group.

Table 38: Network meta-analysis: ORR in the 1 prior therapy group

Overall response rate	OR	95%CI
RELATIVE TO BORT-DEX		
BORT	0.29	0.16-0.52
DEX	0.13	0.06-0.28
LEN-DEX	0.68	0.26-1.79
IXA-LEN-DEX	0.77	0.27-2.23
RELATIVE TO LEN-DEX		
DEX	0.18	0.11-0.32
BORT	0.42	0.20-0.9
BORT-DEX	1.47	0.56-3.83
IXA-LEN-DEX	1.13	0.72-1.77

4.11.1.5 Summary of the ERG exploratory network meta-analyses

The ERG has undertaken several network-meta-analyses to provide new estimates of the relative clinical effectiveness of IXA-LEN-DEX compared to BORT-DEX focusing on PFS (1+ and 1 prior therapy group), OS (1+ and 1 prior therapy group) and ORR (1 prior therapy group). We acknowledge the exploratory nature of these analyses since we did not conduct a full systematic review to search for potential sources of additional of information. Secondly, the same methodological critiques as those emphasized in the report of the CS NMA apply here. For example, in the 1+ prior therapy group, the included studies have considerable heterogeneity as illustrated by the baseline characteristics of patients. This is of particular importance regarding the number of prior lines of treatment, which is known to be an effect modifier. However, using relevant studies from additional literature searches, the ERG believes that these exploratory analyses of PFS are more robust compared to those in the company.

The ERG's NMA on OS in the 1+ prior therapy group gives a considerably different estimate for the HR of IXA-LEN-DEX relative to BORT-DEX. While the company estimated the HR at 0.31 (95%CrI 0.13, 0.65), the ERG has estimated the HR at 0.91 (95% CI 0.43-1.92). In a previous section, the ERG described the error leading to this dioscrepancy.

In the next section of the report, we describe a further exploratory analysis corroborating the findings from the ERG's NMA. Overall, the results from the ERG's NMA for OS appear plausible. Our findings indicate that there is no evidence that the BORT-DEX is more or less effective than LEN-DEX for PFS (HR for progression or death: 0.981 (95% 0.56-1.71)) and OS (HR for death 0.99 (95%CI 0.54-1.83). Again, this contrasts markedly with Table 65 in the CS reporting the HR for progression or death 1.06 (95%CrI 0.61, 1.85) and the HR for death 3.11 (95%CrI 1.52, 6.35) which is not plausible.

4.11.2 Comparison of observed data in contributory trials with CS models

4.11.2.1 Indication 1 overall survival

CS page 196 indicates that the company modelled OS for BORT + DEX patients by applying the NMA HR for BORT + DEX vs LEN+ DEX (3.11; CS Table 65) to an exponential model for the LEN + DEX arm. The resulting BORT + DEX curve is as shown in CS Figure 39 (Figure 14). This procedure imposes an exponential shape on the BORT + DEX arm. The modelled difference between arms is substantial indicating that OS will be a major driver of the ICER in cost effectiveness analysis.

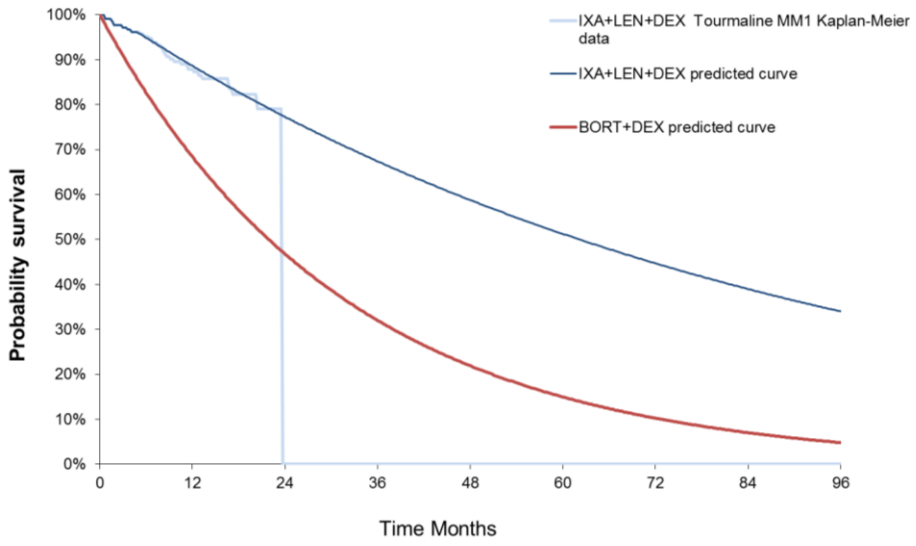


Figure 14: CS Figure 39 Red line is modelled OS for BORT + DEX (one prior therapy)

The ERG: [a] compared the CS modelled BORT + DEX OS curve with the "observed" OS reported in the NMA studies that included a BORT + DEX arm; [b] compared the shape of well-fitting models for these BORT + DEX arms with that imposed in the CS model. Four CS NMA studies (CS Table 43) supply OS KM plots for patients treated with BORT + DEX (listed in Table 39). KM plots and IPD were reconstructed from the published KM plots and associated information (number of events, patients at risk at stated times) using the method of Guyot et al. 2012.[59] The reconstructed KM plots were over-layered on the original plots to visually test for correspondence (available on request). Information criteria were used to identify best fit parametric models for

reconstructed plots (available on request). It should be appreciated that reconstructions are estimates of the original KM plot and underlying IPD. The reconstructed KM plots and best fit models were superimposed on CS Figure 39 so as to inspect how dispersion through time and the shape of the reconstructed "observed" OS for the four studies with BORT + DEX arms compared with the company model for BORT+ DEX.

Table 39: Studies from the CS NMA with a BORT + DEX arm KM for OS

Study	Sources	Therapy line	Information available
ENDEAVOR	[35, 36]; Amgen submission[21]	2'nd (no previous BORT) ¥	KM, risktable, events
PANORAMA 1	[41, 60-62]	2'nd or 3'rd§	KM, risktable, events
Matched pairs 3 trials	[45]	2'nd	KM, risktable, events
eVOBS	[44]	2'nd or more *	KM
Φ CS to NICE [id 934][21] for carfilzomib for MM; **§** ERG have used data from[41]; **¥** data from Figure 4.15 of the Amgen submission. BORT= Bortezomib * * not reported			

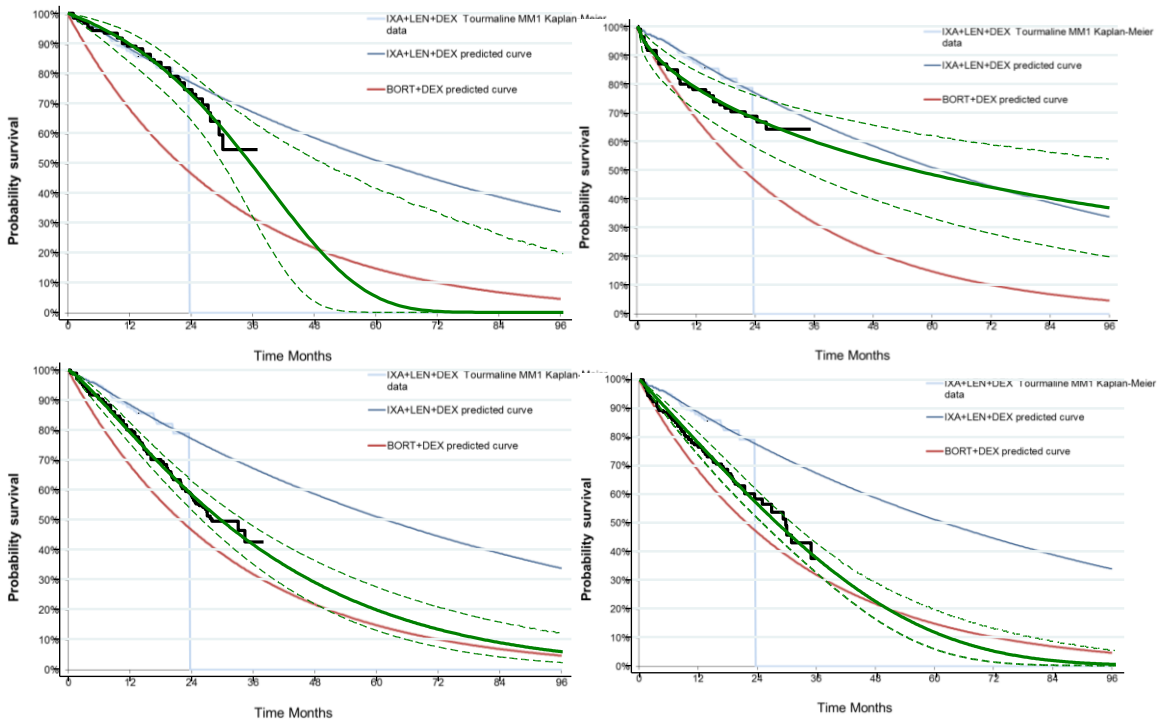


Figure 15: "Observed" OS in NMA BORT + DEX arms compared with the CS model for BORT + DEX (red line). Upper left = KM and Weibull model Matched pairs study; lower left = KM and Weibull model eVOBS; upper right = KM and Weibull model Matched pairs study: lower right = KM and Weibull model eVOBS

.

In all four studies the "observed" OS is noticeably superior to the CS model for BORT + DEX, and the lower 95% CI of the best parametric fits in all four is superior to the CS model for most of the time span. These results imply that the NMA HR of 3.11 used in company modelling may largely depend on input data from studies that lacked a BORT + DEX arm. It is possible that differences in study populations and in the number and type of prior treatments, may explain some of the discrepancy between "observed" and CS modelled curves, however taken in the round, the ERG considers the differences to be too large and consistent to be explained in this way. In the opinion of the ERG the fact that all "observed" OS plots for BORT + DEX are considerably superior to that modelled by the company threatens the face validity of the company model. The CS failed to supply NMA inputs for the NMAs conducted. The ERG requested this data in clarification; a systematic examination of all the submitted NMAs was precluded by time constraints, however the ERG believe they have identified an error in the relevant NMA that explains the anomalous difference between modelled OS and "observed" OS (see section on the critique of NMA results). These results also indicate that relative to observed OS, the company exponential model for BORT + DEX represents only a poor reflection of the shape of the "observed" OS. So as to view the CS NMA HR of 0.31 (IXA LEN DEX vs. BORT DEX, CS Table 45) in the context of the "observed" evidence the ERG have derived HRs for IXA + LEN + DEX (from the TMM-1 trial for the one prior treatment population) versus each BORT + DEX study arm. Although unsatisfactory methodologically this procedure makes use of the available data in the absence of direct comparison evidence. HRs were estimated using Cox proportional hazards and also using exponential parametric models since the CS has imposed an exponential model on the BORT + DEX arm. The results are summarised in Table 40 together with median survival predicted with exponential models.

Table 40: OS hazard ratios (HR for death) ; IXA + LEN + DEX vs BORT + DEX

BORT+DEX source	HR$^{\Psi}$ IXA+LEN+DEX vs. BORT+DEX	HR; exponential models	Median, exponential models and *CS*
eVOBS[26]	0.69 (0.57-0.85)	0.65 (0.53-0.78)	26.66 (23.24-30.58)
Matched pairs [45]	0.60 (0.36-0.99)	0.64 (0.39-1.03)	40.79(29.00-57.38)
Endeavor [35]	1.01 (0.85-1.22)	0.93 (0.79-1.09)	50.85 (36.51-70.82)
Panorama[51]	0.85 (0.78-0.94)	0.83 (0.76-0.92)	31.4 (26.8-36.9)
CS BORT+DEX*	0.31 (0.13-0.65)		*~21.7*

* based on CS 1.3.5 and CS Table 45; Ψ Cox regression.

The "observed" HRs are all distinctly larger than the CS NMA HR of 0.31 (95% CI: 0.13-0.65). A random effects meta-analysis of the "observed" HRs from the three randomised studies (Figure 16) similarly yields a much larger HR (0.878, 95% CI: 0.732 – 1.054) than that derived in the CS NMA. For completeness, the ERG has also presented a random effects meta-analysis of the "observed" HRs from the three randomised studies and the non-RCT study (eVOBS),[44] which results in an HR of 0.82 (95% CI 0.69 to 0.98) (Figure 17).

These estimates are strongly consistent with those of the ERG's NMAs.

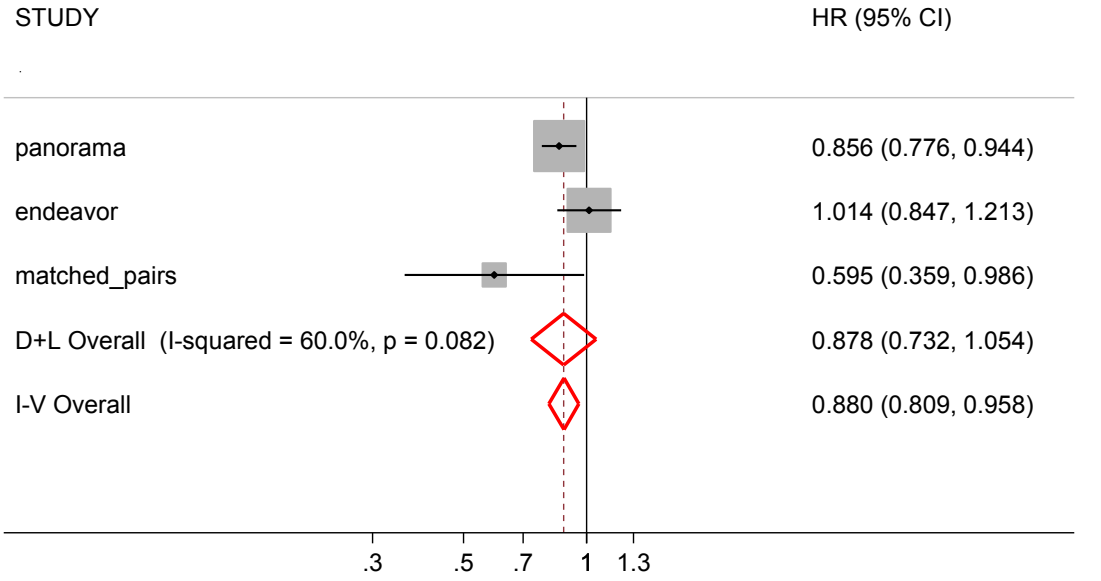


Figure 16: Meta-analysis of hazard ratios (IXA + LEN + DEX vs BORT + DEX) from 3 studies included in the company's NMA for OS.

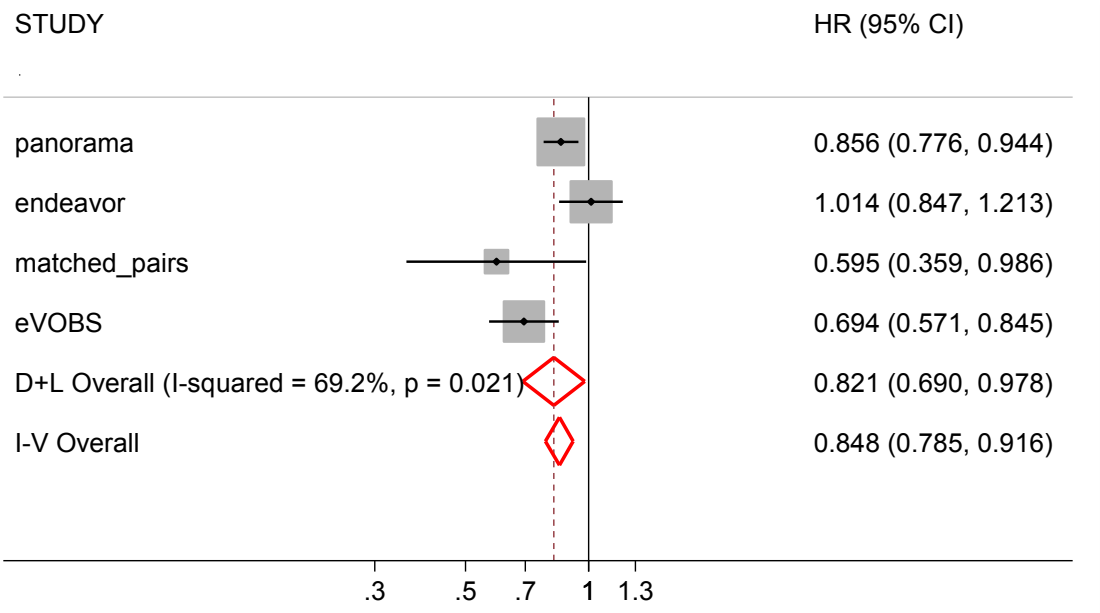


Figure 17: Meta-analysis of hazard ratios (IXA + LEN + DEX vs BORT + DEX) from 3 RCT studies and 1 non-RCT included in the company's NMA for OS.

4.11.2.2 Indication 1 progression free survival

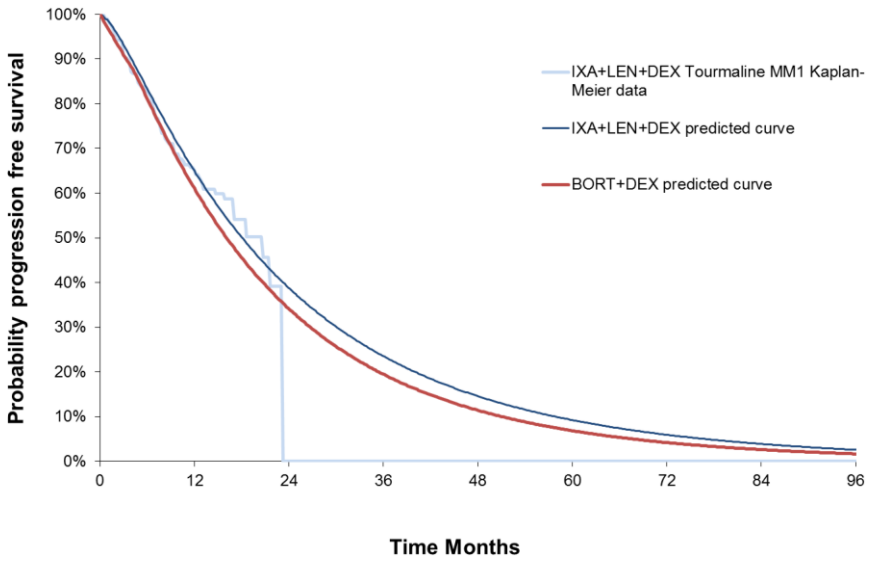


Figure 18: CS Figure 37 showing modelled PFS for BORT + DEX and IXA + LEN + DEX recipients. Note that there is little difference between the models of compared arms.

The CS modelled PFS in the IXA + LEN + DEX arm by applying a "treatment effect" HR of 0.94 (95% CI: 0.72-1.22) to a generalised gamma model fit to the LEN + DEX arm. CS PFS for the BORT + DEX arm was then obtained by applying an NMA HR of 1.06 (BORT + DEX vs. LEN + DEX, CS Table 65) to the gamma model for the LEN + DEX arm. This procedure brings CS modelled PFS for IXA + LEN + DEX and BORT + DEX close together (CS Figure 37).

CS Table 44 reports the NMA HR for the comparison IXA + LEN + DEX versus LEN + DEX to be 0.74, (95% CI: 0.59-0.94), and for the comparison IXA + LEN + DEX versus BORT + DEX to be 0. 72. Using these NMA HRs and the HR for BORT DEX vs. LEN DEX in CS Table 65 yields a larger difference between arms than that obtained using the CS procedure. This is indicated diagrammatically in Figure 19.

Ixa+len dex vs. len+dex Table 44	Ixa+len+dex vs. bort+dex Table 44	Bort+dex vs. len+dex Table 65	Ixa+len+dex vs. len+dex text
0.74	0.72	1.06	0.94
Inverse 1.35	Inverse 1.39	Inverse 0.94	Inverse 1.06

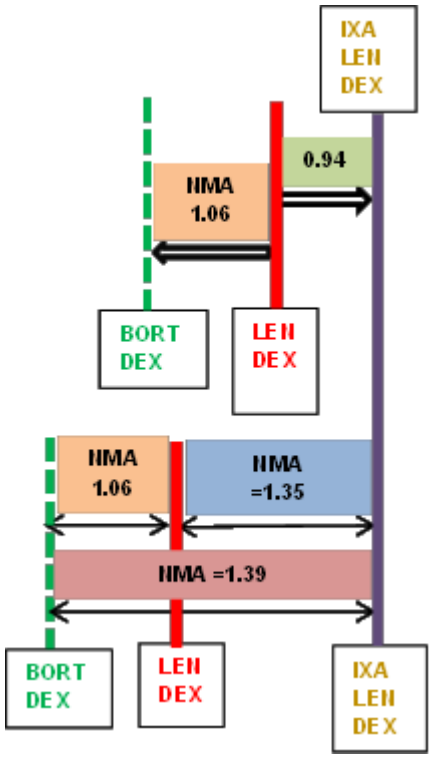


Figure 19: Diagram of the difference between IXA + LEN + DEX and BORT +DEX arms as modelled in the CS and using the CS NMA HR values presented in Tables 44 and 65.

In view of the CS possible overestimation of PFS for BORT + DEX recipients the ERG used the reconstruction method described above to test how the CS modelled PFS curve for BORT + DEX (CS Figure 37) compared with the "observed" PFS reported in the four NMA studies that included a BORT + DEX arm.

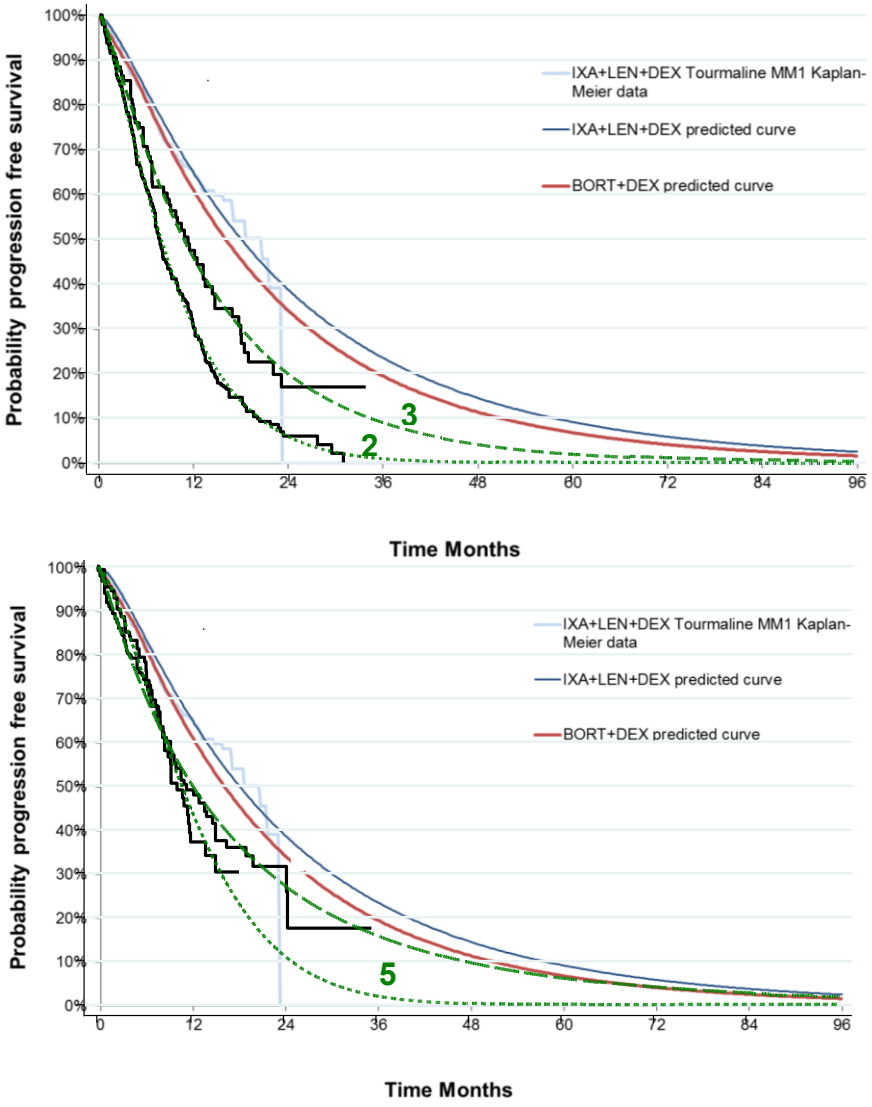


Figure 20: Reconstructed "observed" KM and gamma models of PFS in BORT + DEX arms compared with the CS model for BORT + DEX (red line). 2 = PANORAMA, 3 = matched pairs, ENDEAVOR (Amgen submission id 934), 5 = eVOBS

The results are summarised in Figure 20. In contrast to OS, the CS modelled PFS is superior to the reconstructed "observed" PFS from the four studies with BORT + DEX arms. Again the ERG consider the fact that gamma models for all four BORT + DEX arms provide substantially less favourable PFS than the CS model threatens the face validity of the company model. In Table 4 Appendix 5.1 the arms are listed incorrectly as BORT DEX CYCLO versus LEN DEX.

CS Table 44 reports the PFS NMA HR for IXA + LEN + DEX versus BORT + DEX to be 0.72 (95% CI: 0.41-1.19); as indicated above this appears at odds with CS Figure 37 in which the modelled curves show little difference between treatments. So as to view this estimated HR in the context of the "observed" evidence the ERG have derived the HR for the IXA + LEN + DEX arm of the TMM-1 trial (one prior treatment population) versus each BORT + DEX study arm. Although methodologically unsatisfactory this procedure makes use of the available data in the absence of direct evidence; HRs for progression or death were estimated using Cox proportional hazards, the results are summarised in Table 41. These HRs appear reasonably in line with the NMA value of 0.72 supporting the suspicion that the BORT +DEX PFS of the company model may be overestimated.

Table 41: Hazard ratios for progression or death for IXA LEN DEX vs BORT DEX

BORT+DEX source	HR for progression or death IXA+LEN+DEX vs. BORT+DEX
eVOBS BORT+DEX [a] [44]	0.90 (0.84 - 0.96)Ψ
BORT+DEX [b] Matched pairs [45]	0.74 (0.63 - 0.88)Ψ
BORT+DEX [c] Endeavor [35]	0.56 (0.40 - 0.80)Ψ
BORT+DEX [d] Panorama[51]	0.71 (0.65 - 0.77)Ψ
CS NMA	0.72 (0.41 – 1.19)*
* based CS Table 44 Ψ Cox regression.	

A random effects meta-analysis of the "observed" HRs from the four studies with BORT + DEX arms (Figure 21) yields a similar HR (0.75; 95% CI: 0.63 – 0.89).

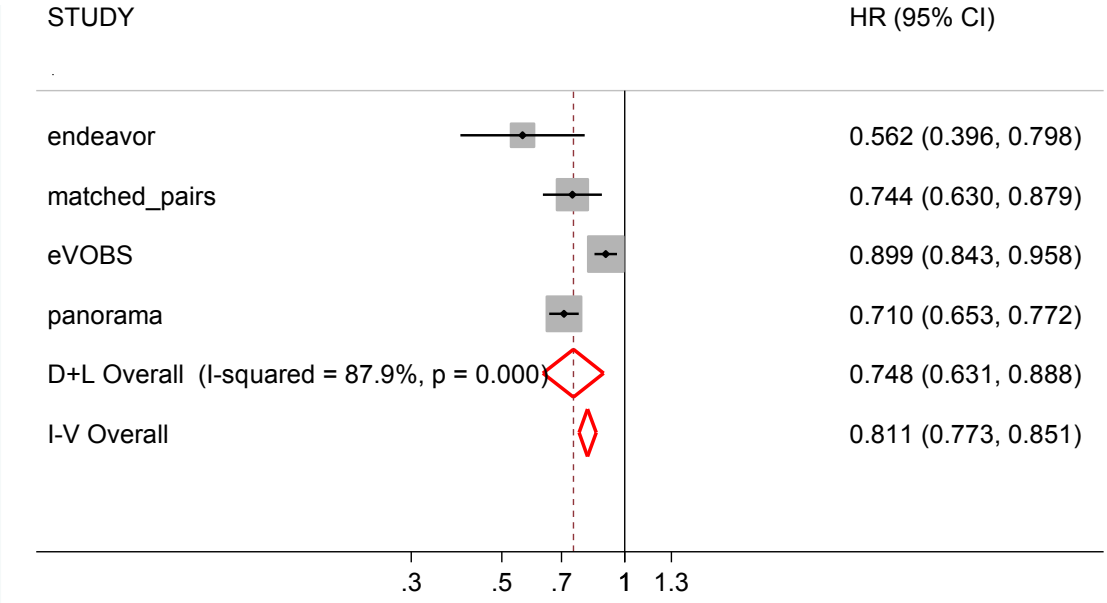


Figure 21: Meta-analysis of hazard ratios (IXA + LEN + DEX vs BORT + DEX) from 4 studies included in the company's NMA for PFS

By apparently overestimating BORT + DEX PFS and underestimating BORT + DEX OS the company models squeeze the difference between OS and PFS (post progression survival) to a relatively small proportion of OS when compared to that seen in the "observed" studies (Figure 22). Cartier et al. 2015[56] undertook a systematic review of clinical studies reporting PFS and OS HRs reported in clinical studies of different treatments for MM. The authors used regression methods to examine the relationship between HRs for progression or death and OS using 25 pairs of HRs between treatments. Figure 23 summarises the results reported by Cartier et al. and compares these with the ERG estimated HRs for progression or death and for OS for the four NMA studies with a BORT + DEX arm, and with the NMA HRs reported in the company submission. Under this comparison the ERG estimates based on the four NMA studies are reasonably consistent with the Cartier regression while the CS NMA hazard ratio pair appears to represent a distinct outlier.

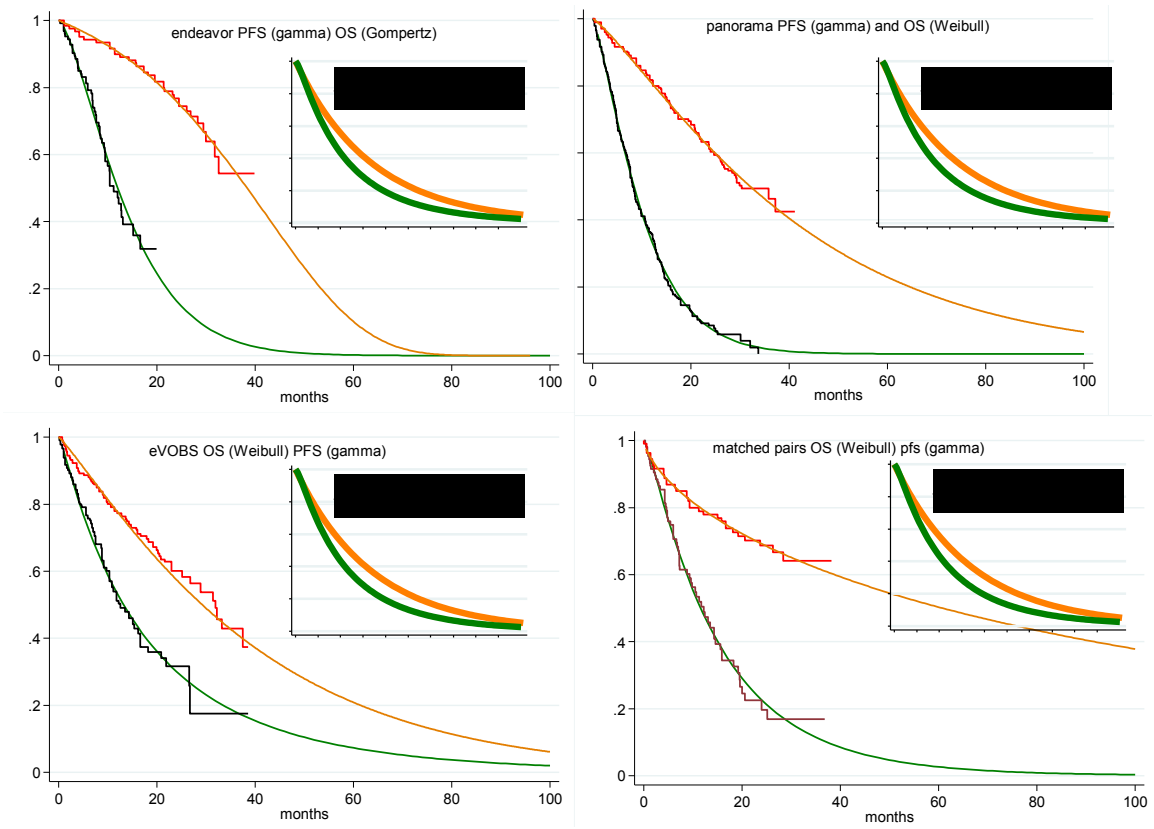


Figure 22: OS and PFS compared between "observed" studies and submission models.

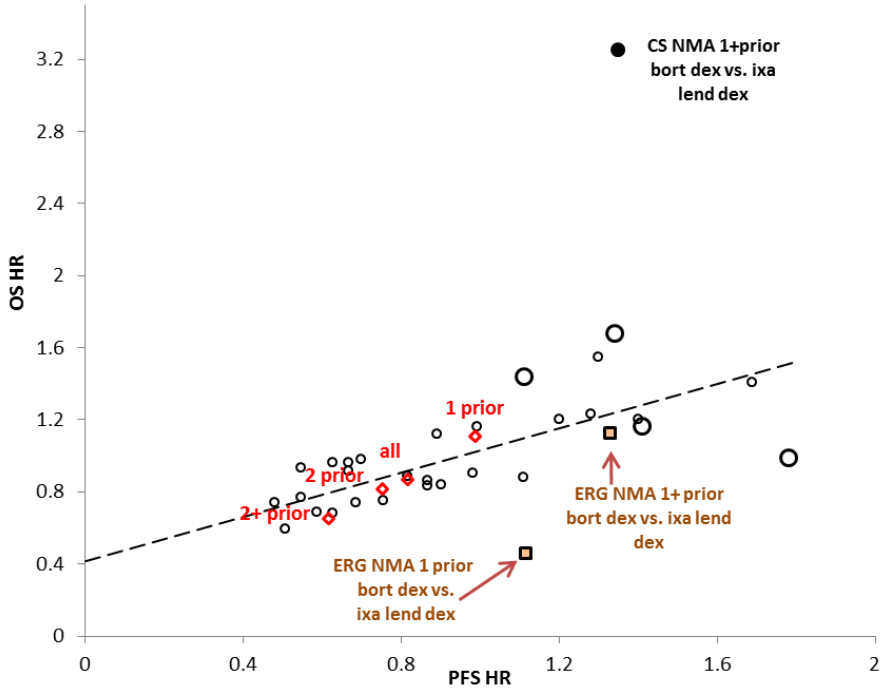


Figure 23: Relationship between OS and PFS hazard ratios for MM treatments. Hollow small circles = 25 HR pairs reported by Cartier et al., 2015; Dashed line = Cartier linear regression line; large open circles = ERG estimates based on four NMA studies with a BORT + DEX arm; Open diamonds = Tourmaline populations; Filled squares = ERG NMA results. Filled large cicle = CS NMA.

Summary

- The company model comparing OS between BORT + DEX and IXA + LEN + DEX appears to considerably underestimate OS for the former. This conclusion is supported when comparing the CS modelled OS for BORT +DEX with that observed in published studies used in the company NMA. The ERG believe the under-estimation may be traced to an error in the CS NMA input.
- The company model comparing PFS between BORT +DEX and IXA + LEN + DEX appears to strongly overestimate PFS for the former. This conclusion is supported when comparing the CS modelled PFS for BORT +DEX with that observed in published studies used in the company NMA. The overestimation may be related to the use of a HR of 0.94 for the comparison IXA+LEN +DEX vs LEN + DEX rather than the NMA HR of 0.74.

- The paired HRs for OS and PFS used in CS modelling are inconsistent with those seen amongst 25 studies reported by Cartier et al. 2015.

4.11.3 Exploratory analyses in the 2 prior therapies population of the TMM-1 trial

The company did not submit analyses regarding the 2 prior population. Because randomisation in TMM-1 was stratified by 1 prior and 2 or 3 prior therapies, the company took the view that a post hoc analysis of the 2 prior only population would carry several limitations. The ERG notice that the results for the 2+ prior population appear strongly driven by relatively favourable performance in OS and PFS for the relatively small subgroup of three prior patients (data summarised in Table 42); the ERG therefore considers that an analysis of the 2 prior population may be of interest to the appraisal committee.

Table 42: OS and PFS hazard ratio data for 2 prior, 3 prior and 2+ prior subgroups

Population (N) data cut	OS HR (95% CI) (IXA + LEN + DEX versus LEN + DEX)	PFS HR (95% CI) (IXA + LEN + DEX versus LEN + DEX)
2 + prior IA1	0.62 (0.35 – 1.09) CIC AIC ¥	0.58 (0.40 – 0.84) ¥
2 + prior IA2	0.65 (0.41 – 1.02) CIC AIC ¥	0.62 (0.45 – 0.86) ¥
2 prior (208) IA1	0.770 (0.382 – 1.553) Φ	0.75 Ψ
2 prior (208) IA2	0.725 (0.419 – 1.256) Φ	
3 prior (73) IA1	0.318 (0.100 – 1.017) Φ	0.37 Ψ
3 prior (73) IA2	0.455 (0.181 – 1.146) Φ	
¥ data from CS Table 41. Φ data from clarification document. Ψ data from CS Table 19, 95% CI not reported.		

During clarification the company supplied Kaplan-Meier data for OS, PFS and ToT for the 2 prior population. The ERG used this to generate KM plots for OS, PFS and ToT.

OS and PFS KM plots are shown in Figure 24

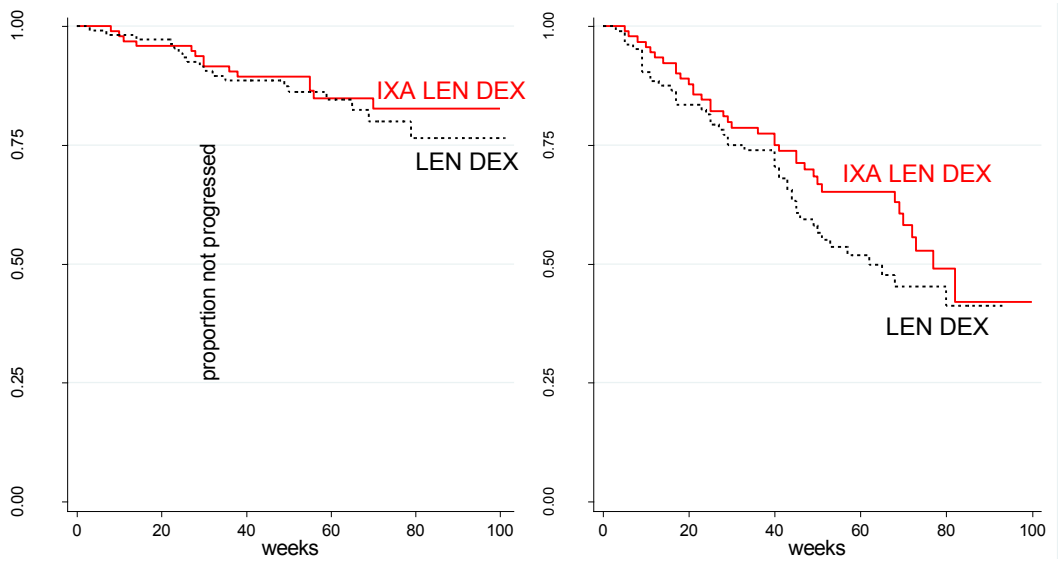


Figure 24: Kaplan Meier plots of OS and PFS for the two prior population

The difference between treatments is moderate; unadjusted hazard ratios (IXA + LEN + DEX versus LEN + DEX) were: 0.81 (95%CI: 0.40 – 1.64) for OS and 0.76 (95%CI: 0.49 – 1.17) for PFS. These values are distinctly less favourable for IXA + LEN + DEX than is the case for the 2+ prior subgroup.

The clarification data were used to fit exponential, Weibull, Gompertz, loglogistic, lognormal and generalised gamma models for OS, PFS and ToT (available on request). These were used to estimate the cost effectiveness of IXA + LEN + DEX versus LEN + DEX for the 2 prior group; the results are fully described in the cost-effectiveness section.

4.12 Conclusions of the clinical effectiveness section

Ixazomib combined with lenalidomide and dexamethasone was evaluated against lenalidomide and dexamethasone as part of the Tourmaline MM1 RCT. Owing to good methodological quality of the trial, the ERG does not have any reason to consider the results of this trial to be significantly biased. However, clinical effectiveness data are characterised by a high degree of immaturity since the benefit of ixazomib on OS cannot yet be determined.

Regarding the primary endpoint of TMM, the HR from the first interim analysis suggested a 26% reduction in risk of progression or death (HR 0.74, 95% CI 0.5, 0.94) from a first interim analysis. The benefit appears to be reduced with more mature data for the second interim analysis (HR 0.82, 95% CI 0.67, 1.0; p=0.054). In the 1 prior therapy group, there was clearly no benefit with ixazomib compared to placebo. In the 2-3 prior therapy group, the benefit with ixazomib was more convincing for PFS ($HR_{\text{1st interim analysis}}$ 0.58, 95%CI 0.40, 0.84).

To date, OS data are very immature to draw conclusions on the impact of ixazomib.

For the indirect comparison of ixazomib-based regimen to bortezomib-dexamethasone, the CS's NMA has several major limitations and contains an unfortunate error in the analysis on OS.

The revised NMAs proposed by the ERG conclude that, in the 1+ prior therapy group, the HR for progression or death of ixazomib+lenalidomide+dexamethasone relative to bortezomib + dexamethasone is 0.75 (95%CI 0.41, 1.38) while the HR for death for ixazomib+lenalidomide+dexamethasone relative to bortezomib + dexamethasone is 0.91 (95%CI 0.43-1.92). The ERG also provided additional NMA in the 1 prior therapy group but these results presented for OS in this subgroup are more subject to caution owing to the heterogeneity of included studies and the immaturity of OS data from the TMM-1 trial.

5 COST EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

5.1.1 Description of searches for cost-effectiveness studies.

A combined search strategy, reported in section 5.1 of the CS, was used for cost-effectiveness and cost and resource use studies. Databases searched were the Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, Medline, and PubMed. Key international Health Technology Assessment (HTA) websites were searched for relevant HTAs/models including NICE, Pharmaceutical Benefits Advisory Committee (PBAC), Canadian Agency for Drugs and Technologies in Health (CADTH), NHS Economic Evaluation Database. Relevant studies were also identified from reference lists of included economic evaluations and systematic reviews. Only conference proceedings or abstracts presented within the last year were included, as it was thought that any high-quality studies should have been reported as journal articles within this time. The searches were last updated on October 2016. Screening of abstracts and full-texts articles were conducted by two independent reviewers. There were 842 primary records screened, with 46 studies being included for data extraction.

5.1.2 Critique of cost-effectiveness searches

The ERG considers that the databases searched and terms used were suitable for the research question, but felt that only including abstracts published in the past year was too restrictive (given that a meeting abstract from 2010 was included in the NMA for clinical effectiveness).

5.1.3 Description of searches to for health-related quality-of-life (HRQoL) studies

Databases searched for HRQoL studies were the Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, Medline, Econlit, PubMed, NHS Economic Evaluation Database (EED). Also key international and HTA websites were searched and reference lists of reviews were checked. Only conference proceedings or abstracts

presented within the last year were included. Searches were last carried out in October 2016.

Primary screening of titles and abstracts was performed for 652 records and 58 of these were included for full text screening. To be included, studies were required to report utility values derived from generic HRQoL instruments, or to map from disease specific measures to generic ones. Data were extracted from 5 studies, reporting results from 4 trials.

5.1.4 Critique of the HRQoL searches

The ERG consider that the searches were comprehensive and appropriate to the research question, but felt that the decision to remove abstracts at the screening stage unless they were published in the last year was not justified.

5.1.5 Conclusions from the available data

There is an extensive company literature review of cost effectiveness studies, quality of life and resource use. Indeed, it forms much if not the majority of the economics of the submission. The company appears to conclude that little of this is relevant to the current submission, other than quality of life values from TA171 [20, 63] and TA338.[64] Given the extent of the submission, its appendices and the company clarification response the ERG has not critiqued the company literature review in detail.

The main element of immediate interest is the company summary of the EQ-5D values of the MM-003[42] trial which apparently recruited patients who had failed on at least two previous therapies; i.e. the 2+ prior subgroup. The values reported by the company are 0.61 to 0.73 for best response prior to progression and 0.50 at progression. The value at progression is considerably below that of the company analysis. Applying this within the economics would worsen the cost effectiveness estimates: the company base case cost effectiveness estimate for the 1 prior subgroup worsens from [redacted] per QALY to [redacted] per QALY and for the 2+ prior subgroup worsens from [redacted] per QALY to [redacted] per QALY.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist

Table 43: NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	For the 1 prior subgroup the company compares IXA+LEN+DEX with BORT+DEX. For the 2+ prior subgroup the company compares IXA+LEN+DEX with LEN+DEX.
Patient group	As per NICE scope. "People with relapsed or refractory multiple myeloma who have had at least 1 therapy "	The patient group of the TMM-1 trial is split into those with: • 1 prior therapy • 2+ prior therapies This is as per the stratification within the TMM-1 trial.
Perspective costs	NHS & Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Cost utility analysis.
Time horizon	Sufficient to capture differences in costs and outcomes	25 years. Relatively few patients are modelled as remaining alive at the end of the time horizon.
Synthesis of evidence on outcomes	Systematic review	The overall survival (OS), progression free survival (PFS) and time on treatment (ToT) curves for IXA+LEN+DEX and LEN+DEX are estimated from

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
		the TMM-1 subgroup specific trial data. The OS and PFS curves for BORT+DEX are based upon applying the NMA OS HR to the LEN+DEX OS curve and the NMA PFS HR to the LEN+DEX PFS curve. The BORT+DEX ToT curve is assumed to be the same as the LEN+DEX ToT curve.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes. For the main health states of the model the TMM-1 EQ-5D data is used. The method used to describe the 0.025 utility decrement for subcutaneous administration of bortezomib is unclear.
Benefit valuation	Time-trade off or standard gamble	For the main health states of the model the time trade-off of the UK social tariff. The method used to value the 0.025 utility decrement for subcutaneous administration of bortezomib is unclear.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes. For the main health states of the model the UK social tariff

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
		has been applied to the TMM-1 trial EQ-5D data. The source of preferences for the utility decrement for subcutaneous administration of bortezomib is unclear.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Probabilistic modelling	Probabilistic modelling	Yes.
Sensitivity analysis		A range of sensitivity analyses and scenario analyses are presented.

In the opinion of the ERG the construction of the electronic model is convoluted and opaque. The ERG has rebuilt the deterministic company model in a less convoluted form and gets a very good correspondence with the company model results. In the light of this, much of the explanation of the company model is taken from the ERG rebuild[1] rather than the original company model. The company base case results and sensitivity and scenario analyses that are reported below are taken from the company submission or the company model. On occasion, where a scenario is of interest but implementing it is

[1] In the light of this, the ERG has uploaded a copy of its rebuild alongside its revised company model to NICEdocs.

complex within the company model a clearly signposted exploratory analysis from the ERG rebuild is also presented.

Throughout the economics for reasons of space, the tables and the figures typically abbreviate the treatments along the following lines:

- IXA+LEN+DEX to IXAL
- LEN+DEX to LEND
- BORT+DEX to BORD

5.2.2 Model structure

The company implements a partitioned survival model with a weekly cycle length and a 25 year time horizon.

The model structure is relatively straightforward, though as mentioned the electronic implementation of it is convoluted. In essence and in common with many cancer models, patients are modelled as being in either progression free survival (PFS), post progression survival (PPS) or dead. The OS curve of a treatment defines those alive and those dead through time. The PFS curve of the treatment subdivides the proportion modelled as alive into those in PFS and those in PPS.

The company notes that some patients were treated beyond progression. This is used as the justification for the additional element of the time on treatment (ToT) which determines the treatment costs, the curve for which is not synonymous with the PFS curve. Treatment holidays and missed doses are separately accounted for and are not part of the ToT. This only considers treatment cessation. The main effect is not to model treatment costs extending beyond PFS but to reduce treatment costs to be substantially less than PFS.

Those in PFS are further subdivided by their Best Overall Response (BoR) which can be either very good partial response or complete response (VGPR+), partial but not very

good response (PR) or stable disease (SD). The distribution between BoR states is treatment specific and assumed to apply to patients over their entire PFS.

This results in the following health states:

- Progression free survival (PFS) with treatment specific static distributions between BoR applying for the duration of PFS:
    - BoR - very good partial response or complete response (VGPR+)
    - BoR - partial but not very good response (PR)
    - BoR – stable disease (SD)
- Post progression survival (PPS)
- Dead

Note that the above health states relate to the patient benefit side of the equation and do not account for costs which are primarily determined by the ToT curves.

5.2.3 Population

The economics considers two patient groups:

- Those at 2nd line: This is modelled using the TMM-1 1 prior subgroup
- Those at 3rd line: This is approximated by the TMM-1 2+ prior subgroup.

The company states that for those at 3rd line the TMM-1 2 prior subgroup cannot be used due to stratification during randomisation being by 1 prior and 2+ prior. It would consequently be necessary to control for confounding variables if using the TMM-1 2 prior subgroup. The company views it as statistically more robust to use the 2+ prior subgroup as a proxy for the 2 prior subgroup[2].

[2] See pages 179 and 180 of the company submission.

5.2.4 Interventions and comparators

For the 1 prior group the intervention and comparators are:

- Ixazomib+lenalidomide+dexamethasone (IXA+LEN+DEX)
- Bortezomib+dexamethasone (BORT+DEX)

For the 2+ prior group the intervention and comparators are:

- Ixazomib+lenalidomide+dexamethasone (IXA+LEN+DEX)
- Lenalidomide+dexamethasone (LEN+DEX)

5.2.5 Perspective, time horizon and discounting

The perspective is as per the NICE reference case. The time horizon is 25 which is close to a lifetime horizon within the modelling, though for some modelling the end of the OS curve is slightly curtailed. Costs and benefits are discounted at 3.5%.

5.2.6 Treatment effectiveness and extrapolation

The company states that that "At the decision problem meeting with NICE it was agreed the primary data cut IA1 was appropriate for the base case of the economic analysis". Treatment effectiveness in terms of OS, PFS and time on treatment (ToT) and their extrapolation are based on parameterised curves estimated from the 1st interim data cut. There is only a limited presentation of this within the company submission so it is dwelt upon at some length in what follows in the Unadjusted and adjusted parameterised curves: Details section. Details of the parameterised curves, best overall responses and SAEs follow in the next 6 pages followed by the Unadjusted and adjusted parameterised curves: Details section. For many readers this level of detail may not be necessary. Some may wish to read the three summary sections that follow and then move on to section 5.2.7 on quality of life section.

5.2.6.1 Summary of the approach to modelling OS, PFS and ToT curves

- Parameterised curves for OS, PFS and ToT have been estimates using subgroup specific Kaplan Meier TMM-1 data, pooled across the arms. Within this pooled

analysis a treatment effect for ixazomib is estimated. When estimating the relevant curve for IXA+LEN+DEX the treatment effect is added to the constant of the parameterised curve, while for the LEN+DEX curve only the constant of the parameterised curve is applied.

- The parameterised curves of the company base case use the 1st interim analysis.
- The company base case adjusts the curves for a number of baseline covariates.
    - The covariates that are included for the 1 prior subgroup are:
        - OS: Baseline age 65+
        - PFS: Light chain myeloma status
        - ToT: Light chain myeloma status and renal dysfunction status
- The covariates that are included for the 2+ prior subgroup are:
    - OS: ISS stage III, plus ECOG 2 status for the delayed exponential
    - PFS: ISS stage III, ECOG 2 status and primary refractory status
    - ToT: ISS stage III
- The company model also includes unadjusted parameterised curves[3] that do not include the covariates of the above bullet, but these are not presented in the company submission. The AIC and BIC of the adjusted curves are typically somewhat better than those of the unadjusted curves.
- For the 1 prior subgroup for OS a delayed exponential using the data from 5+ months is also estimated, apparently due to proportionate hazards being a poor assumption for the first 5 months of the data.
    - In the IXA+LEN+DEX arm the Kaplan Meier curve is applied for the 1st 5 months and the delayed exponential thereafter.

[3] Though these still include a treatment effect for ixazomib use.

    - In the BORT+DEX arm the LEN+DEX delayed exponential is applied from baseline, conditioned by the NMA hazard ratio for BORT+DEX relative to LEN+DEX.

- For the 1 prior subgroup the BORT+DEX curves are estimated by applying the NMA hazard ratios estimated for the ITT 1+ prior patient group to the LEN+DEX curves:
    - OS: An HR of 3.11 from the NMA
    - PFS: An HR of 1.06 from the NMA
    - ToT: An HR of 1.00 by assumption due to a lack of data
- For the 1 prior subgroup the functional forms of the company base case are:
    - OS: Delayed exponential, preceded by 5 months Kaplan Meier data
    - PFS: Generalised gamma
    - ToT: Weibull
- For the 2+ prior subgroup the functional forms of the company base case are:
    - OS: Weibull
    - PFS: Generalised gamma
    - ToT: Exponential

This results in the following curves[4] for IXA+LEN+DEX and BORT+DEX in the 1 prior subgroup for the company base case.

[4] Due to the complexity of the company model the curves presented in the ERG report have been taken from the ERG rebuild of the deterministic company model. A selection of the values of each curve have been cross checked with the values in the company model when this is specified as an input in the company model. But in the light of this both the ERG amended company model and the ERG rebuild have been uploaded to NICEdocs to permit error checking by the company.

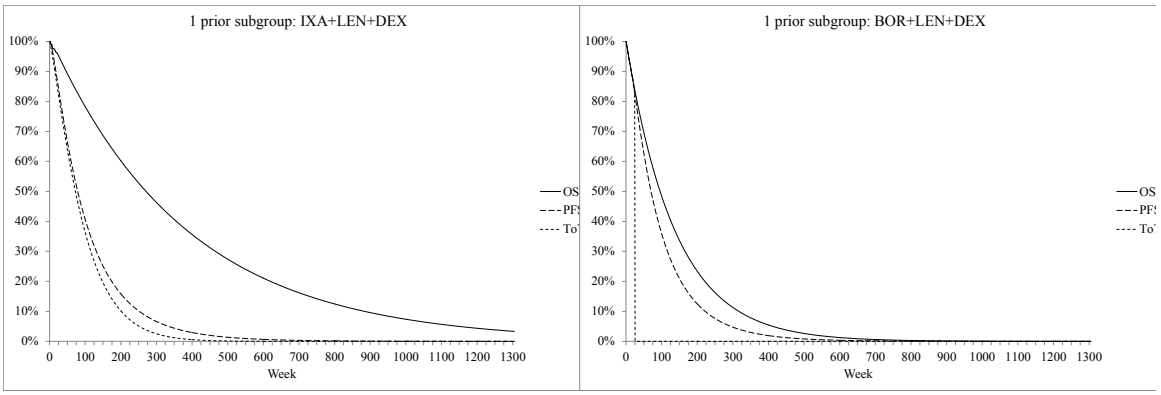


Figure 25: 1 Prior: Company base case curves

Immediately apparent from the above is the difference in terms of time on initial therapy, with IXA+LEN+DEX being much as per the PFS curve but BORT+DEX being restricted to 9 three week cycles to yield 24 weeks of treatment.

There is also only limited additional PFS survival subsequent to PFS survival for BORT+DEX but a great deal of additional PFS survival subsequent to PFS for IXA+LEN+DEX. IXA+LEN+DEX appears to have altered the course of the disease subsequent to progression compared to BORT+DEX.

The OS and the PFS curves modelled for each comparator can also be presented alongside one another.

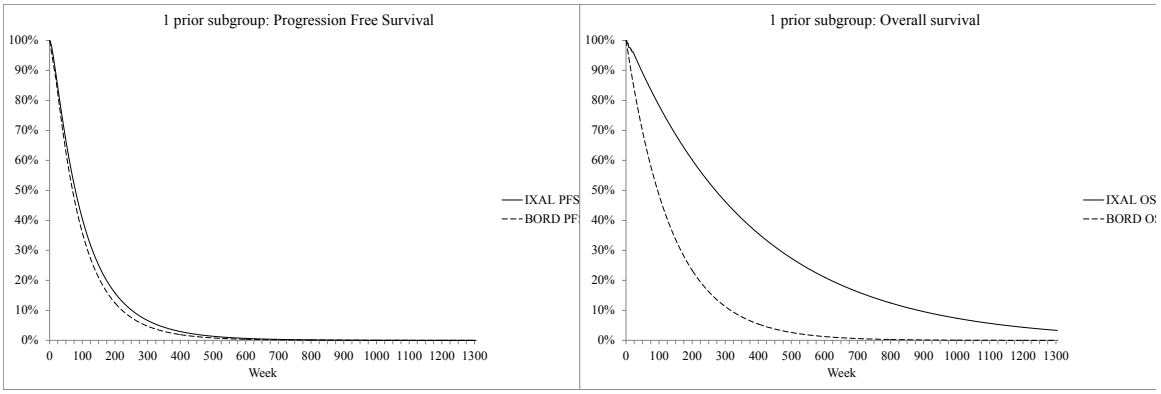


Figure 26: 1 Prior: Company base case OS and PFS curves[5]

[5] Within the tables and figures of the economics, in order to economise on space IXA+LEN+DEX is abbreviated to IXAL, LEN+DEX is abbreviated to LEND and BORT+DEX is abbreviated to BORD.

The PFS curve of IXA+LEN+DEX is estimated to be slightly superior to that of BORT+DEX. The OS curve of IXA+LEN+DEX is estimated to be very much superior to that of BORT+DEX.

The corresponding curves for the 2+ prior subgroup for IXA+LEN+DEX and LEN+DEX are as below.

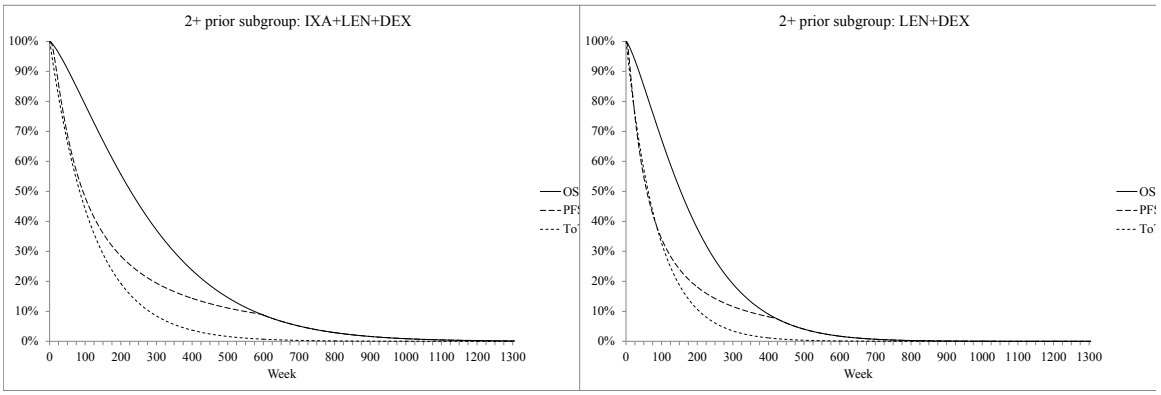


Figure 27: 2+ Prior: Company base case curves[6]

The ToT curves which determine the proportion of PFS patients that incur treatment costs is quite close to the PFS curve during the trial period. During extrapolation the ToT curve drops to somewhat below the PFS curve, reducing the proportion of PFS patients that incur treatment costs.

For both arms the PFS curve is constrained by the OS curve after around 12 years in the IXA+LEN+DEX arm and after around 8 years in the LEN+DEX arm. The ToT curve in the IXA+LEN+DEX arm lies everywhere below the PFS curve, but in the LEN+DEX arm rises above the PFS curve between week 21 and week 84.

[6] Within the tables and figures of the economics, in order to economise on space IXA+LEN+DEX is abbreviated to IXAL, LEN+DEX is abbreviated to LEND and BORT+DEX is abbreviated to BORD.

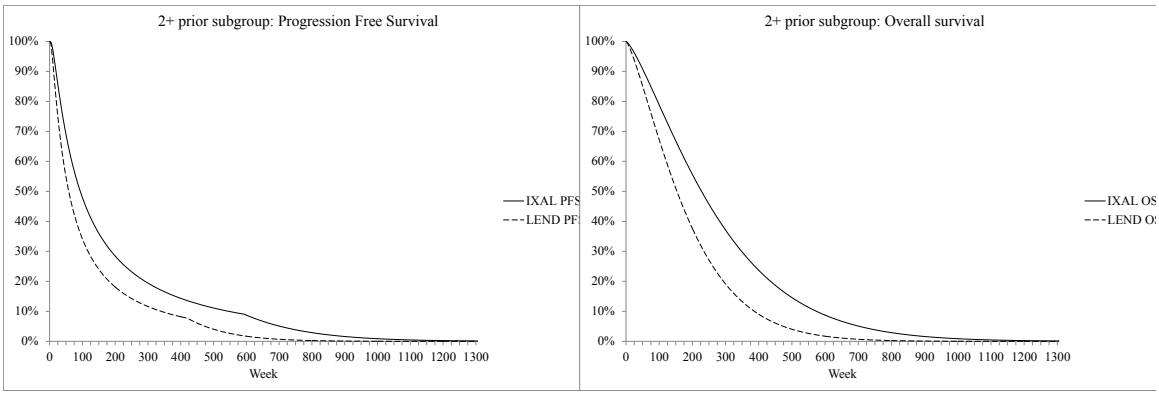


Figure 28: 2+ Prior: Company base case OS and PFS curves

There is a lesser difference between the PFS curves than between the OS curves. IXA+LEN+DEX is anticipated to increase both PFS and PPS compared to LEN+DEX.

5.2.6.2 Summary of the approach of estimating the PFS distribution between BoR responses

Additional treatment effects relate to the breakdown of PFS into stable disease (SD) and partial response (PR+). Partial response is further subdivided into partial response (PR) and very good partial response or complete response (VGPR+). The model takes these rates directly from the TMM-1 trial patient count data for IXA+LEN+DEX and LEN+DEX. Patient count data for BORT+DEX is reportedly taken from the PANORAMA-1 trial as reported in San Miguel et al (2014).[41]

The TMM-1 data suggests that among the 1 prior subgroup in the LEN+DEX arm 66 + 93 = 159 patients out of a total with BoR data of 204 patients, i.e. 78%, have a BoR of PR or VGPR+ which yields an odds of 3.53. This is coupled with an odds ratio of response for BORT+DEX of 2.28 which implies an odds of 8.04 for BORT+DEX, hence a BoR of PR or VGPR+ among 89% of patients for BORT+DEX. This is split in proportion to the patient count data of 52:2 to yield BoR estimates of 86% with PR and 3% with VGPR+. The remaining patient count data 22:162 is used to split the 11% of patients into 1% PD and 10% SD.

Table 44: Derivation of distribution of best overall responses (BoR) during PFS: 1 prior[7]

			PPS	PFS					
		Missing	PD	SD	PR	VGPR+	Resp.	Odds	OR
IXAL	N	12	10	27	68	95	82%		1.13
	Dist.	..	5%	14%	34%	48%			
	PFS Dist.	..	..	14%	36%	50%			
LEND	N	9	12	33	66	93	78% →	3.53	
	Dist.	..	6%	16%	32%	46%		↓	
	PFS Dist.	..	..	17%	34%	48%			
BORD	N	..	22	162	54	2	89% ←	8.04 ←	2.28
	Dist.	..	1%	10%	86%	3%			
	PFS Dist.	..	..	10%	87%	3%			

The difference between the patient numbers for BORT+DEX which suggest a response rate of 23% compared to the 89% estimate using the NMA odds ratio of 2.28 is quite marked. This in turn may question the reasonableness of the 54:2 ratio that is used to split the 89% into 86% PR and 3% VGPR+

Note that the electronic model also contains an odds ratio for BoR of 1.13 for IXA+LEN+DEX relative to LEN+DEX. This is not used but if applied would result in a marginally worse distribution than that above. The patient count data suggests an odds ratio of 1.24.

Table 45: Derivation of distribution of best overall responses (BoR) during PFS: 2+ prior

			PPS	PFS		
		Missing	PD	SD	PR	VGPR+
IXAL	N	9	7	13	41	78

[7] Within the tables and figures of the economics, in order to economise on space IXA+LEN+DEX is abbreviated to IXAL, LEN+DEX is abbreviated to LEND and BORT+DEX is abbreviated to BORD.

	Dist.	..	5%	9%	29%	56%
	PFS Dist.	..	..	10%	31%	59%
LEND	N	15	8	26	52	48
	Dist.	..	6%	19%	39%	36%
	PFS Dist.	..	..	21%	41%	38%

The above PFS BoR distributions are assumed to apply for the entire duration that patients remain in PFS and are used to provide treatment specific quality of life values for PFS.

5.2.6.3 Summary of SAEs

The SAE rates for those remaining on treatment for IXA+LEN+DEX and LEN+DEX are drawn from the TMM-1 trial. For BORT+DEX they are reportedly drawn from those for BORT+DEX in the PANORAMA-1 trial by San-Miguel et al (2014).[41] Where SAEs are not reported by San-Miguel et al (2014)[41] the rates for BORT+DEX are assumed to be equal to those of LEN+DEX. The number of patients experiencing an event is coupled with the total patient exposure to yield annualised rates which within the model are converted to weekly rates for those remaining on treatment.

Table 46: SAE numbers and annual rates

	Patient numbers			Annual rates		
	IXAL	LEND	BORD	IXAL	LEND	BORD
Number of patients	360	360	377			
Average treatment exposure in months	11.32	11.05	6.10			
Patient-years of exposure	338	333	192			
Anaemia	41	61	72	11%	17%	31%
Cardiac failure	9	7	7	3%	2%	4%
Deep vein thrombosis	2	3	..	1%	1%	1%
Diarrhoea	28	8	30	8%	2%	14%
Fatigue	14	9	45	4%	3%	21%
Upper respiratory tract infection/Pulmonary	3	3	6	1%	1%	3%
Ischaemic heart disease	2	3	0	1%	1%	0%

	Patient numbers			Annual rates		
	IXAL	LEND	BORD	IXAL	LEND	BORD
Nausea	6	0	2	2%	0%	1%
Neutropenia	155	124	43	37%	31%	20%
Peripheral neuropathy	1	3	55	0%	1%	25%
Pneumonia	36	39	39	10%	11%	18%
Pulmonary embolism	8	8	1	2%	2%	1%
Rash-related	20	5	..	6%	1%	1%
Renal failure	6	17	0	2%	5%	0%
Thrombocytopaenia	76	22	118	20%	6%	46%
Vomiting	4	2	5	1%	1%	3%
New primary malignancy	1	2	..	0%	1%	1%

The detail of the parameterised curves follows. As already noted this level of detail may not be required by many readers and some may wish to move forward to section on quality of life (5.2.7)

5.2.6.4 Unadjusted and adjusted parameterised curves: Details

The company electronic model provides subgroup specific parameterised curves estimated from TMM-1 data pooled between the IXA+LEN+DEX arm and the LEN+DEX arm.

Within these analyses treatment with ixazomib is treated as a covariate, the estimated coefficient for this being added to the constant of the parameterised curve when constructing the parameterised curve for IXA+LEN+DEX but not being added to the constant when constructing the curve for LEN+DEX. The other curve parameters are restricted to being the same for both IXA+LEN+DEX and LEN+DEX.

The unadjusted analyses only control for treatment arm. The adjusted analyses also control for a range of other covariates within the baseline TMM-1 data. The coefficients for the covariates are conditioned by the pooled trial baseline characteristics before again being added to the constant of the parameterised curve. The TMM-1 baseline characteristics of the covariates variously included in the adjusted curves are as below.

Table 47: TMM-1 baseline characteristics for parameterised curves

	1 Prior	2+ Prior
ISS Stage III	12%	13%
Age >65	52%	53%
ECOG 2	4%	8%
Primary Refractory	6%	7%
Light chain myeloma	21%	21%
Renal dysfunction	12%	14%

The requirement to adjust the parameterised curves is dependent upon the baseline characteristics differing between the arms for the relevant subgroup.

5.2.6.5 Overall Survival curves: 1 Prior subgroup

The economic model provides the following unadjusted and adjusted curves for the 1 prior subgroup, with the AIC and BIC values being taken from appendix 11 of the company submission and the company response to the ERG clarification questions.

Table 48: 1 Prior: Unadjusted parameterised OS curve

	Expo	Weib	Gomp	LogL	LogN	Gamm	D. Expo
IXAL Tx	0.211	-0.169	0.211	-0.183	-0.259	-0.242	0.083
Constant	-4.762	4.353	-4.998	4.230	4.626	4.599	-4.504
Gamma		0.225	0.028				
Sigma				0.270	0.479	0.394	
Kappa						0.151	
AIC	647.78	646.73	648.47	646.35	645.74	647.70	495.54
BIC	655.88	658.89	660.63	658.50	657.89	663.91	503.55

The AIC and BIC for the delayed exponential are not readily comparable with those of the other curves due to the delayed exponential being estimated from a shorter data set.

Table 49: 1 Prior: Adjusted parameterised OS curves

	Expo	Weib	Gomp	LogL	LogN	Gamm	D. Expo
IXAL Tx	0.193	-0.151	0.189	-0.173	-0.266	-0.232	0.114
ISS Stage III	1.111	-0.889	1.108	-0.982	-1.092	-1.055	0.828
ECOG 2							1.105
Constant	-4.961	4.510	-5.189	4.370	4.759	4.714	-4.733
Gamma		0.225	0.028				
Sigma				0.290	0.447	0.317	
Kappa						0.229	
Information criteria in appendix 11							
AIC	647.78	646.73	648.47	646.35	645.74	647.70	485.58
BIC	655.88	658.89	660.63	658.50	657.89	663.91	501.61
Information criteria supplied at 2nd clarification							
AIC	n.a.	638.02	636.94	635.12	638.76	635.43	485.58
BIC	n.a.	650.17	653.15	651.33	654.97	651.63	501.61

The adjusted curves' AIC and BIC supplied in appendix 11 of the submission are apparently incorrect. The company has supplied some additional AIC and BIC at 2nd clarification but some uncertainty remains around these as they appear to supply the delayed exponential but label it as exponential and not supply the exponential which may raise questions about the labelling of the other AIC and BIC values.

As for the unadjusted curves, the treatment coefficient is added to the constant term when constructing the IXA+LEN+DEX curves but not when constructing the LEN+DEX curves. In a similar manner the ISS stage III and ECOG 2 coefficients are added to constant term, once they have been conditioned by the 1 prior subgroup proportions pooled across the arms of 12% and 4% respectively.

The values supplied at 2nd clarification suggest that the adjusted curves are superior to the unadjusted curves. Of the comparable AICs the log normal has the lowest value at 635.12

but this is not much different from the generalised gamma at 635.43. The Weibull has the lowest BIC.

The company base case applies the delayed exponential and justifies this on the following grounds:

"When analysing the LCHP, it is evident that the violation of the proportional hazards assumption exists in the initial stages of the survival data, most notably prior to month 5. For this reason, the model uses Kaplan-Meier data to inform OS from month 0 to month 5; an exponential parametric curve was then fit to the data from month 5 onwards."

For IXA+LEN+DEX this applies the hazards of the Kaplan Meier curve for the first 5 months; i.e. to week 21, and applies the 0.0026 weekly hazard of the delayed exponential thereafter.

The median baseline age within the TMM-1 trial was 66 years which with a time horizon of 25 years extends to 91. UK lifetables 2013-15 suggest that 20% of men aged 66 survive to 91 year, and that 30% of women aged 66 survive to 91 years[8]. As graphed below, extrapolating using the gompertz suggests a very much poorer overall survival than the other curves. The Weibull suggests that patient survival drops to near zero by the end of the 25 year time horizon. The delayed exponential suggests that a little over 3% will survive in the IXA+LEN+DEX arm and a little under 5% in the LEN+DEX arm at the end of the 25 year horizon. The other curves suggest larger proportions surviving at the end of the 25 year time horizon and despite its AIC the Log Normal appears implausible.

[8]https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables

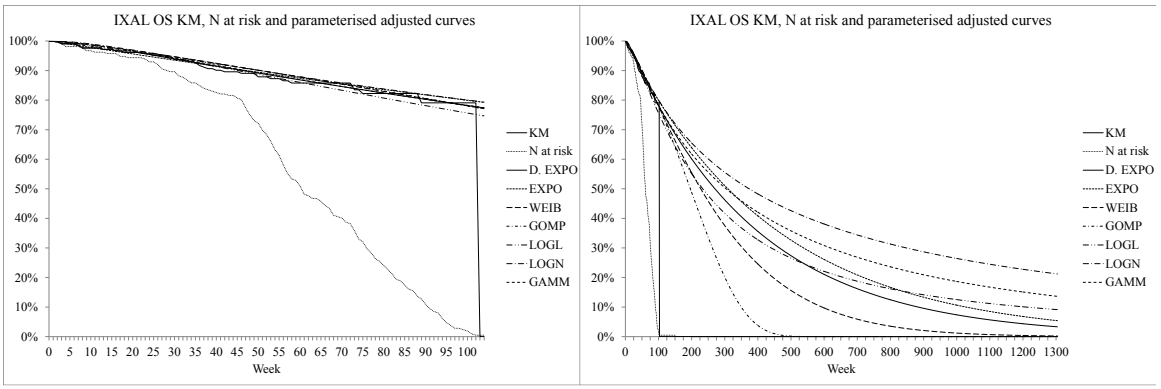


Figure 29: 1 Prior: IXA+LEN+DEX OS KM, N at risk and adjusted parameterised curves

As is often the case, the parameterised curves show only a limited divergence up to week 50 when reasonable numbers remain at risk. The numbers at risk thereafter begin to drop to somewhat less than the Kaplan Meier curve. But by week 102 the parameterised curves have begun to diverge slightly. The main divergence, which for some curves such as the gompertz is quite dramatic, occurs after week 102 during extrapolation.

The parallel curves for the LEN+DEX arm are as below, the delayed exponential applying the hazards of the Kaplan Meier curve for the first 5 months and applying the 0.0023 weekly hazard of the delayed exponential thereafter. The ratio between the 0.0023 hazard and the 0.0026 hazard is a hazard ratio of 0.89 in favour of LEN+DEX; i.e. the OS curves underlying the 1 prior analysis suggest that survival with IXA+LEN+DEX worse than survival with LEN+DEX.

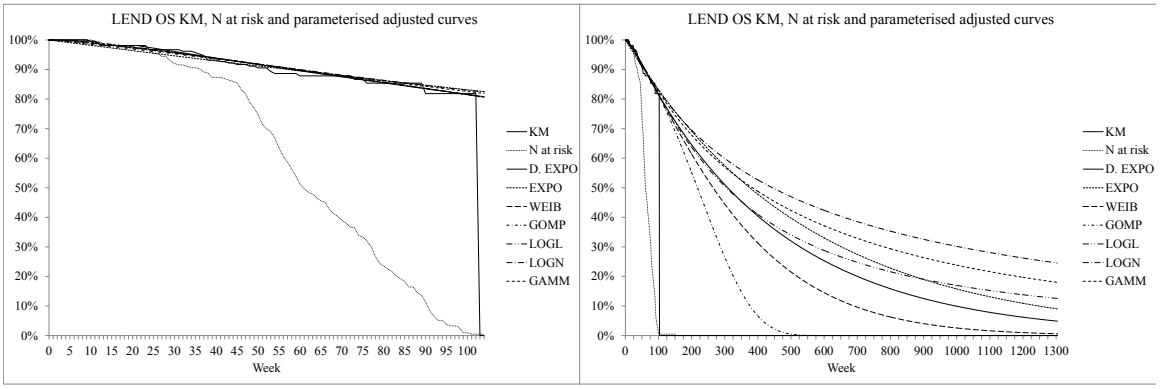


Figure 30: 1 Prior: LEN+DEX OS KM, N at risk and adjusted parameterised curves

The Weibull also appears to be a reasonable candidate for modelling OS for the 1 prior subgroup on the basis of the information criteria and the above extrapolations.

To derive the OS curve for BORT+DEX the company first derives a smooth curve for LEN+DEX by applying the 0.0023 weekly hazard of the delayed exponential from week 0; i.e. the delayed exponential is "non-delayed" for LEN+DEX. The hazard ratio of 3.11 for BORT+DEX is applied to this to yield an estimated 0.0073 weekly hazard. This 0.0073 weekly hazard is applied for BORT+DEX as graphed below.

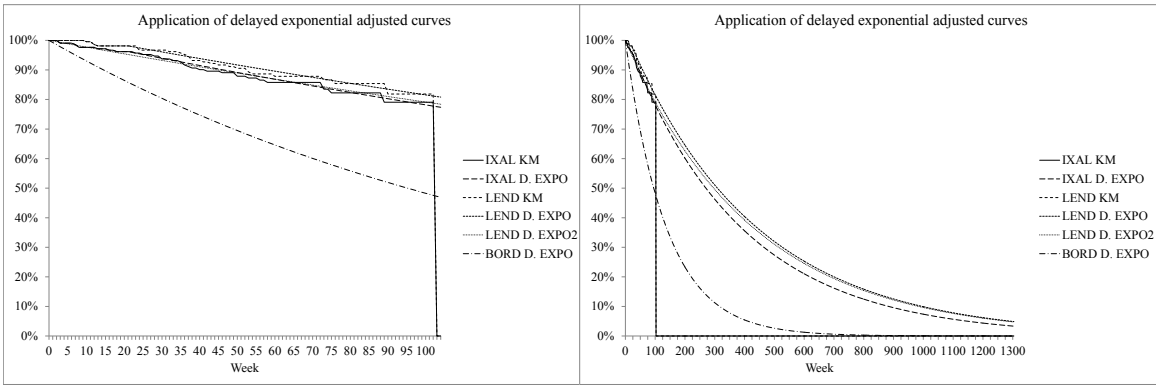


Figure 31: 1 Prior: Company base case OS curves: Delayed exponentials

Applying the delayed exponential for IXA+LEN+DEX, IXAL D. EXPO in the above, and the "non-delayed" delayed exponential for LEN+DEX, LEND D. EXPO2, results in similar curves for both arms during the prior of the TMM-1 trial despite the company hazard ratio being in favour of LEN+DEX.

The application of the 3.11 hazard ratio and resulting 0.0073 weekly hazard for BORT+DEX to the LEN+DEX "non-delayed" delayed exponential results in a very much poorer survival curve as would be anticipated with few patients surviving beyond 10 years with BORT+DEX.

5.2.6.6 Overall Survival curves: 2+ Prior subgroup

The economic model provides the following unadjusted and adjusted curves for the 2+ prior subgroup, with the AIC and BIC values being taken from appendix 11 of the company submission and the company response to the ERG clarification questions.

Table 50: 2+ Prior: Unadjusted parameterised OS curve

	Expo	Weib	Gomp	LogL	LogN	Gamm
IXAL Tx	-0.470	0.373	-0.479	0.378	0.429	0.423
Constant	-4.145	3.810	-4.402	3.654	3.878	3.882
Gamma		0.255	0.033			
Sigma				0.314	0.393	0.352
Kappa						0.082
AIC	537.32	535.86	537.89	535.52	534.73	537.32
BIC	544.70	546.94	548.97	546.60	545.81	544.70

Table 51: 2+ Prior: Adjusted parameterised OS curves

	Expo	Weib	Gomp	LogL	LogN	Gamm
IXAL Tx	-0.501	0.395	-0.509	0.403	0.444	0.433
Age 65+	0.814	-0.634	0.819	-0.651	-0.690	-0.681
Constant	-4.627	4.180	-4.897	4.019	4.248	4.253
Gamma		0.259	0.034			
Sigma				0.326	0.373	0.264
Kappa						0.212
AIC and BIC of appendix 11						
AIC	531.75	530.15	532.23	529.30	529.85	531.22
BIC	542.83	544.93	547.00	544.08	544.62	549.69
AIC and BIC supplied at 2nd clarification						
AIC	n.a.	531.75	530.15	529.30	532.23	529.85
BIC	n.a.	542.83	544.93	544.08	547.00	544.62

The AIC and BIC of the unadjusted curves are superior to those of the adjusted curves. The company applies the adjusted curves. Of these the lowest AIC value of 529.30 occurs with the log logistic but this is little different from the values for the log normal. The lowest BIC value occurs with the Weibull. The company applies the Weibull for the base case on the basis of the extrapolated values being more credible.

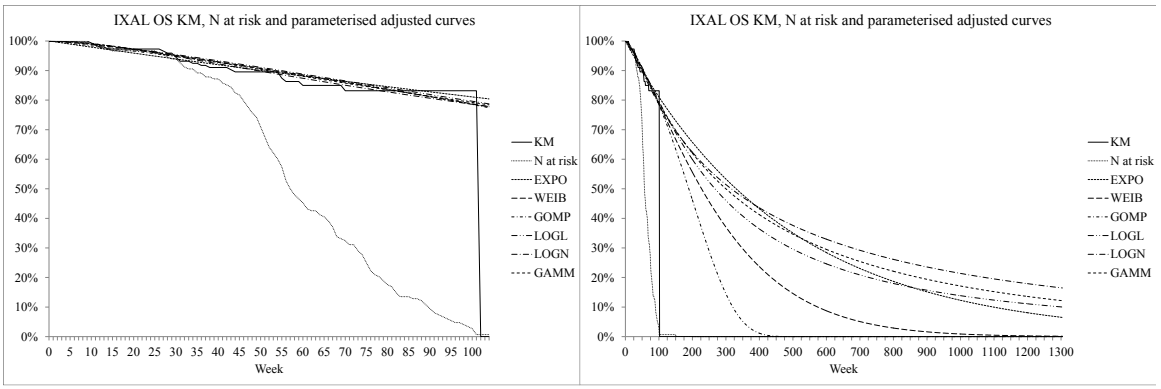


Figure 32: 2+ Prior: IXA+LEN+DEX OS KM, N at risk and adjusted parameterised curves

For IXA+LEN+DEX there is limited separation between the parameterised curves up to week 52, but some degree of separation becomes apparent by week 102. The exponential has risen above the other curves with the Weibull being towards the bottom of the range. This continues during the period of extrapolation with the exponential suggesting a little over 6% survive at the end of the 25 year time horizon, while the Weibull suggests that fewer than 1% survive after around 18 years.

The parallel curves for the LEN+DEX arm are as below with a similar pattern being observed.

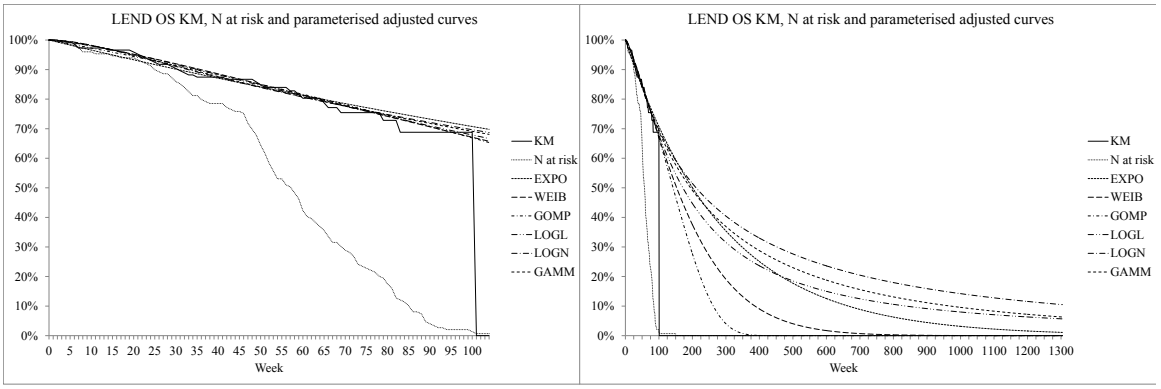


Figure 33: 2+ Prior: LEN+DEX OS KM, N at risk and adjusted parameterised curves

This results in the following Weibulls being applied in the company base case for the 2+ prior subgroup.

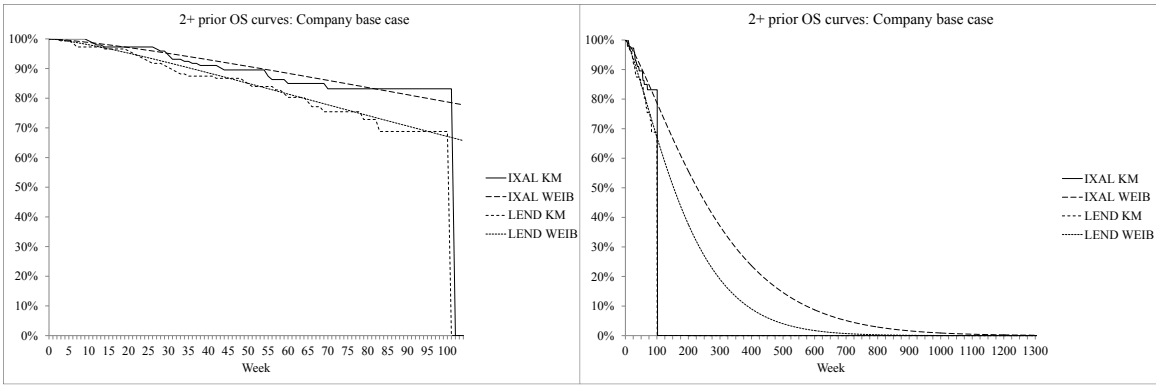


Figure 34: 2+ Prior: Weibull OS curves

5.2.6.7 Progression Free Survival curves: 1 Prior subgroup

The economic model provides the following unadjusted and adjusted curves for the 1 prior subgroup, with the AIC and BIC values being taken from appendix 11 of the company submission and the company response to the ERG clarification questions.

Table 52: 1 Prior: Unadjusted parameterised PFS curve

	Expo	Weib	Gomp	LogL	LogN	Gamm
IXAL Tx	-0.101	0.088	-0.110	0.059	0.046	0.056
Constant	-3.233	3.101	-3.431	2.835	2.879	2.941
Gamma		0.209	0.028			
Sigma				0.353	0.238	0.163
Kappa						0.215
AIC	1442.41	1435.73	1441.03	1433.62	1431.73	1433.38
BIC	1450.52	1447.88	1453.18	1445.78	1443.88	1449.59

Table 53: 1 Prior: Adjusted parameterised PFS curves

	Expo	Weib	Gomp	LogL	LogN	Gamm
IXAL Tx	-0.100	0.089	-0.114	0.043	0.028	0.064
ISS Stage III	0.627	-0.511	0.634	-0.540	-0.548	-0.540
ECOG 2	0.656	-0.615	0.739	-0.586	-0.579	-0.611
Prim.Refrac.	-1.023	0.818	-1.028	0.801	0.719	0.793

	Expo	Weib	Gomp	LogL	LogN	Gamm
Constant	-3.293	3.140	-3.528	2.884	2.928	3.073
Gamma		0.230	0.033			
Sigma				0.385	0.216	-0.023
Kappa						0.593
AIC	1423.56	1414.99	1421.00	1415.57	1416.96	1415.72
BIC	1443.82	1439.30	1445.31	1439.88	1441.27	1444.09

The AIC and BIC of the adjusted curves are somewhat superior to those of the unadjusted curves. The company base case applies the adjusted curves.

In line with the adjusted OS curves the adjusted PFS curves include ISS Stage III as a covariate, but also add ECOG 2 status and primary refractory status as covariates.

For the adjusted curves the Weibull has the lowest AIC and the lowest BIC. The company applies the generalised gamma for the base case which has a similar AIC to the Weibull but a higher BIC. It is not obviously justified to prefer the gamma over the Weibull.

The graphs of the adjusted curves for IXA+LEN+DEX are as below.

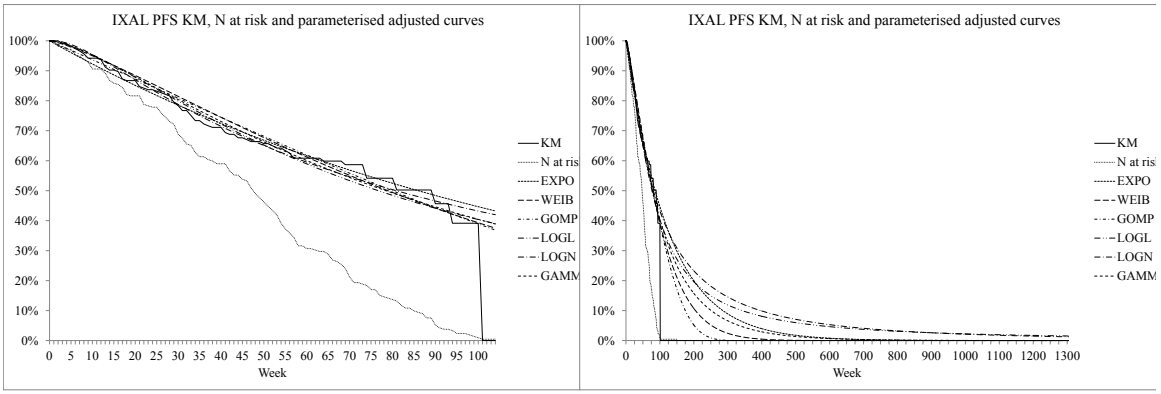


Figure 35: 1 Prior: IXA+LEN+DEX PFS KM, N at risk and adjusted parameterised curves

The graphs of the adjusted curves for LEN+DEX are as below.

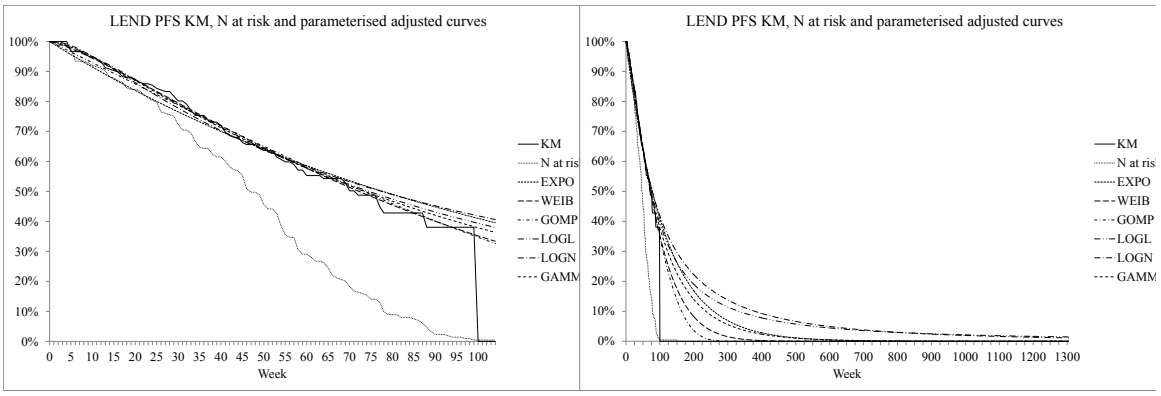


Figure 36: 1 Prior: LEN+DEX PFS KM, N at risk and adjusted parameterised curves

The gamma is the curve third from the bottom during the extrapolation period for both IXA+LEN+DEX and LEN+DEX.

To estimate the PFS curve for BORT+DEX the company applies the NMA estimate of the hazard ratio of 1.059 from the all patient data to the hazards of the LEN+DEX curve as graphed below.

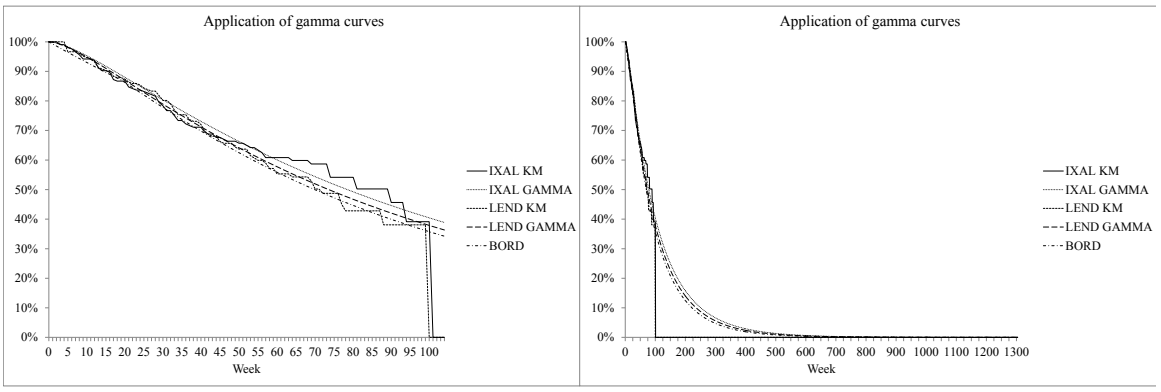


Figure 37: 1 Prior: Company base case PFS curves: Generalised gammas

5.2.6.8 Progression Free Survival curves: 2+ Prior subgroup

The economic model provides the following unadjusted and adjusted curves for the 2+ prior subgroup, with the AIC and BIC values being taken from appendix 11 of the company submission and the company response to the ERG clarification questions.

Table 54: 2+ Prior: Unadjusted parameterised PFS curve

	Expo	Weib	Gomp	LogL	LogN	Gamm
IXAL Tx	-0.544	0.469	-0.560	0.483	0.485	0.485

	Expo	Weib	Gomp	LogL	LogN	Gamm
Constant	-2.948	2.857	-3.093	2.552	2.574	2.553
Gamma		0.199	0.022			
Sigma				0.356	0.216	0.233
Kappa						-0.061
AIC	988.94	985.30	989.57	983.12	979.77	981.75
BIC	996.33	996.38	1000.65	994.20	990.85	996.53

Table 55: 2+ Prior: Adjusted parameterised PFS curves

	Expo	Weib	Gomp	LogL	LogN	Gamm
IXAL Tx	-0.533	0.475	-0.571	0.480	0.480	0.474
Light Mel.	0.479	-0.406	0.489	-0.528	-0.557	-0.584
Constant	-3.053	2.942	-3.210	2.660	2.692	2.601
Gamma		0.205	0.024			
Sigma				0.374	0.192	0.255
Kappa						-0.262
AIC	986.00	981.96	986.42	977.86	973.86	975.51
BIC	997.08	996.73	1001.20	992.63	988.64	993.98

The AIC of the adjusted curves are somewhat superior to the unadjusted, but the BIC are more similar. The company base case applies the adjusted curves.

For the adjusted curves the log normal has the lowest AIC and the lowest BIC but this is not applied due to its long tail. The company applies the generalised gamma for the base case which has the lowest AIC and BIC of the curves, excluding the log normal and the log logistic.

The graphs of the adjusted curves for IXA+LEN+DEX are as below.

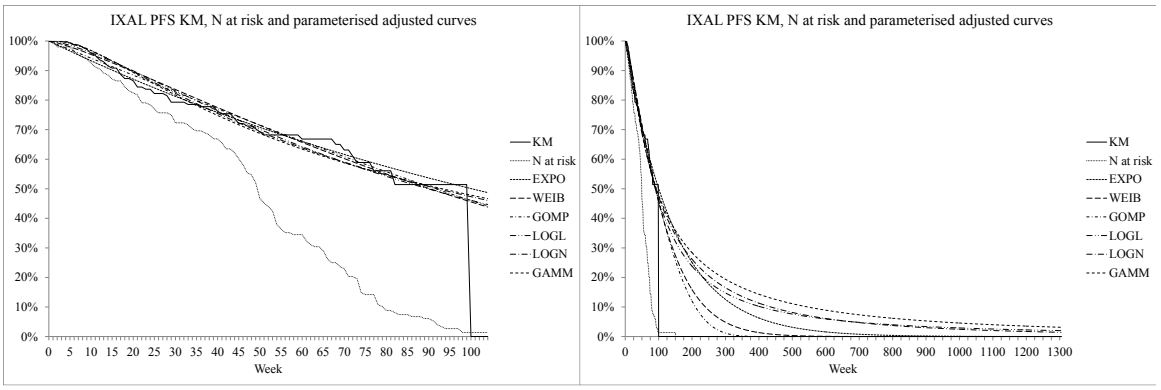


Figure 38: 2+ Prior: IXA+LEN+DEX PFS KM, N at risk and adjusted parameterised curves

The graphs of the adjusted curves for LEN+DEX are as below.

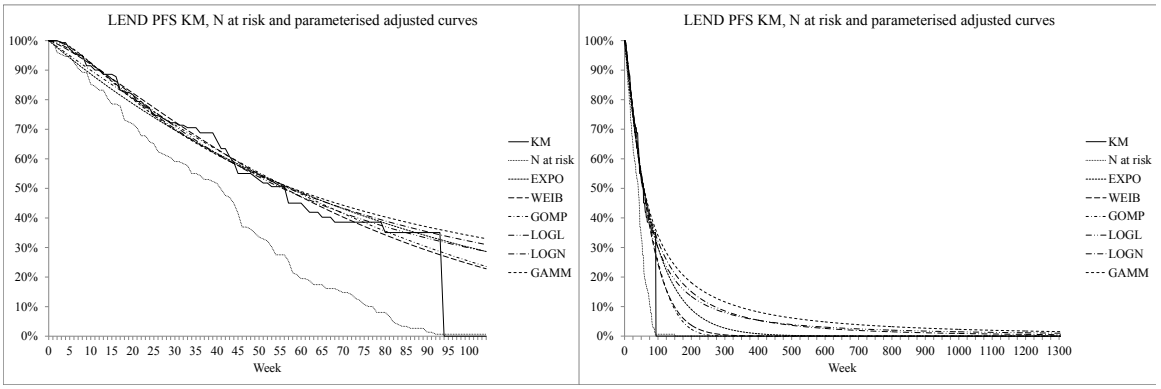


Figure 39: 2+ Prior: LEN+DEX PFS KM, N at risk and adjusted parameterised curves

The gamma is the uppermost curve for both IXA+LEN+DEX and LEN+DEX during the extrapolation period.

These curves are constrained to be no greater than the applied OS curve, as shown previously in Figure 27 and Figure 28.

5.2.6.9 Time on treatment (ToT): 1 Prior subgroup

The economic model provides the following unadjusted and adjusted curves for the 1 prior subgroup, with the AIC and BIC values being taken from appendix 11 of the company submission and the company response to the ERG clarification questions. Note

that these parameterisations are based upon time being measured in weeks rather than in months.

Table 56: 1 Prior: Unadjusted parameterised ToT curves

	Expo	Weib	Gomp	LogL	LogN	Gamm
IXAL Tx	0.039	-0.031	0.032	-0.094	-0.157	-0.027
Constant	-4.694	4.603	-4.897	4.342	4.433	4.609
Gamma		0.152	0.006			
Sigma				0.303	0.349	-0.178
Kappa						1.047
AIC	2228.32	2225.07	2226.41	2227.17	2242.23	2227.05
BIC	2236.41	2237.21	2238.56	2239.31	2254.37	2243.24

Table 57: 1 Prior: Adjusted parameterised ToT curves

	Expo	Weib	Gomp	LogL	LogN	Gamm
IXAL Tx	0.023	-0.014	0.012	-0.089	-0.162	-0.008
ISS Stage III	0.634	-0.553	0.643	-0.609	-0.611	-0.545
Constant	-4.776	4.671	-4.984	4.419	4.516	4.677
Gamma		0.157	0.007			
Sigma				0.316	0.343	-0.187
Kappa						1.055
AIC	2220.04	2216.41	2217.88	2219.22	2236.81	2218.37
BIC	2232.18	2232.60	2234.07	2235.41	2253.00	2238.61

The AIC and the BIC of the adjusted curves are somewhat superior to the unadjusted curves. The company base case applies the adjusted curves.

The Weibull has the lowest AIC and its BIC is only marginally above that of the exponential. The company base case applies the Weibull, but as graphed below this is little different for both IXA+LEN+DEX and LEN+DEX. It should be recalled that the gamma PFS curve is applied in the company base case despite its AIC and BIC, and it might be anticipated that the PFS and ToT curve would have similar functional forms.

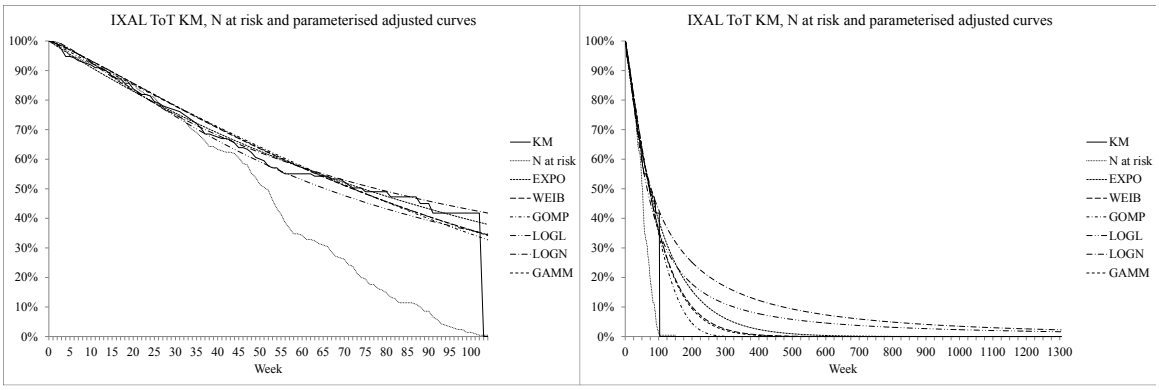
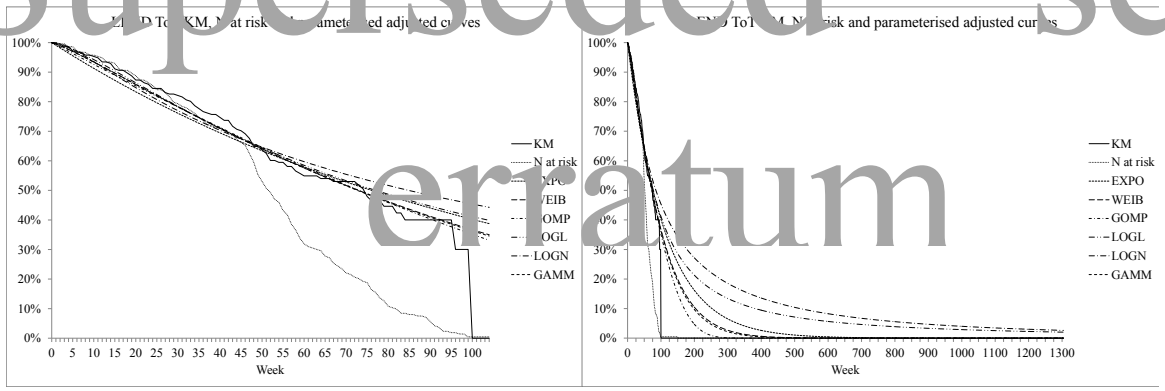


Figure 40: 1 Prior: IXA+LEN+DEX ToT KM, N at risk and adjusted parameterised curves

The graphs of the adjusted curves for LEN+DEX are as below.

Figure 41: 1 Prior: LEN+DEX ToT KM, N at risk and adjusted parameterised curves



The gompertz is the lowest curve for both IXA+LEN+DEX and LEN+DEX. The Weibull and the gamma are the pair of curves lying above this, and are little different from one another.

The BORT+DEX arm is assumed to have the same ToT curve as the LEN+DEX arm despite being estimated to have an inferior PFS curve to the LEN+DEX arm. In the absence of alternative data the more natural assumption might have been to apply the PFS hazard of 1.059 to the LEN+DEX ToT curve. BOR+LEN_DEX is only administered for

8 three week cycles, which curtails its ToT curve to 24 weeks[9]. Note that the Weibull for IXA+LEN+DEX lies slightly below that for LEN+DEX.

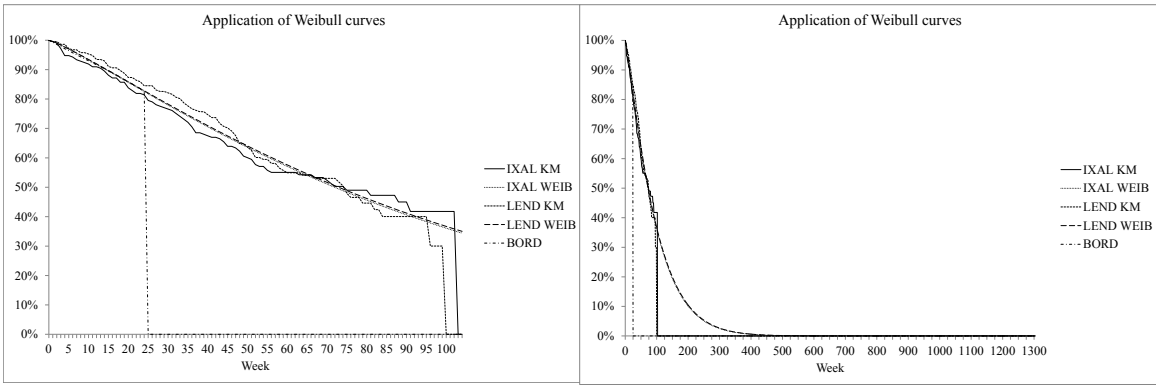


Figure 42: 1 Prior: Company base case ToT curves: Weibulls

5.2.6.10 Time on treatment (ToT): 2+ Prior subgroup

The economic model provides the following unadjusted and adjusted curves for the 1 prior subgroup, with the AIC and BIC values being taken from appendix 11 of the company submission and the company response to the ERG clarification questions.

Table 58: 2+ Prior: Unadjusted parameterised ToT curves

	Expo	Weib	Gomp	LogL	LogN	Gamm
IXAL Tx	-0.312	0.523	0.308	0.168	0.139	0.249
Constant	-4.476	4.497	-4.377	4.113	4.153	4.407
Gamma		-0.044	-0.003			
Sigma				0.108	0.506	0.211
Kappa						0.680
AIC	1542.37	1544.05	1543.66	1543.55	1547.47	1545.33
BIC	1549.75	1555.13	1554.74	1554.64	1558.55	1560.11

Table 59: 2+ Prior: Adjusted parameterised ToT curves

[9] Or rather 25 weeks in the model given half cycle correction.

	Expo	Weib	Gomp	LogL	LogN	Gamm
IXAL Tx	-0.307	0.315	-0.304	0.368	0.388	0.338
Light Myel.	0.500	-0.514	0.497	-0.615	-0.633	-0.557
Renal Dis.	0.472	-0.484	0.464	-0.489	-0.556	-0.502
Constant	-4.663	4.683	-4.581	4.314	4.369	4.616
Gamma		-0.032	-0.003			
Sigma				0.129	0.489	0.173
Kappa						0.727
AIC	1533.40	1535.23	1534.95	1535.21	1540.18	1536.64
BIC	1548.18	1553.70	1553.42	1553.68	1558.65	1558.80

The AIC of the adjusted curves are somewhat superior to the unadjusted curves, and the BIC are also a bit better. The company base case applies the adjusted curves.

Of the adjusted curves the exponential has the lowest AIC and the lowest BIC. The company applies the exponential in the base case. It should be borne in mind that the generalised gamma PFS curves are applied in the company base case and that the ToT curve rises above the PFS curve for LEN+DEX between week 21 and week 84.

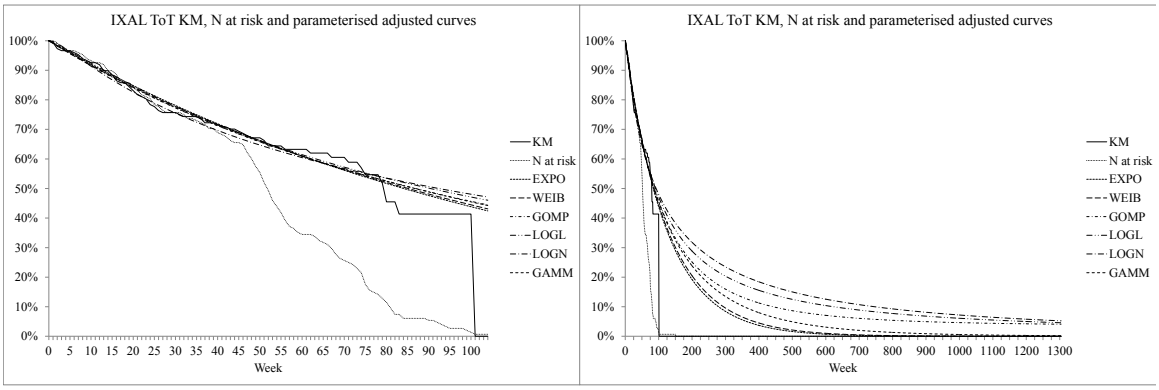


Figure 43: 2+ Prior: IXA+LEN+DEX ToT KM, N at risk and adjusted parameterised curves

The graphs of the adjusted curves for LEN+DEX are as below.

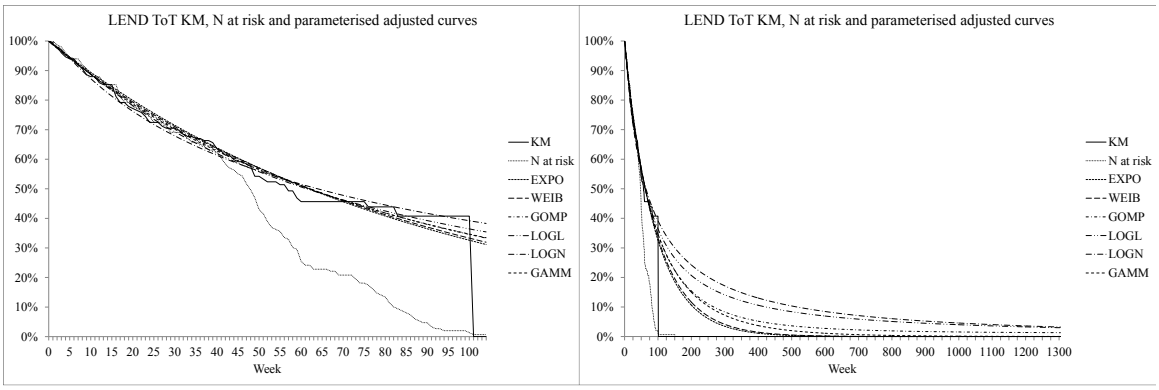


Figure 44: 2+ Prior: LEN+DEX ToT KM, N at risk and adjusted parameterised curves

The exponential is the lowest curve for both IXA+LEN+DEX and LEN+DEX. The ToT curve has no impact upon QALYs[10] but determines the direct drug costs.

5.2.7 Health related quality of life

There are a number of aspects to the health related quality of life of the model:

- PFS and PPS quality of life values, with the PFS values being treatment specific
- Utility decrements for adverse events
- Utility decrements for new primary malignancies
- Utility decrements for being within 3 months of end of life
- Utility decrements for subcutaneous and intravenous administrations

The first four are estimated from TMM-1 EQ-5D data, with treatment specific response rate estimates contributing the calculation of the treatment specific PFS values.

[10] There is a minor impact in the BORT+DEX arm for the company base case due to the company applying a quality of life disutility for subcutaneous injections.

5.2.7.1 TMM-1 EQ-5D Quality of life data and regression

The company presents the results of a regression analysis of the TMM-1 trial EQ-5D data, pooled across the 1 prior and the 2+ prior groups. EQ-5D data was collected in TMM-1 4 weekly while patients remained on treatment and 12 weekly after progression.

Table 60: TMM-1 EQ-5D Quality of life data and regression

	Coef.	s.e.	p-value
Intercept	-1.245	0.038	<.0001
PR	0.122	0.056	0.029
SD	0.187	0.061	0.002
PPS	0.182	0.054	0.001
Hospitalisation	0.219	0.203	0.279
Grade 3/4 TEAE	0.055	0.036	0.129
New Primary Malignancy	0.713	0.052	<.0001
EOL 0-3 mths pre-death	0.378	0.081	<.0001

There is little else provided within the company submission. The hospitalisation coefficient does not appear to be used within the model.

5.2.7.2 PFS and PPS quality of life values

The regression coefficients are on the log scale and results in the following quality of life estimates for the main health states:

- VGPR+: 1- exp (-1.245) = 0.712
- PR: 1- exp (-1.245+0.122) = 0.674
- SD: 1- exp (-1.245+0.187) = 0.653
- PPS: 1- exp (-1.245+0.182) = 0.654

The company notes that the quality of life value for PPS is better than for SD and suggests that this is due to the benefits of subsequent lines of treatment.

These quality of life values can be weighted by the estimated treatment specific distributions between VGPR+, PR and SD to yield treatment specific PFS quality of life estimates[11].

Table 61: PFS QoL values

		1 prior subgroup				2+ prior subgroup	
		IXAL		LEND	BORD	IXAL	LEND
	Utility	NMA	Trial	Trial	NMA	Trial	Trial
VGPR+	0.712	47%	48%	46%	3%	59%	38%
PR	0.674	33%	34%	32%	86%	31%	41%
SD	0.653	15%	14%	16%	10%	10%	21%
PFS QoL	..	0.690	0.690	0.689	0.674	0.694	0.684

For the 1 prior subgroup the company chooses the TMM-1 trial BoR distribution for IXA+LEN+DEX PFS QoL value, which is marginally superior to that of the NMA. This seems reasonable and is aligned with the company approach to modelling the OS, PFS and ToT curves for the 1 prior subgroup. The resulting PFS QoL of 0.690 for IXA+LEN+DEX is similar to the 0.689 for LEN+DEX. Both are somewhat superior to the estimate of 0.674 for BORT+DEX due to the low estimated proportion of VGPR+ in the BORT+DEX arm.

For the 2+ prior subgroup the PFS QoL of 0.694 for IXA+LEN+DEX is superior to the estimate of 0.684 for LEN+DEX due to the low proportion of VGPR+ in the LEN+DEX arm.

A common 0.654 quality of life value for PPS is applied to all treatments for both the 1 prior and the 2+ prior subgroups.

[11] Note that these do not sum to 100% due to around 5% being estimated to have a BoR of progressive disease or PPS. The weighting effectively adjusts these percentages so that they sum to 100% within the PFS health state.

5.2.7.3 Utility decrements for SC and IV administration

A quality of life decrement of -0.025 for subcutaneous administration is applied to patients in the BORT+DEX arm. This is drawn from two unspecified previous assessments for lung cancer treatments and reportedly brought into TA338[64] and TA427.[65] This quality of life decrement is not limited to the days or weeks when BORT+DEX is actually administered and is applied over the entire 3 week duration of each cycle in the BORT+DEX arm.

In other words, patients receiving BORT+DEX lose 4% of their quality of life due to the subcutaneous injections associated with BORT+DEX over their entire treatment period.

5.2.7.4 Utility decrements due to SAEs

The quality of life loss associated with SAEs is derived from the company EQ-5D regression coefficient of 0.055 and is assumed to be the loss that would be suffered by a patient in VGFR+:

- exp (-1.245) - 1- exp (-1.245+0.055) = 0.712 – 0.696 = 0.016

Similarly, the decrement for new primary malignancies applies the company EQ-5D regression coefficient of 0.713:

- exp (-1.245) - 1- exp (-1.245+0.713) = 0.712 – 0.412 = 0.300

The quality of life estimates are coupled with mean durations in days within the TMM-1 trial and the annual adverse event rates to provide estimates of the treatment specific quality of life SAE decrement for those remaining on treatment.

Table 62: SAE quality of life decrements

	Disutility	Days	Years	IXAL	LEND	BORD
Anaemia	-0.016	42	0.12	12%	18%	38%
Cardiac failure		11	0.03	3%	2%	4%
Deep vein thrombosis		11	0.03	1%	1%	1%
Diarrhoea		31	0.09	8%	2%	16%
Fatigue		63	0.17	4%	3%	23%
Upper respiratory tract infection/Pulmonary		15	0.04	1%	1%	3%

	Disutility	Days	Years	IXAL	LEND	BORD
Ischaemic heart disease		4	0.01	1%	1%	0%
Nausea		21	0.06	2%	0%	1%
Neutropenia		15	0.04	46%	37%	22%
Peripheral neuropathy		50	0.14	0%	1%	29%
Pneumonia		20	0.05	11%	12%	20%
Pulmonary embolism		57	0.15	2%	2%	1%
Rash-related		26	0.07	6%	2%	2%
Renal failure		37	0.10	2%	5%	0%
Thrombocytopaenia		21	0.06	23%	7%	62%
Vomiting		5	0.01	1%	1%	3%
New primary malignancy	-0.300	40	0.11	0%	1%	1%
QoL				-0.00139	-0.00128	-0.00345

While the adverse events are not a driver of results it may be questionable to apply a -0.016 disutility for all SAEs other than new primary malignancy.

5.2.8 Resources and costs

5.2.8.1 Direct drug costs

The direct drug unit costs are as follows.

Table 63: Direct drug costs

	Admin	Pack	Units	per unit	mg/unit
Ixazomib	Oral	£6,336	3	£2,112	4
Bortezomib	SubCut	£762	1	£762	3.5
Lenalidomide	Oral	£4,368	21	£208	25
Dexamethasone	Oral	£49	50	£1	2

The model contains dosing intensities of 93% for IXA+LEN+DEX and 95% for LEN+DEX estimated from the TMM-1 trial. In the absence of data the dosing intensity for BORT+DEX is assumed to be 100%. Due to how the model estimates the dose per patient and rounds up to integer values, for the base case these dosing intensities appear to be irrelevant. But they may affect some of the sensitivity analyses and scenario analyses. Given the lack of data for BORT+DEX it is questionable whether they should be applied at all, and it may be better to set all dosing intensity values to 100%. As they do not affect the base cases[12] and BORT+DEX has been assumed to have 100% dosing intensity, they are not presented in what follows and are not applied in the ERG exploratory base cases of section 5.4.

The bortezomib dose is based upon a requirement of $1.3mgm^{-2}$ and a body surface area of $1.87m^2$.

Table 64: Dosing schedule and cost per treatment cycle at list prices

	Cyc wks	Days	N Days	Dose (mg)	Unit/adm	Unit/Cyc	Cost
Ixazomib	4	1, 8, 15	3	4	1	3	£6,336
Lenalidomide		1 to 21	21	25	1	21	£4,368
Dexamethasone		1,8,15,22	4	40	20	76	£74
Total							**£10,778**
Lenalidomide	4	1 to 21	21	25	1	21	£4,368
Dexamethasone		1,8,15,22	4	40	20	76	£74
Total							**£4,442**
Bortezomib	3	1,4,8,11	4	2.43	0.69	4	£3,050
Dexamethasone		1,2,4,5,8,9,11,12	8	20	10	80	£78
Total							**£3,128**

[12] There may be some minimal effect upon the dexamethasone costs but this is inconsequential.

Within the IXA+LEN+DEX arm the £6,336 cost of ixazomib equates to an annual cost of £[redacted]. The additional LEN+DEX direct drug costs annualise to £57,951, subject to the complex lenalidomide PAS as outlined below. Taking these together gives an annual cost of £[redacted].

Treatment with IXA+LEN+DEX and LEN+DEX is ongoing for the duration of the ToT curve. Treatment with BORT+DEX is determined by the LEN+DEX ToT curve, limited to a maximum of nine 3 week cycles.

Lenalidomide has a complex PAS, with its drug costs being refundable for patients who remain on treatment after 26 treatment cycles. The model assumes that lenalidomide costs are not incurred after 26 four week treatment cycles in both the IXA+LEN+DEX arm and the LEN+DEX arm.

Bortezomib also has a complex PAS. The model contains the facility for the costs of bortezomib among those progressing before the 4th treatment cycle to be refunded. But during this period within the company base case the BORT+DEX PFS curve is constrained by the OS curve, none are modelled as progressing and as a consequence none of the bortezomib costs are refunded.

The direct drug costs are incurred at the start of each treatment cycle: 4 weekly for IXA+LEN+DEX and LEN+DEX and 3 weekly for BORT+DEX. This is reasonable for ixazomib and lenalidomide given their pack size. It will be an overestimate for bortezomib if not all patients complete each treatment cycle.

5.2.8.2 Drug administration costs

The company states that because ixazomib, lenalidomide and dexamethasone are oral therapies and bortezomib is subcutaneous no administration costs are applied.

The company only applies administration costs for the IV therapies that are included in the basket of therapies applied subsequent to progression.

5.2.8.3 PFS initial and ongoing visit costs

The first cycle is associated with 3 outpatient visits and a large number of tests and investigations. This drops to only one visit per cycle thereafter, two full blood counts and two blood chemistry panels. These are costed using NHS reference costs as per the codes below.

Table 65: PFS initial and ongoing visit costs

	Description	Code	Cost	1st cyc.	Sub cyc.
OP visit	Medical Oncology	370	£159	3	1
Full blood count	Haematology	DAPS05	£3	1	2
Bloods - chemistry panel	Clinical Biochemistry	DAPS04	£1	1	2
Bloods - FREELITE test	Immunology	DAPS06	£5	1	0
Bloods - immunofixation	Immunology	DAPS06	£5	1	0
Bloods - SPEP	Clinical Biochemistry	DAPS04	£1	1	0
Bone test - X-Ray	Dexamethasone Scan	RA15Z	£69	1	0
Bone marrow biopsy	Diag. Bone Marrow Extraction	SA33Z	£497	1	0
C-reactive protein	Immunology	DAPS06	£5	1	0
Serum albumin	Clinical Biochemistry	DAPS04	£1	1	0
Serum LDH	Clinical Biochemistry	DAPS04	£1	1	0
Serum β2 microglobulin	Clinical Biochemistry	DAPS04	£1	1	0
Urine - immunofixation	Cytology	DAPS01	£7	1	0
Urine - UPEP	Cytology	DAPS01	£7	1	0
Total cost				£1,081	£167

5.2.8.4 Costs due to SAEs

The costs due to SAEs are based upon the proportion of SAEs that are treated, and the balance between treatment in GP practice and in hospital. Those that are treated in GP practice are assumed to be treated at a single visit at a cost of £46 as drawn from the PSSRU Unit Costs of Health and Social Care.[66] Those that are treated in hospital are costed based upon the average of Elective IP, Non-elective IP, Day case and routine Day

and night admission NHS reference costs within what seem to be a reasonable range of currency codes, though the ERG has not reviewed this in any depth.

Table 66: SAE costs per event

		GP		Hospital		
	Treated	Prop.	Cost	Prop.	Cost	Cost
Anaemia	96%	6%		94%	£1,145	£1,036
Cardiac failure	100%	0%		100%	£2,038	£2,038
Deep vein thrombosis	100%	1%		99%	£627	£622
Diarrhoea	98%	1%		99%	£1,120	£1,087
Fatigue	100%	100%		0%	£1,120	£46
Upper respiratory tract infection/Pulmonary	100%	50%		50%	£1,127	£586
Ischaemic heart disease	100%	50%		50%	£1,700	£873
Nausea	98%	100%		0%	£1,120	£45
Neutropenia	57%	2%	£46	98%	£715	£400
Peripheral neuropathy	82%	2%		98%	£1,253	£1,008
Pneumonia	100%	0%		100%	£2,066	£2,066
Pulmonary embolism	100%	0%		100%	£1,571	£1,571
Rash-related	100%	100%		0%	£1,120	£46
Renal failure	100%	0%		100%	£1,571	£1,571
Thrombocytopaenia	63%	1%		99%	£643	£402
Vomiting	98%	1%		99%	£1,120	£1,087
New primary malignancy	100%	0%		100%	£1,927	£1,927

These are coupled with the treatment specific rates of SAEs to yield the treatment specific SAE related costs on an annualised basis which are then converted to a cost per weekly cycle.

Table 67: SAE costs by treatment

	Cost	IXAL	LEND	BORD
Anaemia	£1,036	12%	18%	38%
Cardiac failure	£2,038	3%	2%	4%

	Cost	IXAL	LEND	BORD
Deep vein thrombosis	£622	1%	1%	1%
Diarrhoea	£1,087	8%	2%	16%
Fatigue	£46	4%	3%	23%
Upper respiratory tract infection/Pulmonary	£586	1%	1%	3%
Ischaemic heart disease	£873	1%	1%	0%
Nausea	£45	2%	0%	1%
Neutropenia	£400	46%	37%	22%
Peripheral neuropathy	£1,008	0%	1%	29%
Pneumonia	£2,066	11%	12%	20%
Pulmonary embolism	£1,571	2%	2%	1%
Rash-related	£46	6%	2%	2%
Renal failure	£1,571	2%	5%	0%
Thrombocytopaenia	£402	23%	7%	62%
Vomiting	£1,087	1%	1%	3%
New primary malignancy	£1,927	0%	1%	1%
Annualised cost		£871	£841	£1,764
Cost per Cycle		£16.66	£16.10	£33.72

Note that the costs for BORT+DEX are only applied while patients are receiving treatment, this being capped at a maximum of 9 three week cycles.

5.2.8.5 Hospitalisation costs

Treatment specific PFS hospitalisation rates and PPS hospitalisation rates are calculated using patient count data and patient years of follow-up data from the TMM-1 trial. Length of stay data is available for all four categories of costs, with only the palliative care costs being conditioned by an average length of stay of 0.87. Costs per admission are drawn from NHS reference costs:

- Acute care: Malignant disorders of lymphatic/Haem: SA17G-H: £1,120

- Palliative care: Inpatient specialist care 19+ SA01A, SD03A: £187
- Critical care: Non-specific adult XC01Z-XC07Z: £1,306
- Hospice care: Day case/ Reg. Night: Inpatient palliative: SD02A: £160 * 0.87 = £140

Table 68: Hospitalisation costs

		PFS patient numbers and rates				PPS patient numbers and rates			
	Cost	IXAL	Annual	LEND	Annual	IXAL	Annual	LEND	Annual
Years FU		383.41		371.65		59.41		79.07	
Acute	£1,120	87	23%	96	26%	17	29%	15	19%
Palliative	£187	7	2%	12	3%	1	2%	3	4%
ICU	£1,306	8	2%	5	1%	2	3%	5	6%
Hospice	£140	10	3%	10	3%	0	0%	1	1%
Cost			£288		£317		£368		£304

The annualised costs are converted to per cycle costs within the model.

The modelling intention may have been to differentiate costs by arm and apply the LEN+DEX costs to BORT+DEX. There may be a programming error causing the LEN+DEX costs to be applied in the IXA+LEN+DEX arm. But the submission in table 94 states that hospitalisation costs are only differentiated by the PFS/PPS split and not by treatment.

5.2.8.6 Concomitant medication costs

In contrast to the hospitalisation resource use data within the model, the number of patients receiving each concomitant medication is pooled across the arms of the TMM-1 trial due to there being no statistically significant difference between the two arms. The ERG did not ask for the patient numbers receiving each concomitant medication split by arm or by subgroup at clarification.

The TMM-1 patient numbers result in estimates of the percentage of patients receiving each concomitant medication. Coupled with unit drug costs these result in an estimate of an annual cost for concomitant medications of £1,613, or £30.93 per weekly cycle. These

costs are applied to those remaining in PFS in the IXA+LEN+DEX arm and in the LEN+DEX arm. They are also applied to those remaining in PFS in the BORT+DEX arm, including cycles after 24 weeks when those remaining in PFS are no longer treated with BORT+DEX. The ERG has not reviewed these costs in any detail. But it can be noted that the SmPC for lenalidomide recommends anti-thrombotics whereas as far as the ERG can see the SmPC for bortezomib does not.

The direct drug costs of most of the concomitant medications are reasonably small compared to the main drug costs. But subcutaneous enoxaparin or nadroparin was used by 25% of the TMM-1 patients. There is no administration costs applied to this. There is also no administration cost applied to the IV administrations of zoledronic and pamidronic acid. The concomitant medication cost estimate may be an underestimate.

The inclusion of the anti-thrombotics for BORT+DEX may slightly bias the analysis against BORT+DEX. Ongoing concomitant medication use after the 9th and final BORT+DEX cycle may also differ from that drawn from the TMM-1 trial.

5.2.8.7 PPS Costs

All patients incur the one off £1,081 treatment initiation cost when they progress.

Due to the proportions receiving other treatments subsequent to progression not being statistically significantly different between the arms, the TMM-1 data is pooled, with the number of patients receiving therapy in PPS during TMM-1 being 176. This is divided by the TMM-1 total patient number of 722 to yield an estimate of 24% of patients that will receive active therapy in PPS. This is an underestimate due to not all the 722 patients of TMM-1 having progressed.

The balance between PPS treatments is also taken from the TMM-1 trial but with panobinostat in conjunction with BORT+DEX being assumed to substitute for some TMM-1 treatments due to them not being funded in the NHS. This provides an estimate of a one off cost of £70,188 for each patient receiving active treatment PPS.

The above results in a one off mean cost per patient when progressing of £17,233. It is important to realise that this is incurred at progression, applies equally in all arms and is not linked to the duration of PPS. Due to it being applied as a one off cost to those

progressing it has only a limited impact upon the cost effectiveness results, much like end of life costs. As a consequence, due to time constraints the £70,188 estimate while appearing significant has not been reviewed in any detail by the ERG and this aspect is explored by the ERG through an illustrative scenario analysis.

The 76% of patients not receiving active PPS treatment are also assumed to be followed up on a ongoing monthly basis with an outpatient visit, blood count and blood chemistry panel at a cost of £163, or £41 per weekly cycle.

5.2.8.8 Terminal care costs

A unit cost of £10,670 for terminal care is taken from the 2015 PSSRU Unit Costs of Health and Social Care and is assumed to apply to 20% of patients to yield a terminal care cost of £2,134.

5.2.9 Cost effectiveness results

For the 1 prior subgroup the company base case estimates the following undiscounted PFS, PPS and OS and discounted QALYs and costs. The main elements that differ between the arms are presented. Adverse events and terminal care costs have been omitted for reasons of space but their effects are included in the totals.

Table 69: Company base case ICERs: 1 prior[13]

	Undisc. LY			QALYs			Costs			
	PFS	PPS	OS	PFS	PPS	Total	Drug	ConMed	Ongoing	Total
BORD	1.916	0.716	2.632	1.219	0.410	1.596	£28,057	£3,957	£3,981	£38,770
IXAL	2.168	5.007	7.175	1.415	2.547	3.932	[redacted]	£9,590	£15,725	[redacted]
Net	0.253	4.291	4.543	0.196	2.138	2.336	[redacted]	£5,633	£11,744	[redacted]
ICER										[redacted]

[13] Within the tables and figures of the economics, in order to economise on space IXA+LEN+DEX is abbreviated to IXAL, LEN+DEX is abbreviated to LEND and BORT+DEX is abbreviated to BORD.

Compared to BORT+DEX, IXA+LEN+DEX is estimated to result in an increase in progression free survival of 0.25 years. But the increase in post progression survival is enormously larger than this at 4.29 years and results in an overall survival gain of 4.54 years. The Company has not commented on this. The ERG believes that there is no plausibility for the considerable increase in PPS knowing that, by definition, at the time of progression most of patients will discontinue the treatment and since nothing in the known mechanism of action of proteasome inhibitors like ixazomib could explain this observation. Such results are observed with the use of novel immunotherapies such as pembrolizumab or nivolumab which acts by reactivating the tumour-specific cytotoxic T lymphocytes and therefore antitumour immunity but again are not realistic within the scope of proteasome inhibitors which directly exert their effect on tumour cells.

These survival gain are reflected in the balance of QALY gains, with the PPS gain of 2.138 QALYs dwarfing the PFS gain of 0.196 QALYs yielding a total net gain of 2.336 QALYs.

These QALY gains are associated with considerable additional direct drug costs of [redacted]. Concomitant medication costs and ongoing costs are also increased by £5,633 and £11,744 respectively. Total costs are [redacted] higher resulting in a company base case cost effectiveness estimate of [redacted] per QALY for the 1 prior group.

The probabilistic modelling estimates net costs of £181k, a net gain of 2.232 QALYs and a cost effectiveness of [redacted] per QALY for IXA+LEN+DEX compared to BORT+DEX.

[redacted]

Figure 45: 1 prior probabilistic modelling: Company base case

There is apparently no prospect of IXA+LEN+DEX being cost effective compared to BORT+DEX at a willingness to pay of £30k per QALY.

The company base case results for the 2+ prior group are as below.

Table 70: Company base case ICERs: 2+ prior

	Undisc. LY			QALYs			Costs			
	PFS	PPS	OS	PFS	PPS	Total	Drug	ConMed	Ongoing	Total
LEND	2.283	1.315	3.598	1.440	0.798	2.204	£73,941	£5,363	£8,805	£91,428
IXAL	3.535	1.776	5.311	2.174	1.033	3.174	[redacted]	£7,598	£9,378	[redacted]
Net	1.252	0.461	1.713	0.733	0.235	0.969	[redacted]	£2,234	£573	[redacted]
ICER										[redacted]

Compared to LEN+DEX, the gains from IXA+LEN+DEX are somewhat more muted and more slanted towards PFS where there is a gain of 1.25 years. But a survival gain of 0.46 years is also anticipated post progression, yielding an overall survival gain of 1.71 years. These survival gains translate into a total patient gain of 0.969 QALYs. Here, the much smaller increase in PPS seems more realistic and this greatly contrasts with the previously shown results in the 1 prior therapy population.

The results presented using the Company's estimates indicate that the total LY for IXAL is 7.175 for patients treated at second line while the total LY is 5.311 for those treated for third line and beyond, which is consistent. Conversely, the total LY is 2.632 for patients treated by BORT-DEX at second line and is 3.598 for those treated by LEN-DEX at 2+ prior line, which suggests that patients with a more advanced disease stage have a better survival compared to those treated from earlier stage. Again, there is no clinical plausibility on these results and the LY for BORT-DEX at second line appears to be strongly underestimated in line with the previous comments of the ERG in the clinical effectiveness.

The overall drug costs for the IXA+LEN+DEX arm for the 2+ prior group are higher than those for the 1 prior group. This is due to its superior Kaplan Meier curve for IXA+LEN+DEX. Large net costs result, with additional drug costs of [redacted] being anticipated. The other net cost impacts are relatively muted and the total impact is a net

cost of [redacted]. Given the 0.969 QALY gain the company base case cost effectiveness estimate is [redacted] per QALY for the 2+ prior group.

The probabilistic modelling estimates net costs of £[redacted], a net gain of 1.020 QALYs and a cost effectiveness of [redacted] per QALY for IXA+LEN+DEX compared to LEN+DEX.

[redacted]

Figure 46: 2+ prior probabilistic modelling: Company base case

There is apparently no prospect of IXA+LEN+DEX being cost effective compared to LEN+DEX at a willingness to pay of £30k per QALY.

5.2.10 Sensitivity analyses

The company conducts a range of sensitivity analyses based upon 95% confidence intervals, and presents the 10 most influential as below.

Table 71: Company sensitivity analyses: 10 most influential: 1 prior subgroup

	Lower	Upper
OS (NMA (HR)) - BORT+DEX v LEN+DEX HR	[redacted]	[redacted]
TOT (Adj) (Survival) - Treatment - Weibull	[redacted]	[redacted]
TOT (Adj) (Survival) - Constant - Weibull	[redacted]	[redacted]
Coefficient associated with utility regression - PD	[redacted]	[redacted]
Coefficient associated with utility regression - Intercept	[redacted]	[redacted]
TOT (Adj) (Survival) - ISS = Stage III - Weibull	[redacted]	[redacted]
PFS (NMA (HR)) - BORT+DEX v LEN+DEX HR	[redacted]	[redacted]
PFS (Adj) (Survival) - Treatment - Gamma	[redacted]	[redacted]
Coefficient associated with utility regression - PR	[redacted]	[redacted]
TOT (Adj) (Survival) - Gamma - Weibull	[redacted]	[redacted]

As would be expected, the OS hazard ratio is very influential. The ToT curves determine the direct drug costs and so are also influential. The regression quality of life coefficients and values also affect the analysis. All of the sensitivity analyses above suggest that IXA+LEN+DEX is not cost effective compared to BORT+DEX at conventional willingness to pay thresholds.

Table 72: Company sensitivity analyses: 10 most influential: 2+ prior subgroup

	Lower	Upper
OS (Adj) (Survival) - Treatment - Weibull	[redacted]	[redacted]
OS (Adj) (Survival) - Constant - Weibull	[redacted]	[redacted]
TOT (Adj) (Survival) - Treatment – Expon.	[redacted]	[redacted]
TOT (Adj) (Survival) - Constant – Expon.	[redacted]	[redacted]
OS (Adj) (Survival) - Age > 65 years - Weibull	[redacted]	[redacted]
TOT (Adj) (Survival) - Light chain myeloma - Expon.	[redacted]	[redacted]
TOT (Adj) (Survival) - Renal dysfunction - Expon.	[redacted]	[redacted]
PFS (Adj) (Survival) - Treatment - Gamma	[redacted]	[redacted]
Coefficient associated with utility regression - Intercept	[redacted]	[redacted]
PFS (Adj) (Survival) - Kappa - Gamma	[redacted]	[redacted]

The lower bound of the treatment coefficient suggest that LEN+DEX dominates IXA+LEN+DEX. Even at the upper bound the cost effectiveness of IXA+LEN+DEX is well above conventional willingness to pay thresholds. All of the sensitivity analyses above suggest that IXA+LEN+DEX is not cost effective compared to LEN+DEX at conventional willingness to pay thresholds.

The company also present a range of scenario analyses:

- SA01: Horizons of 15 years and 20 years
- SA02: Using the unadjusted rather than the adjusted parameterised curves
- SA03: Cap the ToT curve by the PFS curve rather than the OS curve
- SA04: Applying the other functional forms for PFS, OS and ToT

- SA05: Apply a 25% reduction to the IXA+LEN+DEX ToT curve relative to LEN+DEX
- SA06: ToT assuming that both those censored and those who discontinue in the TMM-1 trial should be modelled as ceasing treatment
- SA07: Using the 2nd interim data cut for PFS, OS and ToT with this also suggesting hazard ratios of 2.30 for OS and 1.06 for PFS for the 1+ prior population
- SA08: Using hazard ratios from the all studies NMA that used doses specific to the marketing authorisation for OS and for ORR, but the studies which included all doses for PFS for reasons of consistency.
- SA09: Quality of life values from TA171 and TA338
- SA10: Applying a £0 price for ixazomib
- SA11: For the 2+ prior group subtracting the LEN+DEX direct drug costs from the IXA+LEN+DEX costs
- SA12: For the 2+ prior group assuming that the LEN+DEX costs are the same in both arms regardless of the ToT curves

The full results of these are presented in table 109 (page 291) and table 112 (page 300) of the company submission. The ERG presents the subset that results show some sensitivity to or are of some interest.

Table 73: Company scenario analyses

	1 prior	2+ prior
Base case	[redacted]	[redacted]
SA02: Unadjusted curves	[redacted]	[redacted]
SA03: Cap ToT by PFS	[redacted]	[redacted]
SA04: OS exponential	[redacted]	[redacted]
SA04: OS Weibull	[redacted]	[redacted]
SA04: OS Gompertz	[redacted]	[redacted]
SA04: OS Log Normal	[redacted]	[redacted]
SA04: OS Log logistic	[redacted]	[redacted]

	1 prior	2+ prior
SA04: OS Gamma	[redacted]	[redacted]
SA04: PFS Weibull	[redacted]	[redacted]
SA04: PFS Gompertz	[redacted]	[redacted]
SA04: ToT exponential	[redacted]	[redacted]
SA04: ToT Weibull	[redacted]	[redacted]
SA04: ToT Gompertz	[redacted]	[redacted]
SA04: ToT Log normal	[redacted]	[redacted]
SA04: ToT Log logistic	[redacted]	[redacted]
SA04: ToT Gamma	[redacted]	[redacted]
SA05: 25% reduction in IXAL ToT curve	[redacted]	[redacted]
SA06: ToT based upon TMM-1 disc. and censored	[redacted]	[redacted]
SA07: 2nd interim data cut	[redacted]	[redacted]
SA08: NMA dose specific studies OS and BoR	[redacted]	[redacted]
SA08: NMA HRs applied for IXAL to LEND	[redacted]	[redacted]
SA09: TA171 QoL values	[redacted]	[redacted]
SA09: TA171 QoL values	[redacted]	[redacted]
SA10: £0 ixazomib price	[redacted]	[redacted]
SA11: Subtracting LEN+DEX direct drug costs	[redacted]	[redacted]
SA12: Same total LEN+DEX costs in both arms	[redacted]	[redacted]

Using the unadjusted curves has relatively little impact for the 1 prior group, but is more influential for the 2+ prior group.

The ToT PFS cap compared to the OS cap of the base case does not affect results, given the parameterised curves of the base case.

Results are general sensitive to the functional form chosen for overall survival and for ToT, and much less so to the functional form chosen for PFS.

The 2nd interim data cut is very detrimental to the 1 prior subgroup, but provides some benefit to the 2+ prior subgroup.

SA10 for the 1 prior group demonstrates that the ToT curve for IXA+LEN+DEX results in additional costs of LEN+DEX that are only barely justified by the additional PFS and additional OS at conventional willingness to pay thresholds. IXA+LEN+DEX does not provide sufficient additional PFS and OS at conventional thresholds to be considered cost effective even if ixazomib is free. This is not the case for the 2+ prior subgroup among whom within the company analyses ixazomib could be cost effective at conventional willingness to pay thresholds at a reduced cost. Note that the company is positioning ixazomib as being primarily for the 2+ prior subgroup.

5.2.11 Model validation and face validity check

The company conducted interviews with 5 UK clinicians who suggested that the proportions remaining on treatment with LEN+DEX after 26 cycles were too high, and supported this with a presentation of data that was apparently also presented at the 2012 ASH conference. It is unclear if this ToT extrapolation was presented alongside the PFS extrapolation. It was observed that the TMM-1 BoR of 72% was higher than the 61% of the MM-009 and MM-010 trials. The TMM-1 median PFS and ToT also exceeded those of the MM-009 and MM-010 trials.

The company highlights the difficulties of arriving at comparable survival estimates for BORT+DEX and suggests that the life years can only be compared with data for either a 2+ prior subgroup or an ITT patient group. Of the studies identified by the company these estimates range between the 2.25 years for a 2+ prior subgroup presented in TA380 to 3.14 years for the group presented in Fragoulakis et al (2013).[67]. The model estimate of 2.45 years for the 1 prior subgroup is towards the lower end of this range. It seems logical to expect the 1 prior subgroup survival to exceed that of both the 2+ prior subgroup and the ITT patient group. For it to be at the bottom end of the range identified by the company suggests that the model underestimates survival for the 1 prior subgroup in the BORT+DEX arm.

The company literature review also outlines a range of survival for LEN+DEX of between 4.20 years and 5.84 years, with the model suggesting 3.32 years for the 2+ prior subgroup.

In the opinion of the ERG the face validity of the modelled PFS and OS for the 1 prior subgroup is poor.

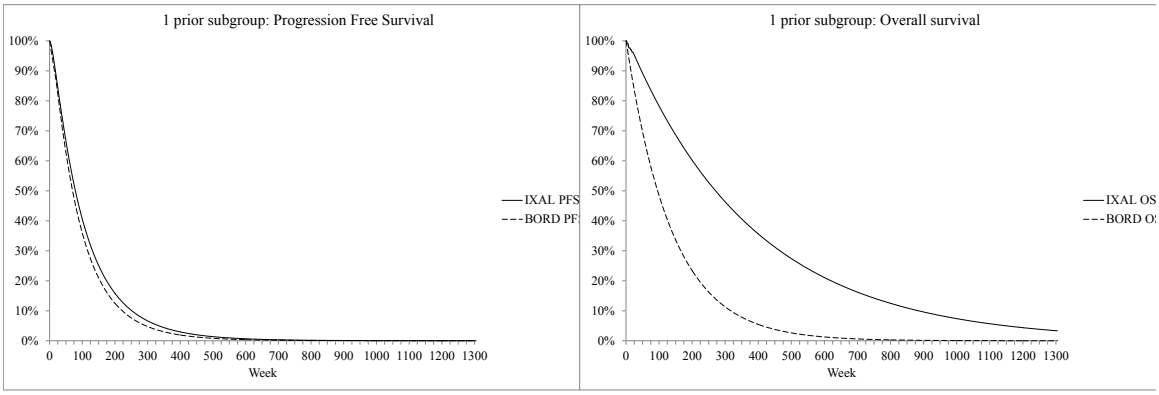


Figure 47: 1 Prior: Reiteration of the company base case OS and PFS curves

The company model anticipates only a moderate 0.25years PFS gain from IXA+LEN+DEX over BORT+DEX, but a very large 4.54 years OS gain. To the ERG this does not seem credible. Even with the revision to the handling of OS so that the 5 month KM data of the TMM-1 trial is applied in a like manner in both arms[14] the 0.25 years PFS gain is still dwarfed by a 4.30 years OS gain.

5.3 ERG cross check and critique

5.3.1 Base case results

The ERG has rebuilt the company deterministic model adopting the company assumptions and gets a good correspondence:

- [redacted] per QALY compared to [redacted] per QALY using the company model
- [redacted] per QALY compared to [redacted] per QALY using the company model

[14] The LEN+DEX KM OS hazards being conditioned by the 3.11 NMA OS HR for BORT+DEX in the BOR_DEX arm.

5.3.2 Data Inputs: Correspondence between written submission and sources cited

5.3.2.1 Split between PR and VGPR+ in the BORT+DEX arm

The quality of life values for PFS are in large part determined by the proportion of patients who are estimated to be in the very good VGPR+ health state. This is only 4% for BORT+DEX.

The company submission suggests that the response data for BORT+DEX is taken from the PANORAMA-1 trial. The economic model suggests that the proportion of PR patients with a VGPR+ response is taken from the APEX trial that compares monotherapy bortezomib with monotherapy dexamethasone as reported in Richardson et al (2005).[33] The model also states that the BORT+DEX patient numbers are assumed to be the same as those of bortezomib monotherapy.

Table 74: BORT+DEX company split between PR and VGPR+and SD and PD

	Company	Richardson et al (2005)	
	BORT+DEX	Bortezomib	Dexamethasone
N	..	315	312
N	..	315	312
CR or PR	56	121	56
CR - immuno fix -ve	2	20	2
PR (inc VGPR)	54	101	54
nCR - immuno fix +ve	..	21	3
Minimal response	25	25	52
No change	137	137	149
PD	22	22	41

The company has accidentally used the CR or PR and CR rates of dexamethasone rather than of bortezomib in its calculations. Furthermore, the VGPR+ category includes a wider group of patients than those with just CR. As a consequence, the company estimates for bortezomib monotherapy are biased on two counts.

It seems peculiar for the company to use the BoR rates for BORT+DEX from a bortezomib monotherapy trial. It is more appropriate to source them from trials that involve BORT+DEX in the treatment experienced such as the ENDEAVOR trial as reported in Dimopoulos et al (2016)[35]or the PANORAMA-1 trial as reported in San-Miguel et al (2014).[41]. Unfortunately San-Miguel et al do not report VGPR numbers. The ENDEAVOR trial was also not limited to the 1 prior patient group but rather recruited patients with 1 to 3 prior treatments. The patient numbers from the ENDEAVOR trial assuming that minimal response should be grouped with stable disease imply the following for BORT+DEX.

Table 75: Distribution of BoR for BORT+DEX: ENDEAVOR trial

	ENDEAVOR
VGPR+	133
PR	157
SD	106
PD	31

These patient numbers, when coupled with the company NMA ORR estimate, imply a patient distribution between SD, PR and VGPR+ for BORT+DEX that is similar to that observed among the 1-prior patient population in the TMM-1 trial. Applying the company quality of life estimates to these proportions suggests mean quality of life values for PFS of 0.690 for IXA+LEN+DEX, 0.689 for LEN+DEX and 0.688 for BORT+DEX. It is questionable whether the PFS quality of life value should be differentiated by treatment for the 1 prior subgroup modelling.

In the light of the above for the base case the ERG will apply the distribution implied by ENDEAVOR for BORT+DEX in the 1 prior group.

5.3.2.2 Quality of life values

The model also contains quality of life values from two previous assessments: TA171 and TA338, with TA338 having now been superseded by TA427.

Table 76: Quality of life values: Sensitivity analyses

	TA171	TA338/TA427
VGPR+	0.810	0.750
PR	0.810	0.750
SD	0.810	0.650
PD	0.640	0.610

In contrast to the TMM-1 regression analysis, the values of PD in both TA171 and TA338 are noticeably lower than those for PFS or SD. PD having a lower quality of life than SD is in line with the company literature review values reported for the MM-003 trial with and expert opinion. The values applied cross check as does the 0.025 decrement for IV or SC therapy with that reported in TA427 though the duration this is applied for in TA427 is not clear.

5.3.2.3 Dexamethasone costs

The cost per 50 pack of dexamethasone 2mg tablets is currently £43 on eMIMs and £52 on the BNF rather than the £49 of the model, but this may be within normal price variation. The ERG has not been able to find a price for 20mg dexamethasone tablets. The dexamethasone costs have minimal impact upon the model and the ERG has not revised this.

5.3.3 Data Inputs: Correspondence between written submission and electronic model

There is a reasonable correspondence between the written submission and the electronic model, and any sins are more of omission than commission.

5.3.4 ERG commentary on model structure, assumptions and data inputs

5.3.4.1 Extrapolation

The trial data is relatively immature particularly for overall survival, with a lot of extrapolation being required over the 25 year time horizon of the model. There is quite a strong argument for exploring a reduction of the treatment effects after the end of the trial

period, in line with the NICE methods guide. This has not been done and is not something that is simple to implement within the company model structure.

5.3.4.2 1 prior subgroup: IXA+LEN+DEX versus LEN+DEX

The company does not consider LEN+DEX as a sensible comparator for IXA+LEN+DEX among the 1 prior subgroup. The company clarification response also states that "*The company is unable to provide clinical and cost-effectiveness results for IXA+LEN+DEX compared with LEN+DEX for people with 1 prior therapy*". The ERG find this surprising. The protocol lists LEN+DEX as a comparator for the 1 prior subgroup, subject to the ongoing NICE appraisal and part review of technology appraisal 171.

The ERG revised company model permits an exploratory analysis of LEN+DEX as a comparator for IXA+LEN+DEX among the 1 prior subgroup[15]. This applies the same TMM-1 curves that underlie the comparison of IXA+LEN+DEX with BORT+DEX. It results in estimates of a net cost of [redacted] and a net loss of 0.395 QALYs, a loss of 0.89 undiscounted life years underlying this. But it should be borne in mind that the company model is both complicated and convoluted, and that the company has not yet cross checked these calculations. The ERG deterministic rebuild currently provides some reassurance around these estimates as it estimates the same net costs of [redacted] and a net loss of 0.394 QALYs. This suggests that for the 1 prior subgroup IXA+LEN+DEX is quite strongly dominated by LEN+DEX.

5.3.4.3 2 prior subgroup rather than 2+ prior subgroup

The company was unable at clarification to provide a sensitivity analysis using the 2 prior subgroup data due to time constraints. The forest plots of the submission, CSR and company response suggest a consistent trend, with hazard ratios of less than 1 favouring

[15] Note that this applies the 5 month KM of the LEN+DEX arm prior to the delayed exponential, paralleling the modelling approach in the IXA+LEN+DEX arm.

IXA+LEN+DEX over LEN+DEX and odds ratios of response of more than 1 favouring IXA+LEN+DEX over LEN+DEX.

Table 77: Treatment effects by 1, 2 and 3 prior treatments

		OS 2nd Interim anal.		OS 1st Interim anal.		PFS 1st Interim anal.		ORR 1st Interim anal.	
N Tx	N	HR	HR C.I.	HR	HR C.I.	HR	HR C.I.	OR	OR C.I.
1	441	1.092	(0.732-1.629)	1.210	(0.727-2.017)	0.832	(0.616-1.123)	1.214	(0.785-1.880)
2	208	0.725	(0.419-1.256)	0.770	(0.382-1.553)	0.749	(0.484-1.161)	1.658	(0.873-3.149)
3	73	0.455	(0.181-1.146)	0.318	(0.100-1.017)	0.366	(0.169-0.791)	2.890	(0.983-8.495)

While the confidence intervals of the 3 prior subgroup and the 2 prior subgroup cross each other, there is a consistent trend for the point estimates for the 3 prior subgroup to be somewhat better than the point estimates for the 2 prior subgroup. Including the 3 prior subgroup patients and using the 2+ prior subgroup to proxy for the 2 prior subgroup seems likely to overestimate the benefits of IXA+LEN+DEX for the 2 prior subgroup. This has been emphasized in previous section of the report for the clinical effectiveness.

While perhaps a little simplistic and prone to giving too much weight to the tails of the Kaplan Meier curves when few are at risk, the differences between the unadjusted Kaplan Meier curves can be compared over the periods that they are defined for both IXA+LEN+DEX and LEN+DEX using the data from the 1st interim analysis.

- For OS for the 2+ prior subgroup the Kaplan Meier curves are defined for both arms for 101 weeks. The difference between the curves is 6.1 weeks.
- For OS for the 2 prior subgroup the Kaplan Meier curves are defined for both arms for 101 weeks. The difference between the curves is 2.2 weeks.
- For PFS for the 2+ prior subgroup the Kaplan Meier curves are defined for both arms for 94 weeks. The difference between the curves is 12.4 weeks.

- For PFS for the 2 prior subgroup the Kaplan Meier curves are defined for both arms for 95 weeks. The difference between the curves is 6.3 weeks. Restricting this to only 94 weeks reduces this by 0.02 weeks.

This suggests that the OS and PFS gains in the 2 prior subgroup will be less than for the 2+ prior subgroup. The Kaplan Meier OS and PFS curves of the 1st interim data cut are presented below.

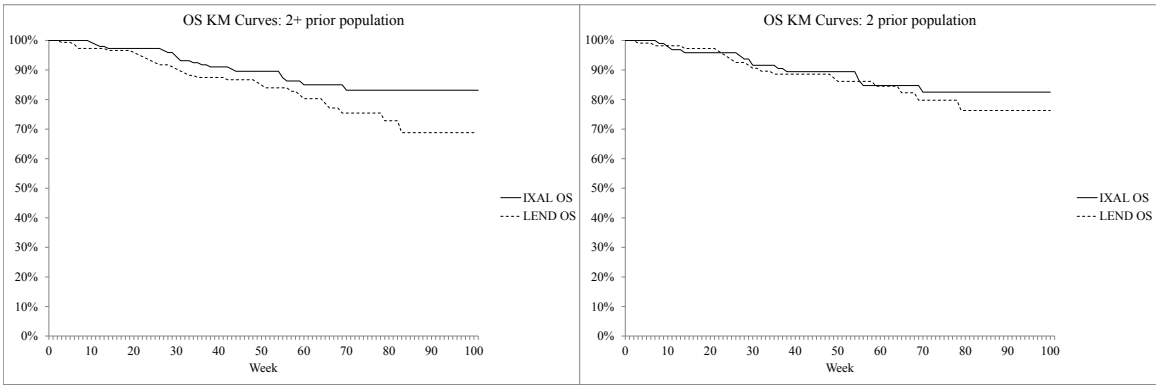


Figure 48: 2+ prior and 2 prior OS Kaplan Meier curves: 1st interim analysis

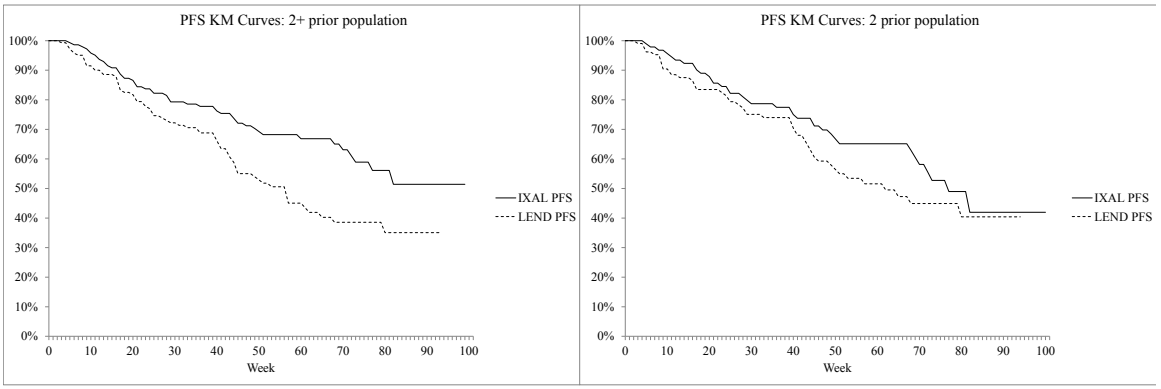


Figure 49: 2+ prior and 2 prior PFS Kaplan Meier curves: 1st interim analysis

A more formal analysis can be conducted that estimates unadjusted parameterised curves for OS, PFS and ToT from the 2 prior subgroup. The ERG has undertaken an exploratory analysis of the Kaplan Meier data and fitted unadjusted curves to the data supplied at clarification. Proportionate hazards appears reasonable, so in common with the company the ERG pools the trial data between the arms and estimates common parameterised

curves, with treatment with ixazomib as a covariate within the analyses. This results in the following parameterised curves for OS, PFS and ToT.

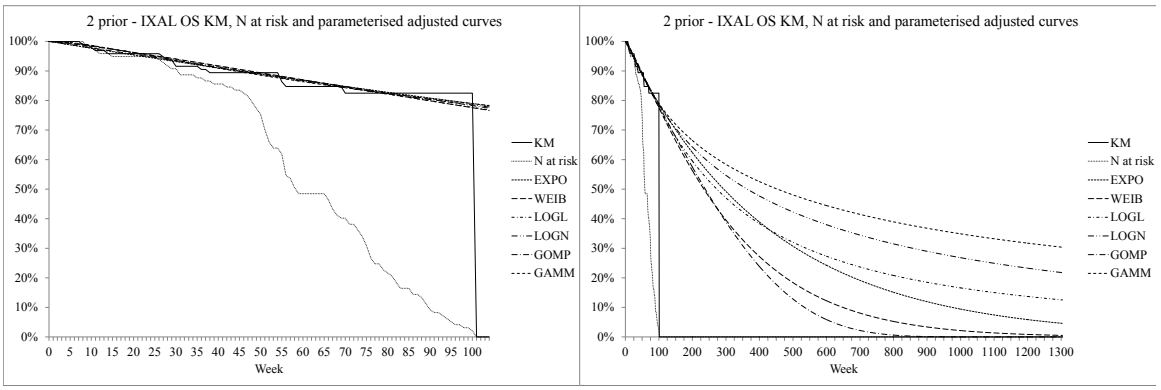


Figure 50: 2 prior: OS parameterised curves: IXA+LEN+DEX

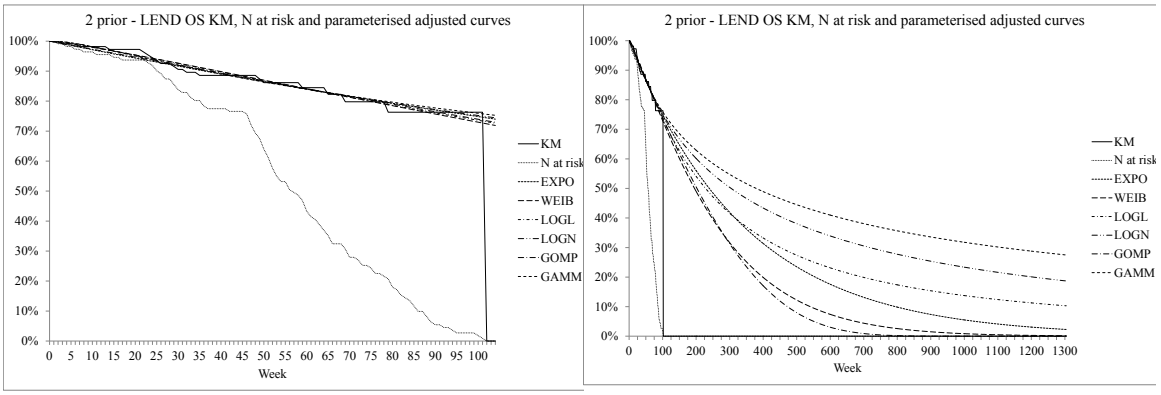


Figure 51: 2 prior: OS parameterised curves: LEN+DEX

For both arms there is limited difference between the parameterised curves during the trial period, particularly during the trial period when reasonable numbers of the baseline n=97 patients in the IXA+LEN+DEX and of the baseline n=111 patients in the LEN+DEX arm remain at risk. It is only during extrapolation when the curves diverge with the exponential and the Weibull being towards the lower of the curves, with only the gompertz below them. The gamma is somewhat higher than the other curves and seems likely to simulate an improbably large proportion remaining alive after 25 years given the baseline average age in the TMM-1 trial of 66 years.

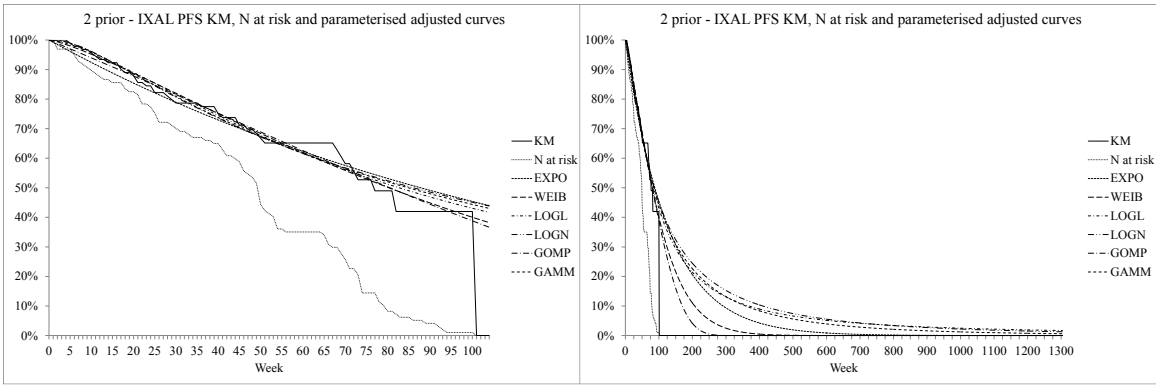


Figure 52: 2 prior: PFS parameterised curves: IXA+LEN+DEX

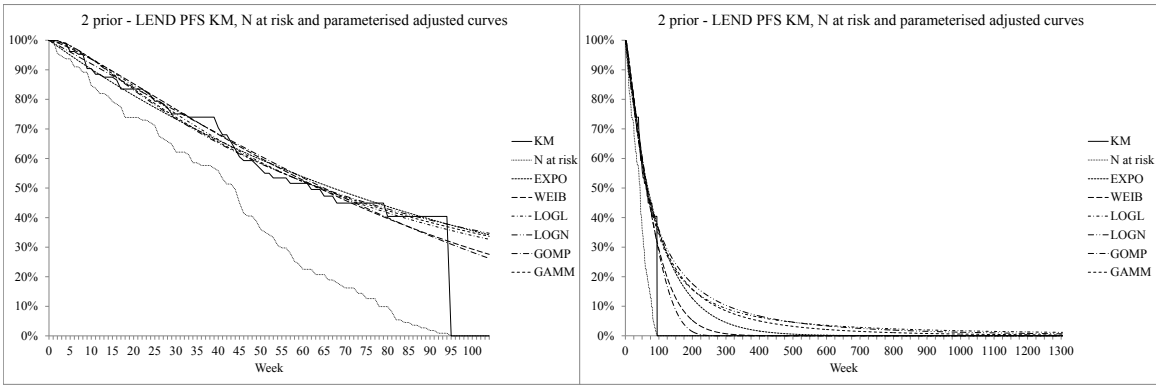


Figure 53: 2 prior: PFS parameterised curves: LEN+DEX

The PFS curves show a slightly greater degree of separation during the trial period than the OS curves, but again the main separation occurs during the extrapolation period.

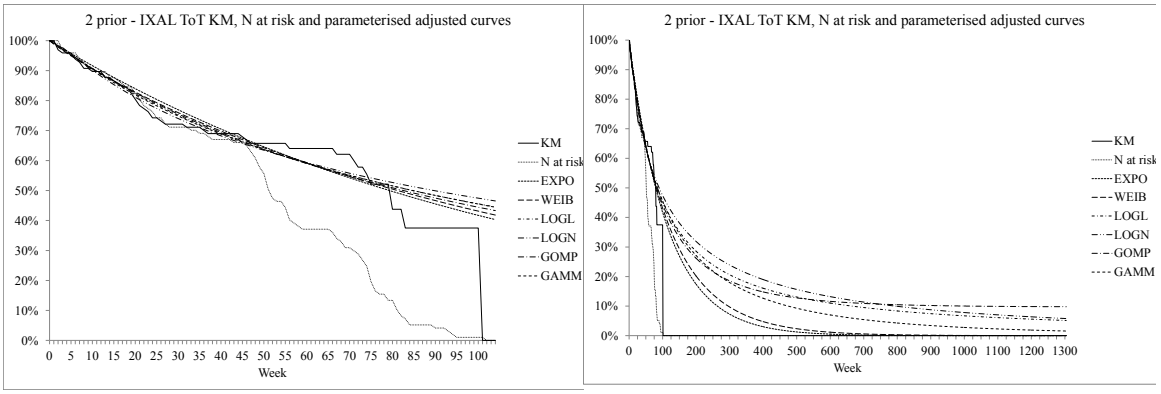


Figure 54: 2 prior: ToT parameterised curves: IXA+LEN+DEX

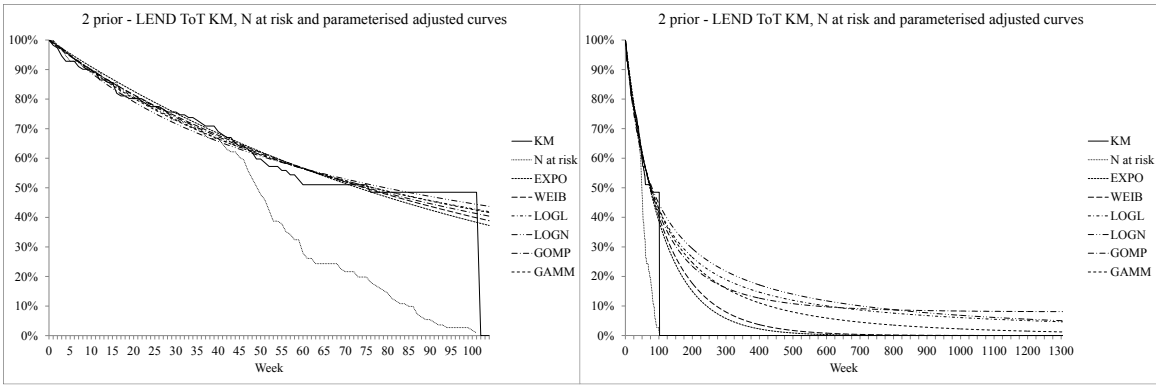


Figure 55: 2 prior: ToT parameterised curves: LEN+DEX

Again, the curves mainly spread out during the period of extrapolation. For a number of the functional forms in the LEN+DEX arm the values for ToT rise somewhat above the values of the same functional form for PFS. Some curves such as the gompertz obviously simulate an infeasible number of patients remaining on treatment in the long term.

The AIC and the BIC for the parameterised curves are as below.

Table 78: 2 prior: parameterised curves AIC and BIC

	EXPO	WEIB	LOGL	LOGN	GOMP	GAMM
OS AIC	**234.99**	236.05	235.69	234.64	236.90	236.52
OS BIC	**241.66**	246.06	245.70	244.65	246.91	249.88
PFS AIC	409.82	406.22	405.48	**404.05**	408.96	405.97
PFS BIC	416.50	416.23	415.49	**414.06**	418.97	419.32
ToT AIC	**507.23**	508.62	508.49	508.41	508.47	509.66
ToT BIC	**513.91**	518.63	518.51	518.42	518.48	523.01

The lowest combined AIC and BIC occur for OS using the exponential, for PFS using the log normal and for ToT using the exponential, resulting in the figures below.

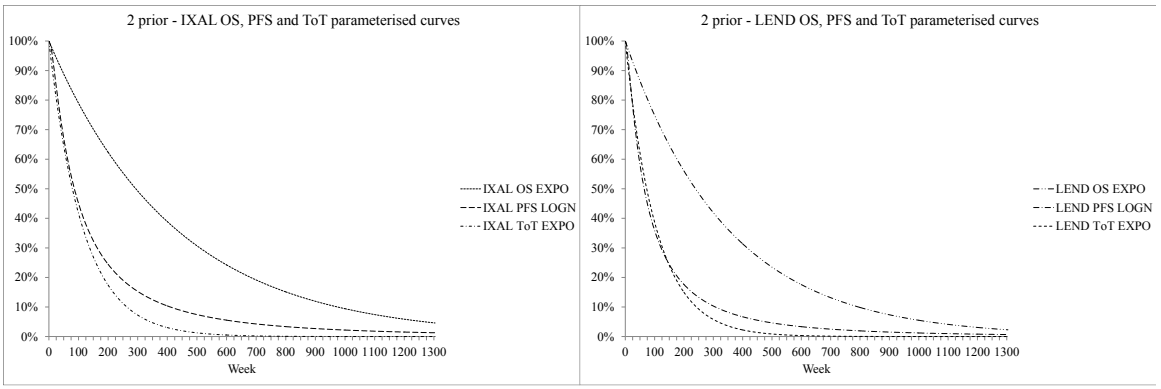


Figure 56: 2 prior: Lowest AIC and BIC parameterised curves

There may be an argument for assuming the exponential for PFS as well. This results in PFS curves that lie only a little above the ToT curves which is perhaps more reasonable to assume. But this has relatively little impact upon results, affecting both the IXA+LEN+DEX and the LEN+DEX arms in a like manner. The OS and PFS curves in each arm can be compared alongside one another to show the net gains over time.

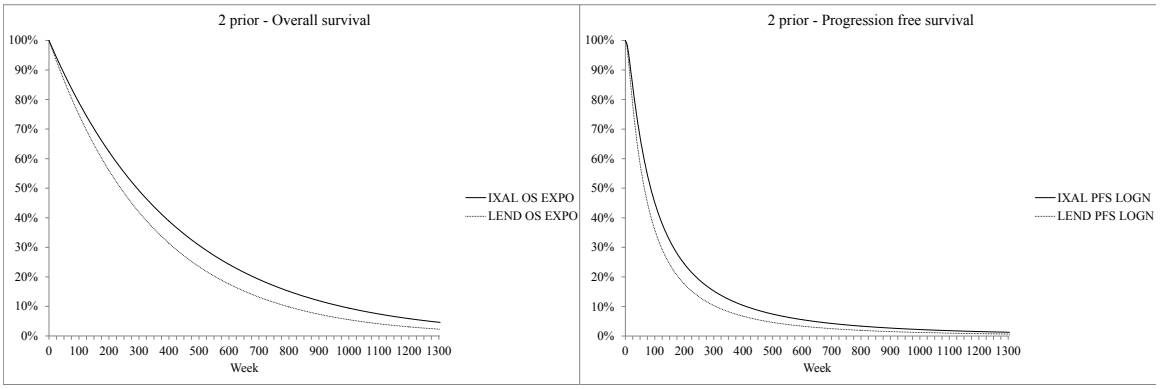


Figure 57: 2 prior: OS and PFS comparison for IXA+LEN+DEX vs LEN+DEX

The ERG has applied these curves within the company model retaining the other company base case assumptions and has cross checked the values of these[16]. The increase

[16] These revisions are documented in the ERG revised model uploaded to NICEdocs.

in undiscounted survival is 1.28 years, with the majority of this occurring in PFS where there is a net gain of 0.76 years but there is still quite a considerable PPS gain of 0.52 years. This results in an estimated net cost of [redacted], a net gain of 0.631 QALYs and a cost effectiveness estimate of [redacted] per QALY for IXA+LEN+DEX compared to LEN+DEX. The cost effectiveness estimate for the 2 prior subgroup using the curves with the lowest combined AIC and BIC is around 40% worse than that of the 2+ prior subgroup. Those results are of importance owing to the preferred positioning of IXA in third line by the Company.

The curves chosen also appear to be the most optimistic of those available. Holding the PFS and ToT curves constant and varying the OS curves to be the Weibull, log normal, log logistic, gompertz and gamma results in cost effectiveness estimates of [redacted] per QALY, [redacted] per QALY, [redacted] per QALY, [redacted] per QALY and [redacted] per QALY respectively. Holding the OS and PFS curves constant and varying the ToT curves to be the Weibull, log normal, log logistic, gompertz and gamma results in cost effectiveness estimates of [redacted] per QALY, [redacted] per QALY, [redacted] per QALY, [redacted] per QALY and [redacted] per QALY respectively.

The ERG has not checked the reasonableness of the parameterised curves with the clinical experts. But even if only on the basis of the Kaplan Meier curves and the company forest plots it seems reasonable to conclude that the cost effectiveness of IXA+LEN+DEX compared to LEN+DEX in the 2 prior group is likely to be worse than in the 2+ prior group.

The company notes that stratification in the trial was only according to 1 prior and 2 or 3 prior treatments. It also applies the adjusted parameterised models rather than the unadjusted models, arguing that controlling for confounding variables such as ISS disease stage is important and that considering the 2 prior subgroup would break randomisation around these confounding variables. Applying the unadjusted curves has virtually no impact upon the cost effectiveness estimate for the 1 prior subgroup, and worsens the cost effectiveness estimate for the 2+ prior subgroup by around 8%. Having confidence in the

TMM-1 randomisation would suggest little need to adjust for covariates when considering the 2+ prior subgroup as seems to be borne out by the company scenario analyses, but would argue for a covariate adjusted analysis when looking at the 2 prior subgroup. It should be borne in mind that the ERG parameterised curves above are unadjusted.

The company argues that it is statistically more robust to assume that the 2+ subgroup proxies for the 2 prior subgroup than to use the 2 prior subgroup data. The company also argues that since only 26% of the combined 2+ prior group were 3 prior, the clinical effectiveness estimates for the 2+ prior group will have been driven by the 2 prior. The differences between the point estimates of the 2 prior and the 3 prior of the company forest plots call this into question.

5.3.4.4 1st interim analysis vs 2nd interim analysis

The company submission notes that "At the decision problem meeting with NICE it was agreed the primary data cut IA1 was appropriate for the base case of the economic analysis". Section 1.4 of the company submission notes that "…the economic argument requires further trial follow-up and real world data". The company is keen for ixazomib to be included in the new CDF. In the light of this the ERG finds it difficult to understand why the company has relied upon the 1st interim data cut (IA1) rather than the 2nd interim data cut (IA2).

This has a reasonable impact upon the company cost effectiveness estimates. The company base case cost effectiveness estimates using the 2nd interim analysis change as follows:

- For the 1 prior subgroup, mainly due to the net gain falling from 2.336 QALYs to 1.842 QALYs, the ICER increases from [redacted] per QALY to [redacted] per QALY: a worsening of 26%.
- For the 2+ prior subgroup the ICER improves by 6% from [redacted] per QALY to [redacted] per QALY: an improvement of 6%.

The originally submitted company model does not contain the data necessary to replicate the company scenario analyses using the 2nd interim analysis. A second company model

was submitted by the company subsequent to clarification that permits replication of the company scenario analyses using what the company describes as the 2nd interim analysis. This model has not been parsed by the ERG. The ERG has made a cursory comparison of the inputs to the company base case of the 2nd interim analysis with the inputs to the company base case of the 1st interim data cut. The ERG notes the following changes:

- The functional forms of the parameterised curves differ:
    - 1 prior subgroup
        - OS: Log logistic
        - PFS: Log normal
        - ToT: Log logistic
    - 2+ prior subgroup
        - OS: Log normal
        - PFS: Log normal
        - ToT: Gamma
- The parameterised curves differ as should be the case
- The covariates of the adjusted parameterised curves differ
- The NMA has not been revised
- The distributions of BoR have not been revised although they should have been
- The HRQoL regression has not been updated.
- The TRAE rates have not been updated.
- The hospitalisation rates have not been updated.
- The PPS rates of treatment and balance between treatments have not been updated.

Time constraints mean that the ERG cannot assess the reasonableness of the above changes. The main immediate concerns the ERG has with the above are:

- Revising the OS and one ToT functional forms to be log logistic and log normal. These both typically have long and often clinically implausible tails.

- Not updating the NMA. If the 1+ prior NMA should be updated for the 2nd interim analysis, the cost effectiveness estimates are not really based upon the 2nd interim analysis but upon a mix of the 1st interim analysis and the 2nd interim analysis.
- Choosing to use the HRQoL regression based upon the 1st interim analysis may cause bias. The direction of any bias is unknown. The HRQoL regression is a key driver of results. The 2nd interim analysis will have more data and should provide more robust estimates, particularly for the PD health state.

A company submission based upon the 2nd interim analysis together, if required, with a revised NMA based upon the 2nd interim analysis would in effect be an entirely new submission. An ERG review would require much the same amount of work as has occurred to data for the submission based upon the 1st interim data cut.

5.3.4.5 1-prior: 5 month delay to parameterised OS curve for IXA+LEN+DEX

The ERG highlighted that it seemed peculiar to have applied the hazards of the IXA+LEN+DEX OS KM curve for five months followed by the hazards of the adjusted parameterised delayed exponential in the IXA+LEN+DEX arm but not to have made the same assumption in the BORT+DEX arm.

Applying the hazards of the LEN+DEX OS KM curve for five months, conditioned by the NMA OS HR of 3.11, followed by the hazards of the adjusted parameterised delayed exponential, also conditioned the NMA OS HR of 3.11, results in a better OS curve for BORT+DEX than the company base case. Adopting this approach, the ICER for the 1 prior subgroup for IXA+LEN+DEX compared to BORT+DEX worsens from [redacted] per QALY to [redacted] per QALY. The ERG rebuild also provides a similar cost effectiveness estimate of [redacted] when this change is made.

The company accepts that its original base case is biased against BORT+DEX and should be a cost effectiveness estimate of [redacted] per QALY.

5.3.4.6 1 prior: Delayed parameterised curves

The company argues that the first 5 months of OS for the 1 prior subgroup does not conform to proportionate hazards and so estimates a delayed exponential from the post 5 months TMM-1 data. It is peculiar and out of keeping with the rest of the submission for the company to not present the range of other functional forms from the Weibull to the generalised gamma estimated from the post 5 months TMM-1 data. This reduces the confidence that can be placed in the delayed exponential.

5.3.4.7 1 prior subgroup consistency of modelling approach

The model applies the IXA+LEN+DEX and the LEN+DEX 1 prior subgroup parameterised curves. These curves are estimated by the company from the 1 prior subgroup specific data and imply hazard ratios between IXA+LEN+DEX and LEN+DEX for the 1 prior subgroup.

- The OS IXA+LEN+DEX to LEN+DEX hazard ratio implied by the delayed exponential is 1.12; i.e. IXA+LEN+DEX is inferior to LEN+DEX.
- The PFS IXA+LEN+DEX to LEN+DEX hazard ratio implied by the generalised gamma ranges from 0.90 to 0.96.

Due to data constraints the 1+ prior NMA hazard ratios for BORT+DEX are applied to the LEN+DEX 1 prior subgroup parameterised curves. It can be argued that it might be more consistent to apply the 1+ prior NMA hazard ratios for IXA+LEN+DEX to the LEN+DEX 1 prior subgroup parameterised curves.

- For OS: 0.90 from the company NMA and 0.90 for the 1+ prior group and 1.24 for the 1 prior subgroup from the ERG exploratory NMA.
- For PFS: 0.88 from the company NMA and 0.74 for the 1+ prior group and 0.88 for the 1 prior subgroup from the ERG exploratory NMA.

The ERG agrees that the company base case approach is superior as it incorporates as much of the TMM-1 1 prior subgroup specific data as is possible. The application of the 1+ prior hazard ratios for BORT+DEX is only required due to data constraints with the company suggesting that estimates are not possible for the 1 prior subgroup. The ERG

has constructed estimates for the 1 prior subgroup but has less confidence in these than those of the 1+ prior subgroup.

The ERG will conduct sensitivity analyses that applies the IXA+LEN+DEX hazard ratios from the 1+ prior company NMA and the 1+ prior ERG NMA.

5.3.4.8 PFS and ToT curves events and censoring

The ERG asked the company to itemise all "happenings" that qualified as events and all "happenings" that qualified as censoring for PFS and for ToT. Unfortunately, the company response for ToT seems to be incomplete. The events that are listed as events for the curves and as censorings for the curves within the company clarification response are as below.

Table 79: Company clarification on events and censoring for PFS and ToT

PFS		ToT	
Event	Censoring	Event	Censoring
• Progression • Death	• Alternative therapy • Dying or progressing after more than 1 missed visit • No baseline/post baseline • No documented death or progression • Lost to follow up • Withdrawal of consent	Discontinuing treatment due to: • Progression • Adverse event • Protocol violation • Study termination by sponsor • Lost to follow up • Withdrawal of consent	n.a.

There is not a complete read across between the PFS and the ToT events and censorings. It appears that lost to follow up and withdrawal of consent was treated as censoring for PFS but as events for ToT. The ERG has not had time to sufficiently consider this. But taking things to the extreme it would be possible for all patients to have been lost to follow up without progression having been measured among them. This would result in

the PFS curve remaining at 100% but the ToT curve being at 0%; i.e. patients retaining the benefits of treatment but incurring none of its costs. It is not obvious to the ERG that all PFS censoring events[17] should have been treated as events for ToT. Treating PFS censorings as events for the ToT curves may unreasonably reduce the ToT curves below the PFS curves and in consequence unreasonably reduce treatment costs for a modelled PFS.

ERG expert opinion notes that time to progression (TTP) is on average around 0.9 months shorter than the time to next treatment. The time to next treatment may also be delayed beyond biochemical progression, depending upon the speed or aggressiveness of relapse. There is an argument that those who stop treatment due to intolerance or adverse events may have stable disease that does not require immediate intervention. The company submission suggests that it is necessary to account for discontinuations due to progression and unacceptable toxicity. Which PFS censoring events should and which should not be treated as events for ToT may be quite a complicated question and should perhaps have been explored as part of the submission.

The ToT curve typically lies somewhat below the PFS curve, particularly during the extrapolation period. For the 1 prior subgroup, in the IXA+LEN+DEX arm the area under the ToT curve is 82% of the area under the PFS curve. For the 2+ prior group in the IXA+LEN+DEX arm the area under the ToT curve is only 65% of the area under the PFS curve, while in the LEN+DEX arm it is 75%. One explanation for this could be that different functional forms are applied for the PFS and the ToT curves. But equalising the ToT functional form with the PFS functional form does not bring the ToT curve into line with the PFS curve.

[17] Given the company clarification response it is not clear to the ERG which PFS events and censoring events were ToT events and censoring events.

Note that this is unrelated to treatment holidays, which are separately accounted for within the modelling through dose intensity calculations which allow for missed doses and dose interruptions. This is treatment cessation prior to progression. In other words, defining eligibility as not having progressed on average:

- Among the 1 prior IXA+LEN+DEX patients:
    - For every 5 treatment cycles patients are eligible for, 1 treatment cycle is not administered.
    - Of the 114 weeks spent in PFS, treatment is received for the first 94 weeks, but it is then stopped and the last 20 weeks of PFS is off treatment.
- Among the 2+ prior IXA+LEN+DEX patients:
    - For every 3 treatment cycles, patients are eligible for 1 treatment cycle is not administered.
    - Of the 186 weeks spent in PFS, treatment is received for the first 122 weeks, but it is then stopped and the last 65 weeks of PFS is off treatment.
- Among the 2+ prior LEN+DEX patients.
    - For every 4 treatment cycles, patients are eligible for 1 treatment cycle is not administered.
    - Of the 119 weeks spent in PFS, treatment is received for the first 89 weeks, but it is then stopped and the last 30 weeks of PFS is off treatment.

These values seem quite low based upon a literal reading of the SmPCs. The ToT curves reduce the drug costs for a given PFS by a corresponding amount. It is also not obviously reasonable that the ToT to PFS ratio should be much lower in the IXA+LEN+DEX arm than in the LEN+DEX arm. It may be more reasonable to use the PFS curve to model treatment costs, and this will be explored as a scenario analysis.

5.3.4.9 Quality of life values for PFS and PPS

Within the company submission there is little other than a brief qualitative account of the quality of life analyses undertaken by the company, and a presentation of the final coefficients that the company chooses for its base case. At clarification the ERG asked

for a copy of the analysis report that underlies the final quality of life function applied by the company. The company response was that "*There is no separate report on the underlying EQ 5D analysis performed using TMM-1 data, and we would refer the ERG to section 5.4.1.1 in the submission that describes the choice of distribution that informed the parameters in table 71 of the submission*".

Some of the coefficients of the company preferred model are not statistically significant but are retained, but treatment as a covariate has apparently been rejected due to not being statistically significant. The hospitalisation coefficient is also not applied within the economic model.

The quality of life calculations in the model also apply the large 0.300 quality of life decrement for new primary malignancies to treatment specific new primary malignancy rates, despite treatment having been rejected as a covariate for the quality of life analysis. These are given as 1 new primary malignancy in the IXA+LEN+DEX arm and 2 new primary malignancies in the LEN+DEX arm for those on treatment.

Data supplied at clarification notes that there were no new primary malignancies in the 1 prior subgroup. For the 2+ prior subgroup there were 2 in the IXA+LEN+DEX arm with 1 being among 173 patients with a BoR of VGPR+ and 1 being among the 17 patients with a BoR of PD[18]. Likewise there were 2 in the LEN+DEX arm among the 141 patients with a BoR of VGPR+. This suggests a total of 3 new primary malignancies among the 314 patients with a BoR of VGFR+, which might in turn argue for reducing the VGPR+ quality of life estimate but only by a rather modest 0.001.

The company has supplied a further two models, the first which excludes the non-significant hospitalisations and TRAEs, and the second which excludes hospitalisations, TRAEs and new primary malignancies.

Table 80: Quality of life regressions varying covariate list

[18] Though interpreting this for the BoR PD group is more problematic due to patients flowing into this classification as patients progress.

	Original model		1st alternate		2nd alternate	
Coefficients	Coef.	p-value	Coef.	p-value	Coef.	p-value
Intercept	-1.245	<.0001	-1.244	<.0001	-1.243	<.0001
PD	0.182	0.001	0.192	0.000	0.191	0.001
PR	0.122	0.029	0.129	0.023	0.127	0.025
SD	0.187	0.002	0.193	0.002	0.192	0.002
Hospitalisation	0.219	0.279				
Grade 3/4 TRAE	0.055	0.129				
New Primary Malignancy	0.713	<.0001	0.708	<.0001		
Within 3ths death	0.378	<.0001	0.387	<.0001	0.398	<.0001
Quality of life values						
VGPR+	0.712		0.712		0.711	
PR	0.674		0.672		0.673	
SD	0.653		0.651		0.650	
PD	0.654		0.651		0.651	

Applying the alternative sets of covariates has minimal impact upon the cost effectiveness estimates of the company base case.

The ERG economic reviewer has been advised that the repeated measure mixed model appropriately controls for differences in values at baseline provided that there are measurements for all the factors at each time point and that the stability of the models to the revised covariates list provides some reassurance around the estimates. The main concern appeared to be not to explore age as a covariate, which would also possibly be linked to the 1 prior / 2+ prior distinction.

The company has provided the mean values by subgroup. The number of responses as a proportion of the number of patients within the relevant data split was consistently high, being typically over 80% and usually over 90% when there were reasonable numbers of

patients eligible to report EQ-5D. The following presents the mean baseline EQ-5D values split by patients' subsequent BoRs.

Table 81: Baseline mean EQ-5D values by subgroup and by subsequent Best Overall Response

	1 prior		2+ prior		Pooled	
	N resp.	EQ-5D	N Resp.	EQ-5D	N Resp.	EQ-5D
VGPR+	176	0.708	119	0.660	295	0.689
PR	128	0.690	87	0.670	215	0.682
SD	58	0.677	35	0.660	93	0.670
PD	20	0.568	15	0.677	35	0.615
Pooled	382	0.690	256	0.664	638	0.680

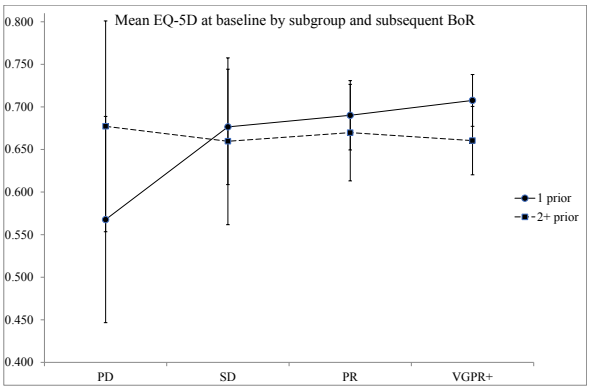


Figure 58: Subgroup baseline mean EQ-5D values by subsequent Best Overall Response

The above presents the mean baseline EQ-5D values and their association with the patients' subsequent BoRs. It does not present the effect that being in a certain response state has upon contemporaneous quality of life.

Considering the 1 prior subgroup there appears to be a trend, even if the means are not statistically significantly different from one another. Those who attain a good BoR are typically those who were relatively well at baseline and had a good baseline quality of life. While the slope between SD and VGPR+ may not be particularly steep it is about 50% the gradient of the quality of life function that is applied within the model.

Within the 1 prior subgroup those who have a BoR of progressive disease appear to have been already relatively poorly at baseline with a poor quality of life, though the absolute number of EQ-5D responses is low at only 20 out of the 22 patients this applies to and the uncertainty around this value is quite large.

The picture is more mixed for the 2+ prior subgroup, though there is perhaps a tendency for the quality of life at baseline to have been worse than that of the 1 prior subgroup at baseline. But the subsequent BoR status among the 2+ prior subgroup does not appear to be strongly associated with the patients' quality of life at baseline.

There may be a problem with the data which could account for the possible oddity of the differences in the PD to baseline EQ-5D mappings between the 1 prior and the 2+ prior subgroups. The number of patients with EQ-5D data at baseline, 1 prior n=404 and 2+ prior n=273, can be compared with the number of patients in the TMM-1 trial, 1 prior n=441 and 2+ prior n=281, to suggest the number with missing data, 1 prior n=37 and 2 prior n=8. The electronic copy of the model suggests missing data for 1 prior n=21 and 2 prior n=24. It appears that in the EQ-5D data supplied at clarification has accidentally reclassified some 1 prior patients as 2+ prior patients.

For the EQ-5D data pooled between the 1 prior and the 2+ prior there is a consistent association at mean values that patients with a better baseline EQ-5D tended to have a better subsequent BoR.

The post baseline mean values within the data supplied at clarification suggest raw values of 0.718 for the 1 prior and 0.702 for the 2+ prior: a difference of only 0.016 which is less than that at baseline. But the mean values among those with subsequent responses in one of the three PFS categories are 0.721 for 1 prior and 0.701: a difference of 0.020 which is not dissimilar to that at baseline. There is again the suggestion that quality of life may decline as patients progress through lines of therapy.

The company argues that splitting the data by the 1 prior / 2+ prior subgroups or including the prior number of treatments as a covariate within the analysis would adversely affect the sample size or degrees of freedom and as a consequence suggests that this has not been explored. It can be noted that the mean baseline EQ-5D value for the 1 prior group was 0.690 compared to 0.664 for the 2+ prior group. This in itself may

question the company conclusion that quality of life does not decline among patients at subsequent lines of therapy. This is subject to the above concern about some 1 prior patients possibly being reclassified as 2+ prior patients in the data supplied at clarification, which if the case might suggest that the true difference at baseline and subsequent to baseline are larger than those reported above.

Given the structure of the model and the analysis of the clinical data it strikes the ERG as surprising that the 1 prior / 2+ prior subgroups were not explored within the quality of life analyses. If it proved to have too detrimental an effect upon the power of the analysis it could be rejected, but to the ERG it seems peculiar to reject it a priori.

It should also be noted that the mean baseline EQ-5D value in the IXA+LEN+DEX arm was 0.687 which is higher than the 0.672 in the LEN+DEX arm: about half the estimated difference between the quality of life for a BoR of PR and a BoR of VGPR+. This also applies to the subset of patients who had a subsequent response that falls into one of the three PFS categories. The company reports finding treatment not to be statistically significant within its analyses, but provides no detail of this.

Table 82: Baseline mean EQ-5D values by arm and by subsequent Best Overall Response

	IXAL		LEND	
	N resp.	EQ-5D	N Resp.	EQ-5D
VGPR+	168	0.687	127	0.691
PR	104	0.698	111	0.666
SD	38	0.686	55	0.659
PD	15	0.613	20	0.616
Pooled	325	0.687	313	0.672
PFS	310	0.691	293	0.676

The higher mean value at baseline for IXA+LEN+DEX can be viewed alongside the association between the mean value at baseline and the subsequent BoR. It may mean that patients in the IXA+LEN+DEX arm were more predisposed to achieving a good BoR. The company adjusts the parameterised curves for a variety of baseline attributes. As far

as the ERG is aware this does not include the baseline quality of life. There is also no adjustment made to the BoR based upon the baseline quality of life.

The differences at baseline between both the 1 prior / 2+ prior subgroups and the arms might suggest exploring the impact of these within the quality of life analyses and reporting the results of these explorations. Or they might suggest examining the relationship between BoR and QoL changes from baseline rather than the absolute QoL values.

Table 83: Post baseline mean EQ-5D values by arm and by subsequent Best Overall Response

	IXAL		LEND		Pooled	
	N resp.	N Resp.	EQ-5D	EQ-5D	N Resp.	EQ-5D
VGPR+	2422	0.722	1911	0.714	4333	0.719
PR	1145	0.731	1271	0.703	2416	0.717
SD	269	0.650	404	0.679	673	0.667
PD	261	0.669	460	0.711	721	0.696
Pooled	4097	0.716	4046	0.707	8143	0.712
PFS	3836	0.720	3586	0.707	7422	0.713

The post baseline mean values within the data supplied at clarification suggest raw values of 0.716 for IXA+LEN+DEX and 0.707 for LEN+DEX: a difference of only 0.009. But the mean values among those with subsequent responses in one of the three PFS categories are 0.720 for IXA+LEN+DEX and 0.707 for LEN+DEX: a difference of 0.013 which is a larger than the 0.001 for the 1 prior and the 0.010 for the 2+ prior of the company model. Perhaps slightly curiously the mean post baseline values for those with a BoR of PD is 0.669 for IXA+LEN+DEX compared to 0.711 for LEN+DEX: the model assumes no difference in these values between IXA+LEN+DEX and LEN+DEX.

5.3.4.10 Quality of life over time

The model simulates patients at a baseline age of 66 over a 25 year time horizon with some patients surviving the entire time horizon. Kind et al (1999) [68] provide data that shows that quality of life in the UK population EQ-5D data set declines over time as

would be expected as comorbidities accumulate. Patients surviving with multiple myeloma will also tend to accumulate comorbidities as they age and, for a given multiple myeloma health state, it would be expected that quality of life would also decline over time.

As reviewed above, the lower baseline quality of life value among the 2+ prior compared to the 1 prior also suggests that quality of life may tend to wane as patients progress through the treatment sequence. ERG expert opinion also suggests that quality of life declines with each relapse.

Both the above suggest the quality of life when moving through different lines of therapy and over the time horizon of the model should be modelled as declining.

5.3.4.11 Quality of life and subcutaneous injections

The company applies a 0.025 quality of life decrement for the entire period patients spend receiving subcutaneous BORT+DEX. This is apparently derived from two previous assessments of treatments for lung cancer and brought into the resubmission for TA338[19]. This is equivalent to patients being willing to sacrifice a little under 4% of the PFS quality of life. The company anticipates that this "*is likely to be an underestimate of the impact in this population as, due to the frailty of patients with MM, greater disruption and impact to daily living is expected from repeated hospital admissions for administration of therapy*". The argument appears to be that it is the hospital visits that result in the disutility rather than the subcutaneous injections themselves, these only lasting 3-5 seconds. The ERG agrees that it is unlikely that four 3-5 second subcutaneous injections over a treatment cycle result in a 4% quality of life drop over the cycle duration of 3, or possibly 5, weeks.

If hospital visits do cause disruption and disutility this should be factored into all treatment options. There may well be more hospital visits associated with IXA+LEN+DEX given the longer

[19] Now superseded and no longer available on the NICE website.

duration of treatment and, in the company base case, the longer overall survival than with either LEN+DEX or BORT+DEX.

The ERG removes this element from its exploratory revised base cases.

5.3.4.12 PFS quality of life and duration of BoR

The PFS quality of life calculations are based upon patients' BoR. Patients will take some time to attain their BoR and will not remain in their BoR for the duration of their PFS.

The durations of response (DoR) reported in the CSR for the 1st interim analysis measure the time from the first documented PR or better to the first documented PD. In other words, the data relates to duration of response and not to duration of BoR. The DoR for patients with VGPR+ will be an overestimate of the duration of the BoR. With this caveat the CSR states that among those with VGPR+ the median DoR for IXA+LEN+DEX was not estimable and for LEN+DEX was 14.7 months. The company base cases suggest a median PFS for LEN+DEX of 15.9 months for the 1 prior subgroup and 14.0 months for the 2+ prior subgroup. These are reasonably aligned with the TMM-1 DoR data for the VGPR+ group.

The company quality of life analysis partitions the EQ-5D data for the PFS health states by patients' BoR and not by their response status contemporary to the EQ-5D collection time points. It is difficult to speculate upon what impact this choice has in the light of the duration of response data. If the analysis was restricted to the trial period, it may be there is no effect. But the PFS is extrapolated well after the trial period and as a consequence the PFS quality of life values may be overestimates for the modelled time horizon.

5.3.4.13 Bortezomib dosing, drug costs and progression based PAS refund

The company model assumes a maximum of 9 cycles of BORT+DEX when it should be a maximum of 8 cycles[20].

[20] In worksheet *Comp1* cells CU10, CU13, CU16, CU19, CU22, CU25, CU28, CU31 and CU34 incur treatment costs.

The company model also assumes that patients complete every BORT+DEX cycle that they start. Some patients will stop treatment mid cycle and it would seem more reasonable to use the PFS or ToT curve to estimate this. Again, this will have overestimated the BORT+DEX treatment costs.

The ToT curve for BORT+DEX is simply assumed to be that of LEN+DEX due to a lack of evidence. In the opinion of the ERG, in the absence of other evidence if the PFS curve has had a hazard ratio applied to it the most reasonable assumption is to apply the PFS hazard ratio to the ToT curve. The company base case again seems likely to overestimate the BORT+DEX treatment costs.

The company model assumes, subject to the maximum number of cycles, that bortezomib treatment is continued, provided that patients remain in PFS.

- Information from the Derby and Burton cancer network suggests that patients who achieve complete response require only a further two cycles. Treatment costs for those achieving complete response are overestimates.
- Information from the Derby and Burton cancer network suggests that patients are discontinued after their 4th cycle if they have not achieved a partial response, defined as a reduction in serum M protein of 50% or more or, where serum M protein is not measurable, an appropriate alternative biochemical measure of response. This is broadly in line with the definition of partial response in the TMM-1 trial of a ≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥ 90% or to < 200 mg per 24 hours. The costs of bortezomib for treatment cycles 5, 6, 7 and 8 are overestimates given the distribution of BoR for BORT+DEX in ENDEAVOR as outlined in section 5.3.2 above.
- Similarly, the company model assumes that only those progressing within 4 cycles of treatment have their bortezomib costs refunded. Information from the Derby and Burton cancer network suggests that the bortezomib drug costs are refunded for those with less than a partial response after 4 cycles of treatment. The bortezomib progression based PAS refunds are likely to be serious underestimates.

Due to the company base case applying the hazard ratio conditioned delayed exponential for OS, and the gamma for PFS, in the BORT+DEX arm, PFS is modelled as being the same as OS up to week 19. Since none are modelled as progressing before the 4th 3 week BORT+DEX cycle, the company base case models no refunds under the bortezomib progression-based PAS refund scheme.

The incident number of progressing patients is estimated to be zero if the change in the prevalent number of patients who are progression free is less than the change in the number of patient surviving. If this does not apply, the incident number of progressing patients is estimated to be the change in the prevalent number of patients who are surviving post progression. Both these elements seem to be an underestimate as they do not account for deaths among those who are surviving post progression. As a consequence, any bortezomib refunds may be underestimates since it seems that the model underestimates the incident number of patients progressing.

5.3.4.14 Drug administration costs

For the 1st line therapies these do not include the NHS reference costs for chemo therapy. These are only applied for subsequent regimes. But the ERG is sympathetic to the company approach given the lack of granularity of the reference cost for delivering subsequent elements of a chemotherapy regime.

In line with ERG expert opinion and the NICE costing template for bortezomib monotherapy the ERG will assume that bortezomib administrations subsequent to the first of each cycle incur a haematology non-consultant led OP follow up appointment at a cost of £92. Actual costs may vary by region, ERG expert opinion suggesting some home care facilities exist in certain areas.

5.3.4.15 PPS rates of retreatment and treatment costs

As already noted a one off cost is applied for the 24% of those who progressed and received further treatment in the TMM-1 trial. The 24% may be an underestimate as it appears to be based upon the TMM-1 number of patients who progressed and received further anticancer therapy (n=176) divided by the baseline number of patients (n=722). This will be quite a large underestimate as the denominator should be the number of

patients who had progressed. Based upon the PFS Kaplan Meier curves the proportion who have progressed by the end of the 1st interim analysis is between 30% and 50%. To the ERG this argues for 60% of the baseline number of patients (n=433) as the denominator and so a PPS treatment rate of 41%.

The application of a one off cost for the proportion receiving treatment of £70,188 is also not likely to be particularly realistic and will to a large extent simply cancel out between the arms, much like end of life costs tend to. It may be more reasonable to apply an incident cost of £1,081 and an ongoing weekly treatment cost. Based upon the information in the electronic model this can be crudely calculated as a weekly treatment costs for those receiving active treatment of £1,561[21]. This estimate is for illustrative purposes. The ERG is not arguing that it is a realistic estimate and it may be too high given the complex lenalidomide and bortezomib PASs. The company should be free to come up with its own estimate.

In the light of this the ERG will conduct sensitivity analyses which increase the proportion receiving active PPS treatment to 41% and apply an ongoing weekly cost of £1,561.

5.3.4.16 Concomitant medication costs

The number of patients receiving each concomitant medication is assumed to remain constant while in PFS. It seems possible that this may vary depending upon whether the main treatment is being received which is determined by the ToT curve. BORT+DEX is also rather different from both IXA+LEN+DEX and LEN+DEX in having a maximum of eight cycles administered.

Concomitant medications are also not associated with any additional administration costs. This is only likely to have any effect upon results if IV administration costs for zoledronic acid and pamidronic acid are applied. This has little effect upon the cost effectiveness estimates.

[21] The details of this are presented in the *PostProgression* worksheet of the ERG revised model.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

The ERG retains the company model structure for the comparisons:

- Using the company NMA for the comparison of IXA+LEN+DEX with BORT+DEX for the 1 prior subgroup
- Using the company 2+ prior adjusted curves for the comparison of IXA+LEN+DEX with LEN+DEX for the 2 prior subgroup

The ERG also supplies three scenario analyses that use the company model:

- Comparing IXA+LEN+DEX with LEN+DEX for the 1 prior subgroup using the company TMM-1 curves for the 1 prior group
- Applying the ERG NMA results for the 1+ prior subgroup rather than the company NMA results for the 1+ prior group to the 1 prior subgroup
- Applying the unadjusted curves derived by the ERG from the 2 prior patient population Kaplan Meier data supplied at clarification

These have only been implemented deterministically due to time constraints.

Each of the 5 scenarios above is based upon the 1st interim data cut.

The ERG makes the following changes to the company base case assumptions:

- Limit BORT+DEX to a maximum of 8 cycles
- For the delayed exponential apply the 5 months' delay equally in both arms
- Apply the BORT+DEX PFS HR to the LEN+DEX ToT curve
- Use the ENDEAVOR BoR distribution for BORT+DEX
- Add a nurse led outpatient cost to each BORT+DEX administration subsequent to the first administration of each cycle
- Remove the company disutility for BORT+DEX administrations
- Apply administration costs for the intravenous concomitant medications

- 100% dosing intensity to align the assumptions between treatments

The ERG also undertakes a range of sensitivity analyses:

- SA01: Varying the OS curves functional forms
- SA02: Varying the PFS curves functional forms
- SA03: Varying the ToT curves functional forms
- SA04: Applying the ERG NMA results of the 1 prior group for the 1 prior subgroup
- SA05: Applying the OS HR and PFS HR of the 1+ prior subgroup for IXA+LEN+DEX versus LEN+DEX
- SA06: Applying the QoL values of TA171 and TA338
- SA07: Assuming a five week cycle for BORT+DEX
- SA08: Costing treatments using the PFS curve rather than the ToT curve.
- SA09: Increasing the PPS proportion receiving active treatment from 24% to 41% and applying an incident cost of £1,081 and an ongoing weekly cost of £1,561.

5.4.1.1 ERG Analysis 1: 1 prior and company NMA: IXA+LEN+DEX vs BORT+DEX

The ERG revisions to the company base case for the 1 prior subgroup result in the following cost effectiveness estimates.

Table 84: ERG revised company base case: 1 prior subgroup[22]

	Undisc. LY			QALYs			Costs			
	PFS	PPS	OS	PFS	PPS	Total	Drug	ConMed	Ongoing	Total
BORD	1.920	0.953	2.873	1.259	0.553	1.779	£27,007	£9,520	£5,504	£44,707

[22] Within the tables and figures of the economics, in order to economise on space IXA+LEN+DEX is abbreviated to IXAL, LEN+DEX is abbreviated to LEND and BORT+DEX is abbreviated to BORD.

IXAL	2.168	5.007	7.175	1.415	2.547	3.932	[redacted]	£21,145	£14,756	[redacted]
Net	0.249	4.054	4.302	0.155	1.994	2.153	[redacted]	£11,626	£9,252	[redacted]
ICER										[redacted]

The ERG revisions to the company base case have some impact upon results for the 1 prior subgroup, worsening the cost effectiveness estimate by around 10%.

The probabilistic modelling suggests mean net costs of [redacted], mean net benefits of 2.13 QALYs and a cost effectiveness of [redacted] per QALY for IXA+LEN+DEX compared to BORT+DEX.

[redacted]

Figure 59: ERG revised company base case: 1 prior subgroup: Probabilistic

There is apparently no prospect of IXA+LEN+DEX being cost effective compared to BORD+DEX among the 1 prior subgroup at conventional willingness to pay thresholds.

5.4.1.2 ERG Analysis 2: 2+ prior subgroup and company TMM-1 curves

The ERG revisions to the company base case for the 2+ subgroup result in the following cost effectiveness estimates.

Table 85: ERG revised company base case: 2+ prior subgroup

	Undisc. LY			QALYs			Costs			
	PFS	PPS	OS	PFS	PPS	Total	Drug	ConMed	Ongoing	Total
LEND	2.283	1.315	3.598	1.440	0.798	2.204	£74,027	£11,826	£8,484	£97,655
IXAL	3.535	1.776	5.311	2.174	1.033	3.174	[redacted]	£16,753	£8,954	[redacted]
Net	1.252	0.461	1.713	0.733	0.235	0.969	[redacted]	£4,927	£471	[redacted]
ICER										[redacted]

The ERG revisions to the company base case have little impact upon results for the 2+ prior subgroup. The probabilistic modelling suggests mean net costs of £202k, mean net benefits of 1.00 QALYs and a cost effectiveness of £202k per QALY for IXA+LEN+DEX compared to LEN+DEX.

Figure 60: ERG revised company base case: 2+ prior subgroup: Probabilistic

There is apparently no prospect of IXA+LEN+DEX being cost effective compared to LEN+DEX among the 2+ prior subgroup at conventional willingness to pay thresholds.

5.4.1.3 ERG Analysis 3: 1 prior: IXA+LEN+DEX vs LEN+DEX and company TMM-1 curves

The ERG exploration of the cost effectiveness of IXA+LEN+DEX versus LEN+DEX for the 1 prior subgroup using the company parameterised curves results in the following cost effectiveness estimates.

Table 86: ERG revised base case: 1 prior subgroup: versus LEN+DEX

	Undisc. LY			QALYs			Costs			
	PFS	PPS	OS	PFS	PPS	Total	Drug	ConMed	Ongoing	Total
LEND	2.033	6.000	8.033	1.330	3.025	4.326	£80,468	£23,319	£16,890	£123,801
IXAL	2.168	5.007	7.175	1.415	2.547	3.932	[redacted]	£21,145	£14,756	[redacted]
Net	0.135	-0.993	-0.858	0.085	-0.478	-0.394	[redacted]	-£2,173	-£2,133	[redacted]
ICER										[redacted]

IXA+LEN+DEX is estimated to be inferior to LEN+DEX in terms of overall survival, this flowing through to a loss of 0.394 QALYs. This is in line with the company clarification response that the 0.89 OS hazard ratio for LEN+DEX versus IXA+LEN+DEX that underlies its modelling for the 1 prior subgroup is in favour of

LEN+DEX. IXA+LEN+DEX also results in considerable additional costs compared to LEN+DEX. As a consequence, LEN+DEX strongly dominates IXA+LEN+DEX.

5.4.1.4 ERG Analysis 4: 1 prior and ERG NMA: IXA+LEN+DEX vs BORT+DEX

The ERG exploration of the cost effectiveness of IXA+LEN+DEX versus BORT+DEX for the 1 prior subgroup using the ERG NMA results for the 1+ prior group for the BORT+DEX versus LEN+DEX clinical effectiveness estimates results in the following cost effectiveness estimates. Note that this retains the 1 prior curves for IXA+LEN+DEX and LEN+DEX of the previous ERG analysis 3, and the worse OS for IXA+LEN+DEX compared to BORT+DEX.

Table 87: ERG revised base case: 1 prior subgroup: ERG NMA 1+ prior

	Undisc. LY			QALYs			Costs			
	PFS	PPS	OS	PFS	PPS	Total	Drug	ConMed	Ongoing	Total
BORD	2.073	6.027	8.099	1.352	3.032	4.356	£27,181	£23,480	£16,865	£69,872
IXAL	2.168	5.007	7.175	1.415	2.547	3.932	[redacted]	£21,145	£14,756	[redacted]
Net	0.096	-1.020	-0.924	0.062	-0.485	-0.424	[redacted]	-£2,335	-£2,109	[redacted]
ICER										[redacted]

Given the slightly better OS HR for BORT+DEX versus LEN+DEX there is a slightly greater loss of 0.424 QALYs for IXA+LEN+DEX compared to a loss of 0.394 QALY when comparing IXA+LEN+DEX with LEN+DEX. The additional costs remain substantial and BORT+DEX dominates IXA+LEN+DEX.

5.4.1.5 ERG Analysis 5: 2 prior subgroup and ERG TMM-1 curves

The ERG exploration of the cost effectiveness of IXA+LEN+DEX versus LEN+DEX for the 2 prior subgroup using the ERG 2 prior group parameterised curves results in the following cost effectiveness estimates.

Table 88: ERG revised base case: 2 prior subgroup: ERG parameterised curves

Undisc. LY	QALYs	Costs

	PFS	PPS	OS	PFS	PPS	Total	Drug	ConMed	Ongoing	Total
LEND	2.488	3.974	6.462	1.537	2.086	3.592	£79,770	£19,300	£12,888	£115,334
IXAL	3.246	4.495	7.741	1.981	2.272	4.222	[redacted]	£22,501	£13,105	[redacted]
Net	0.758	0.521	1.279	0.444	0.185	0.631	[redacted]	£3,200	£216	[redacted]
ICER										[redacted]

The application of the 2 prior subgroup curves estimated by the ERG from the 2 prior subgroup Kaplan Meier data supplied by the company at clarification results in a somewhat lower patient gain compared to the 2+ prior subgroup modelling: 0.631 QALYs compared to 0.969 QALYs. This is as expected given the differences in the subgroups' Kaplan Meier curves. The net costs also fall as a consequence, but by less than the patient gain and the cost effectiveness estimate worsens quite considerably by around 40%.

5.4.1.6 Deterministic sensitivity analyses

Table 89: SA01: OS Curves

Analysis	ERG 1	ERG 2	ERG 3	ERG 4	ERG 5
Subgroup	1 prior	2+ prior	1 prior	1 prior	2 prior
Comparator	BORT+DEX	LEN+DEX	LEN+DEX	BORT+DEX	LEN+DEX
NMA	Comp 1+ prior	n.a.	n.a.	ERG 1+ prior	n.a.
Curves	Comp 1 prior	Comp 2+ prior	Comp 1 prior	Comp 1 prior	ERG 2 prior
Base case.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log Logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For the ERG 1 analysis which revises company comparison of IXA+LEN+DEX with BORT+DEX among the 1 prior subgroup the tail of the log normal curve increases the overall survival gains and improves the cost effectiveness estimate. The Weibull which is often chosen in cancer analyses and seems a reasonable choice for the base case given the AIC and BIC values somewhat worsens the cost effectiveness estimate. The Gompertz is worst of all. It is a similar story for the ERG 2 analysis which revises the company comparison of IXA+LEN+DEX with LEN+DEX among the 2+ prior subgroup. The tail of the log normal curve increases the overall survival gains and improves the cost effectiveness estimate.

For the ERG 3 analysis which uses the company curves to compare IXA+LEN+DEX with LEN+DEX among the 1 prior subgroup, IXA+LEN+DEX remains dominated by LEN+DEX throughout. Similarly, if the ERG NMA HR results for the 1+ prior group are applied to the LEN+DEX 1 prior curves as in ERG analysis 4, BORT+DEX is estimated to dominate IXA+LEN+DEX among the 1 prior subgroup regardless of the functional form chosen for OS.

The ERG analysis 5 which applies the 2 prior subgroup curves uses the exponential for its base case. This is the most optimistic, with the other functional forms worsening the cost effectiveness estimate.

Table 90: SA02: PFS Curves

Analysis	ERG 1	ERG 2	ERG 3	ERG 4	ERG 5
Subgroup	1 prior	2+ prior	1 prior	1 prior	2 prior
Comparator	BORT+DEX	LEN+DEX	LEN+DEX	BORT+DEX	LEN+DEX
NMA	Comp 1+ prior	n.a.	n.a.	ERG 1+ prior	n.a.
Curves	Comp 1 prior	Comp 2+ prior	Comp 1 prior	Comp 1 prior	ERG 2 prior
Base case.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Exponential					
Weibull					
Log Normal					
Log Logistic					
Gompertz					
Gamma					

Due to the quality of life values for PPS survival and stable disease being similar and the ToT curves determining treatment costs, the cost effectiveness estimates are not sensitive to the PFS curves. But if the PFS curves are viewed as a more reasonable basis for modelling treatment costs they become more important. As explored later, costing treatments on the basis of the PFS curve worsens the cost effectiveness estimate for the ERG 1 analysis from £ per QALY to £ per QALY. But if this PFS curve is a Weibull as may be more reasonable the cost effectiveness estimate only worsens to £ per QALY.

Table 91: SA03: ToT Curves

Analysis	ERG 1	ERG 2	ERG 3	ERG 4	ERG 5
Subgroup	1 prior	2+ prior	1 prior	1 prior	2 prior
Comparator	BORT+DEX	LEN+DEX	LEN+DEX	BORT+DEX	LEN+DEX
NMA	Comp 1+ prior	n.a.	n.a.	ERG 1+ prior	n.a.
Curves	Comp 1 prior	Comp 2+ prior	Comp 1 prior	Comp 1 prior	ERG 2 prior
Base case.					
Exponential					
Weibull					
Log Normal					
Log Logistic					
Gompertz					
Gamma					

The sensitivity of results to the ToT curves is as would be expected, and those with the longer tails worsen the cost effectiveness estimates. For the ERG estimated curves for the 2 prior subgroup the base case is the most optimistic, though some of the curves when extrapolated clearly have implausibly long tails.

Table 92: Sensitivity analyses SA04 to SA09

Analysis Subgroup Comparator NMA Curves	ERG 1 1 prior BORT+DEX Comp 1+ prior Comp 1 prior	ERG 2 2+ prior LEN+DEX n.a. Comp 2+ prior	ERG 3 1 prior LEN+DEX n.a. Comp 1 prior	ERG 4 1 prior BORT+DEX ERG 1+ prior Comp 1 prior	ERG 5 2 prior LEN+DEX n.a. ERG 2 prior
Base case.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA04: ERG 1 prior	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA05: IXAL HRs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA06a: TA171 Qol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA06b: TA338 Qol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA07: BORT 5wk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA08: no ToT, PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA09: PPS costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The SA04 of applying the ERG 1 prior NMA results rather than the 1+ prior NMA results for the comparison of BORT+DEX with IXA+LEN+DEX main results in a better overall survival for BORT+DEX and so dominance over IXA+LEN+DEX is maintained.

Within the 1 prior subgroup modelling, applying the 1+ prior HRs for OS and PFS for IXA+LEN+DEX compared to LEN+DEX rather than using the 1 prior curves causes IXA+LEN+DEX to no longer be dominated. The 1+ prior NMA suggests IXA+LEN+DEX yields a survival gain compared to LEN+DEX, while the curves

estimated from the TMM-1 trial for the 1 prior group suggest the reverse. But the estimated cost effectiveness remains extremely poor.

The quality of life values have little impact on the 1 prior subgroup modelling, but they result in some improvements in the cost effectiveness estimates for the 2+ prior and the 2 prior subgroups.

Costing treatment using the PFS curves rather than the ToT curves somewhat worsens the cost effectiveness estimates.

Applying a slightly arbitrary weekly cost of treatment for PPS among those receiving subsequent therapy rather than simply applying a one off cost when progressing coupled with an increase in the proportion receiving subsequent treatment also somewhat worsens the cost effectiveness estimates.

5.5 Conclusions of the cost effectiveness section

The economics of the company submission is incomplete in 3 main areas:

- Relying upon the 1st interim data cut and providing little to no consideration of the 2nd interim data cut. This seems peculiar given the company assertion that longer trial follow-up is needed to properly judge ixazomib.
- Not considering LEN+DEX as a comparator for the 1 prior subgroup. It is specified in the scope. The company states that it cannot provide this. The available evidence suggests that LEN+DEX dominates IXA+LEN+DEX for the 1 prior subgroup.
- Assuming the 2+ prior subgroup is the best proxy for the 2 prior subgroup and not considering the 2 prior subgroup data. This is complicated by the trial being stratified by 1 prior subgroup and 2+ prior subgroup but the company submission, CSR and clarification response provide forest plots differentiated by 1 prior subgroup, 2 prior subgroup and 3 prior subgroup. The available evidence suggests that the cost effectiveness of IXA+LEN+DEX compared to LEN+DEX is somewhat worse for the 2 prior subgroup than for the 2+ prior subgroup.

The economics of the company submission may be biased in a number of areas:

- The NMA results for BORT+DEX compared to LEN+DEX as reviewed in more detail in the clinical effectiveness section suggest overall survival for BORT+DEX is estimated as much too low.
- The costs of BORT+DEX have been overestimated, with a number of biases being introduced within the modelling.
  - Assuming a maximum of 9 cycles rather than 8 cycles
  - Assuming every three week cycle is completed rather than applying the PFS or Time on Treatment (ToT) curve.
  - Assuming treatment is discontinued at progression when partial response at 4 cycles appears to be the appropriate measure
  - Assuming those with complete response continue to the maximum number of cycles when they only receive a further 2 cycles
  - Assuming a hazard ratio of 1.00 for ToT compared to LEN+DEX due to a lack of data when a hazard ratio of 1.06 for PFS compared to LEN+DEX has been applied
  - The progression dependent bortezomib refunds may also have been underestimated, though the ERG in conjunction with NICE is exploring whether these refunds would apply in the context of the BORT+DEX doublet
- Most BORT+DEX patients will receive their subcutaneous injections in hospital, though there are some home care facilities available. The OP visits subsequent to the first of each cycle have not been costed.
- For the 1 prior subgroup the company base case delays the OS exponential for IXA+LEN+DEX by 5 months but does not do so for LEN+DEX, which by the application of the NMA HR flows through to BORT+DEX. The company accepts that this results in bias against BORT+DEX and that the LEN+DEX OS exponential should also be delayed by 5 months.
- The distribution of Best overall Response (BoR) for BORT+DEX is drawn from a study of monotherapy bortezomib against monotherapy dexamethasone. The company has inadvertently used the dexamethasone values. The ERG is of the

opinion that a study of BORT+DEX is more appropriate and that the ENDEAVOR study provides data in the required format.

- The disutility for subcutaneous injection seems too large and may, as argued by the company, for a frail population be related more to the inconvenience of hospital visits than the 3-5 seconds subcutaneous injection. If so, the disutility should be attached to the number of hospital visits and not to a treatment that involves a small number of subcutaneous injections.
- The quality of life as patients relapse and cycle through treatments seems likely to decline. It will also decline with age.
- The proportion of patients receiving active treatment in PPS is based upon using the number in the trial as the denominator rather than the number who had progressed at the 1st interim data cut. This underestimates the treatment proportion.
- The cost of treatment among those who have progressed and receive another active treatment is modelled as a one off incident cost so may unreasonably tend to cancel out between arms, much like end of life costs. It may be more accurate to model this as an ongoing cost among those in PPS.

Remaining areas of uncertainty include:

- The degree of extrapolation required. Given the immaturity of the data the parameterised curves are extrapolated for much of the time horizon of the model. For the main trial period there are very limited differences between the parameterised curves. But they diverge quite radically after the numbers at risk have dropped off and during the extrapolation period. The model should also explore the impact of reducing the clinical effectiveness estimates over time, in line with the NICE methods guide.
- The company argues that the first 5 months of OS for the 1 prior subgroup does not conform to proportionate hazards and so estimates a delayed exponential from the post 5 months TMM-1 data. It is peculiar and out of keeping with the rest of the submission for the company to not present the range of other functional forms estimated from the post 5

months TMM-1 data. This reduces the confidence that can be placed in the delayed exponential.

- The TMM-1 quality of life regression. There is no analysis report. The evolution of the analysis should have been reported in more detail, together with the effect of the treatment covariate. Given the model structure and baseline quality of life values it seems unusual for the company not to have explored the 1 prior / 2+ prior split within the quality of life analysis, even if only to subsequently reject it.
- The baseline quality of life was higher in the IXA+LEN+DEX arm than the LEN+DEX arm. There is the suggestion that a better baseline quality of life increases the likelihood of a good response, particularly among the 1 prior subgroup. The company adjusted the parameterised curves for a number of factors, but the baseline quality of life does not appear to have been explored. The company does not perform any adjustment to the BoR data when it might be anticipated that a similar range of covariates including the baseline quality of life, which differed between the arms, might be factors.
- BoR is assumed to apply throughout the PFS extrapolation period. Patients will not spend all this time in their BoR.
- The handling and use of the ToT curves significantly reduces treatment costs to below that which would be estimated had the PFS curves been used. This applies with particular force to IXA+LEN+DEX. It is currently unclear whether events and censorings have been sensible handled. It is also unclear whether the estimated balances between PFS time on treatment and PFS time off treatment, which can be as large as 65:35, are reasonable.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG amends the company modelling of the 1 prior subgroup and the 2+ prior subgroup in a number of ways. This mainly affects the 1 prior subgroup modelling with the revisions causing the cost effectiveness estimate for IXA+LEN+DEX compared to BORT+DEX worsening from [redacted] per QALY to [redacted] per QALY. The cost effectiveness estimate in the 2+ prior subgroup for IXA+LEN+DEX compared to LEN+DEX only worsens from [redacted] to [redacted] per QALY.

The main additional analyses of the ERG modelling:

- Compare IXA+LEN+DEX with LEN+DEX for the 1 prior subgroup using the company TMM-1 curves for the 1 prior group. This suggests that IXA+LEN+DEX is dominated by LEN+DEX.
- Apply the ERG NMA results for the 1+ prior subgroup rather than the company NMA results for the 1+ prior group to the 1 prior subgroup. This suggests that IXA+LEN+DEX is dominated by BORT+DEX.
- Apply the unadjusted curves derived by the ERG from the 2 prior patient subgroup Kaplan Meier data supplied at clarification. This suggests a cost effectiveness of [redacted] per QALY for IXA+LEN+DEX compared to LEN+DEX for the 2 prior subgroup

For the 1 prior subgroup estimating the IXA+LEN+DEX curves by applying the 1+ prior NMA estimates to the 1 prior LEN+DEX TMM-1 curves improves the cost effectiveness estimate based upon the company NMA from [redacted] per QALY to [redacted] per QALY. IXA+LEN+DEX also ceases to be dominated by LEN+DEX, and has a cost effectiveness estimate of [redacted] per QALY. Similarly, when using the ERG NMA IXA+LEN+DEX ceases to be dominated by BORT+DEX, and has a cost effectiveness estimate of [redacted] per QALY.

There is uncertainty about the reasonableness of the time on treatment curves. These are better labelled time to complete cessation of treatment curves and are used to estimate the treatment costs. They suggest that perhaps as little as the first 65% of IXA+LEN+DEX PFS is spent receiving treatment with the remaining 35% of IXA+LEN+DEX PFS being spent off treatment. Costing treatment using the PFS curves:

- For the 1 prior subgroup using the company NMA worsens the cost effectiveness estimate for IXA+LEN+DEX compared to BORT+DEX from [redacted] per QALY to [redacted] per QALY.
- For the 2+ prior subgroup using the company TMM-1 curves worsens the cost effectiveness estimate for IXA+LEN+DEX compared to LEN+DEX from [redacted] per QALY to [redacted] per QALY.
- For the 1 prior modelling using the company TMM-1 curves still suggests IXA+LEN+DEX is dominated by LEN+DEX.
- For the 1 prior modelling using the ERG NMA still suggests IXA+LEN+DEX is dominated by BORT+DEX.
- For the 2 prior subgroup modelling using the ERG TMM-1 curves worsens the cost effectiveness estimate for IXA+LEN+DEX compared to LEN+DEX from [redacted] per QALY to [redacted] per QALY.

The main sensitivity of results in terms of the curves functional forms, restricting attention to those that may be reasonable to apply for OS is:

- For the 1 prior subgroup using the company NMA the cost effectiveness estimate for IXA+LEN+DEX compared to BORT+DEX worsens from [redacted] per QALY to [redacted] per QALY if the Weibull is used for overall survival.
- For the 2+ prior subgroup using the company TMM-1 curves the cost effectiveness estimate for IXA+LEN+DEX compared to LEN+DEX improves from [redacted] per QALY to [redacted] per QALY if the exponential is used for overall survival. But there is uncertainty about the AIC and BIC values for the exponential. It also suggests a fair proportion of patients remain alive after 25 years: over 6% for IXA+LEN+DEX and 1% for LEN+DEX.

- For the 2 prior subgroup modelling using the ERG TMM-1 curves the cost effectiveness estimate for IXA+LEN+DEX compared to LEN+DEX worsens quite considerable from [redacted] per QALY if anything other than the exponential is used for overall survival.

The parallel for the ToT curves is:

- For the 2+ prior subgroup using the company TMM-1 curves the base case ToT curve provides the best cost effectiveness estimates, the Weibull worsening the cost effectiveness estimate from £[redacted] per QALY to £[redacted] per QALY.
- For the 2 prior subgroup modelling using the ERG TMM-1 curves the cost effectiveness estimate for IXA+LEN+DEX compared to LEN+DEX worsens quite considerable from [redacted] per QALY if anything other than the exponential is used for overall survival. The Weibull is the least worst of the alternatives, only worsening it to [redacted] per QALY.

The 1 prior modelling using the company TMM-1 curves and the ERG NMA suggests that IXA+LEN+DEX remains dominated by LEN+DEX and by BORT+DEX regardless of the functional forms that are chosen.

The modelling of treatment costs after progression is questionable and may unreasonably cancel out between arms. Revising the proportion that receives post progression treatment and exploring an ongoing weekly cost for this:

- For the 1 prior subgroup using the company NMA worsens the cost effectiveness estimate for IXA+LEN+DEX compared to BORT+DEX from [redacted] per QALY to [redacted] per QALY.
- For the 2+ prior subgroup using the company TMM-1 curves worsens the cost effectiveness estimate for IXA+LEN+DEX compared to LEN+DEX from [redacted] per QALY to [redacted] per QALY.
- For the 1 prior modelling using the company TMM-1 curves still suggests IXA+LEN+DEX is dominated by LEN+DEX.

- For the 1 prior modelling using the ERG NMA still suggests IXA+LEN+DEX is dominated by BORT+DEX.
- For the 2 prior subgroup modelling using the ERG TMM-1 curves worsens the cost effectiveness estimate for IXA+LEN+DEX compared to LEN+DEX from [redacted] per QALY to [redacted] per QALY.

The use of the 2nd interim analysis within the company modelling appears to somewhat worsen the cost effectiveness estimate for the 1 prior subgroup, but to improve it to a degree for the 2+ prior subgroup. But the ERG has not parsed this modelling, it is a mix of elements from the 1st interim analysis and the 2nd interim analysis, there are a number of uncertainties around it and the curves chosen by the company may not be reasonable either in terms of their AIC and BIC or in terms of their clinical plausibility.

For overall survival among the 1 prior subgroup, due to proportionate hazards being questionable over the first 5 months, the company chooses to use the Kaplan Meier data for the first 5 months and estimate an exponential curve from the post 5 months trial data. No other curves are presented for this post 5 month data set which is not in keeping with the rest of the submission. This reduces the confidence that can be placed in the delayed exponential of the 1 prior subgroup.

Extrapolation that maintains the relative treatment effect of the trials over the 25 year time horizon may exaggerate the differences. The analysis should explore reducing the extrapolated clinical effectiveness. This will probably worsen the company cost effectiveness estimates and the ERG 2 prior subgroup cost effectiveness estimates, and reduce but not eliminate the ERG 1 prior subgroup estimated dominance of BORT+DEX and LEN+DEX over IXA+LEN+DEX.

Addressing the costing issues around BORT+DEX will worsen the cost effectiveness of IXA+LEN+DEX for this comparison. The implementation of the complex progression based PAS for bortezomib if applicable also underestimates the probable refunds. But the complex progression based PAS for bortezomib may not apply to the BORT+DEX doublet. Removing this from the modelling has minimal impact upon the cost effectiveness estimates for IXA+LEN+DEX compared to BORT+DEX.

The treatment effect in the quality of life regression is not reported, and the 1 prior / 2+ prior split is not explored at all. The direction of effect of these is not known by the ERG.

If quality of life declines with each relapse and with age as seems likely this will probably worsen the cost effectiveness of the treatment with the greater overall survival, though this will also be determined by the balance between PPS and PFS which may differ between treatments.

Modelling PPS costs as a function of PPS duration rather than a one off incident cost appears to worsen the cost effectiveness of the more effective treatment, though this will depend upon the balance between PFS and PPS which may differ by treatment.

7 End of life

End of life does not apply.

8 Overall conclusions

Regarding the clinical effectiveness, Ixazomib combined with lenalidomide and dexamethasone was evaluated against lenalidomide and dexamethasone as part of the Tourmaline MM1 RCT. The ERG does not have any reason to consider the results of this trial to be significantly biased but clinical effectiveness data are characterised by a high degree of immaturity.

Regarding the primary endpoint of TMM, the HR from the first interim analysis suggested a 26% reduction in risk of progression or death from a first interim analysis but the benefit appears to be reduced with more mature data for the second interim analysis. In the 1 prior therapy group, there was clearly no benefit with ixazomib compared to placebo. In the 2-3 prior therapy group, the benefit with ixazomib was more convincing for PFS. To date, OS data are very immature to draw conclusions on the impact of ixazomib.

For the indirect comparison of ixazomib-based regimen to bortezomib-dexamethasone, the CS's NMA has several major limitations and contains an unfortunate error in the analysis on OS.

The revised NMAs proposed by the ERG conclude that, in the 1+ prior therapy group, the HR for progression or death of ixazomib+lenalidomide+dexamethasone relative to bortezomib + dexamethasone is 0.75 (95%CI 0.41, 1.38) while the HR for death for ixazomib+lenalidomide+dexamethasone relative to bortezomib + dexamethasone is 0.91 (95%CI 0.43-1.92). The ERG also provided additional NMA in the 1 prior therapy group but these the results presented for OS in this subgroup are more subject to caution owing to the heterogeneity of included studies and the immaturity of OS data from the TMM-1trial.

Regarding the cost-effectiveness analyses, the main differences of opinion between the company and the ERG are:

- Should the analysis be based upon the 1st interim analysis or upon the 2nd interim analysis?
- What hazard ratios should be applied for BORT+DEX compared to LEN+DEX for the 1 prior subgroup modelling?
- Should LEN+DEX be a comparator for the 1 prior subgroup modelling?
- Is the 2+ prior subgroup data the most reasonable proxy for the 2 prior subgroup modelling or should the 2 prior subgroup data be used or explored?
- What is the appropriate source and values for the distribution of best overall responses in the BORT+DEX arm?
- Should the quality of life analysis have explored the 1 prior / 2+ prior split?
- Is it appropriate to include a disutility for subcutaneous injections that last 3-5 seconds or is the disutility more associated with hospital visits? How large should the disutility be?

- Does quality of life decline by each relapse and with age? Is the value for progressive disease credible given that only 24% or 41% of those progressing in TMM-1 received further active treatment during TMM-1 follow-up? Is this in line with the values from other assessments and the company literature review?
- How should treatment costs be estimated? Is the construction of the ToT curves reasonable and given the SmPCc do they result in sensible estimates of the proportion of PFS time spent on treatment before treatment cessation?
- Have the costs of BORT+DEX been overestimated in the model?
- What proportion should be modelled as receiving active treatment post progression?
- How should post progression active treatment costs be modelled, as a one off cost at progression or as an ongoing cost

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Appendix: PAS inclusive analyses

The company provides a PAS which is a simple [redacted]% reduction in the list price, reducing the 4 weekly cost per pack if ixazomib from £6,336 to £[redacted]. This reduces the annual cost of ongoing dosing with ixazomib from £82,651 to £[redacted].

Company base case results

As in the ERG report the main elements that differ between the arms are presented. Adverse events and terminal care costs have been omitted for reasons of space. For the 1 prior subgroup the costs effectiveness estimates of the company base case are as below.

Table 1: Company base case ICERs: 1 prior: With IXA PAS

	Undisc. LY			QALYs			Costs			
	PFS	PPS	OS	PFS	PPS	Total	Drug	ConMed	Ongoing	Total
BORD	1.916	0.716	2.632	1.219	0.410	1.596	£28,057	£3,957	£3,981	£38,770
IXAL	2.168	5.007	7.175	1.415	2.547	3.932	£172,745	£9,590	£15,725	£201,274
Net	0.253	4.291	4.543	0.196	2.138	2.336	£144,688	£5,633	£11,744	£162,503
ICER										£69,565

The central probabilistic estimates from running the model over 10,000 iterations are net costs of £163k, a net gain of 2.24 QALYs and a cost effectiveness of £72,660 per QALY.

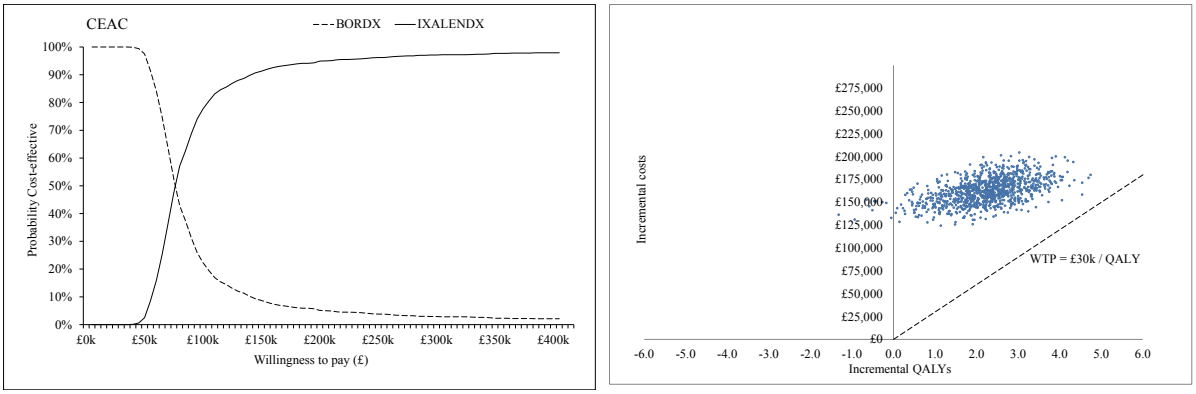

Figure 1: 1 prior probabilistic modelling results: 1 prior

There is apparently no prospect of ixazomib being cost effective at a willingness to pay of £30k per QALY.

For the 2+ prior subgroup the costs effectiveness estimates of the company base case are as below.

Table 2: Company base case ICERs: 2+ prior: With IXA PAS

	Undisc. LY			QALYs			Costs			
	PFS	PPS	OS	PFS	PPS	Total	Drug	ConMed	Ongoing	Total
LEND	2.283	1.315	3.598	1.440	0.798	2.204	£73,941	£5,363	£8,805	£91,428
IXAL	3.535	1.776	5.311	2.174	1.033	3.174	£201,828	£7,598	£9,378	£222,532
Net	1.252	0.461	1.713	0.733	0.235	0.969	£127,886	£2,234	£573	£131,104
ICER										£135k

The central probabilistic estimates from running the model over 10,000 iterations are net costs of £131k, a net gain of 0.971 QALYs and a cost effectiveness of £135k per QALY.

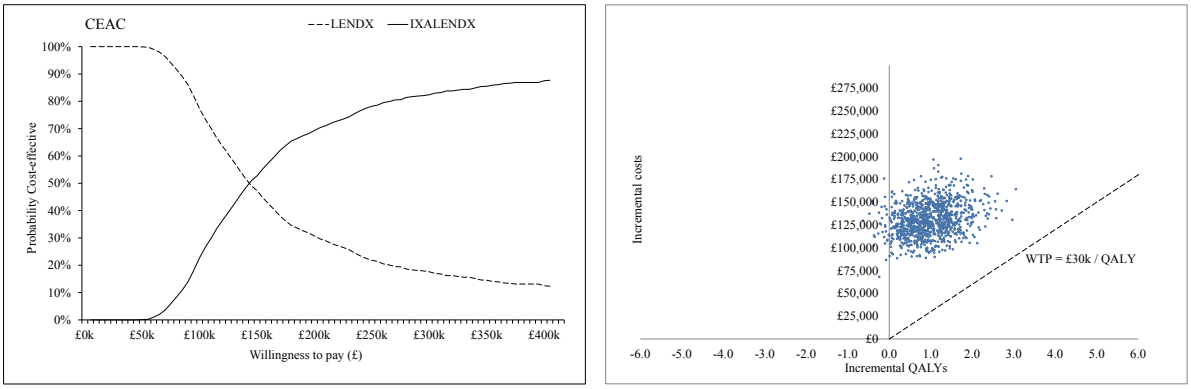

Figure 2: 1 prior probabilistic modelling results: 2+ prior

There is apparently no prospect of ixazomib being cost effective at a willingness to pay of £30k per QALY.

Company sensitivity analyses

The PAS inclusive sensitivity analyses and scenario analyses are as below.

Table 3: Company sensitivity analyses: 10 most influential: 1 prior subgroup

	Lower	Upper
OS (NMA (HR)) - BORT+DEX v LEN+DEX HR	£162,673	£54,355
TOT (Adj) (Survival) - Treatment - Weibull	£57,526	£83,313
TOT (Adj) (Survival) - Constant - Weibull	£60,006	£80,418
Coefficient associated with utility regression - PD	£66,373	£73,489
Coefficient associated with utility regression - Intercept	£67,175	£72,341
TOT (Adj) (Survival) - ISS = Stage III - Weibull	£67,554	£71,630
PFS (NMA (HR)) - BORT+DEX v LEN+DEX HR	£71,304	£67,295
PFS (Adj) (Survival) - Treatment - Gamma	£70,913	£67,986
Coefficient associated with utility regression - PR	£70,437	£68,618
TOT (Adj) (Survival) - Gamma - Weibull	£68,284	£69,822

Table 4: Company sensitivity analyses: 10 most influential: 2+ prior subgroup

	Lower	Upper
OS (Adj) (Survival) - Treatment - Weibull	-£2,3mn	£59,215
OS (Adj) (Survival) - Constant - Weibull	£209k	£96,365
TOT (Adj) (Survival) - Treatment – Expon.	£189k	£90,504
TOT (Adj) (Survival) - Constant – Expon.	£167k	£110k
OS (Adj) (Survival) - Age > 65 years - Weibull	£164k	£113k
TOT (Adj) (Survival) - Light chain myeloma - Expon.	£144k	£127k
TOT (Adj) (Survival) - Renal dysfunction - Expon.	£142k	£129k
PFS (Adj) (Survival) - Treatment - Gamma	£142k	£129k
Coefficient associated with utility regression - Intercept	£131k	£140k
PFS (Adj) (Survival) - Kappa - Gamma	£133k	£139k

Table 5: Company scenario analyses

	1 prior	2+ prior
Base case	£69,595	£135k
SA02: Unadjusted curves	£68,879	£146k
SA03: Cap ToT by PFS	£69,565	£136k
SA04: OS exponential	£68,442	£90,364
SA04: OS Weibull	£99,076	£135k
SA04: OS Gompertz	£157k	£172k
SA04: OS Log Normal	£53,135	£198k
SA04: OS Log logistic	£72,051	£190k
SA04: OS Gamma	£60,955	£156k
SA04: PFS Weibull	£69,708	£138k
SA04: PFS Gompertz	£69,953	£140k
SA04: ToT exponential	£75,263	£135k
SA04: ToT Weibull	£69,565	£139k
SA04: ToT Gompertz	£65,392	£172k
SA04: ToT Log normal	£100k	£198k
SA04: ToT Log logistic	£84,420	£190k
SA04: ToT Gamma	£69,044	£156k
SA05: 25% reduction in IXAL ToT curve	£51,930	£85,104
SA06: ToT based upon TMM-1 disc. and censored	£43,578	£67,769
SA07: 2nd interim data cut	..	..
SA08: NMA dose specific studies OS and BoR	£56,034	..
SA08: NMA HRs applied for IXAL to LEND	£56,034	£147k
SA09: TA171 QoL values	£71,168	£124k
SA09: TA171 QoL values	£75,091	£131k
SA10: £0 ixazomib price	£29,800	£14,109

	1 prior	2+ prior
Base case	£69,595	£135k
SA11: Subtracting LEN+DEX direct drug costs	..	£63,675
SA12: Same total LEN+DEX costs in both arms	..	£126k

ERG analyses of section 5.4 of ERG report

The ERG revised base cases and sensitivity analyses inclusive of the ixazomib PAS are as below.

ERG Analysis 1: 1 prior and company NMA: IXA+LEN+DEX vs BORT+DEX

The ERG revisions to the company base case for the 1 prior subgroup result in the following cost effectiveness estimates.

Table 6: ERG revised company base case: 1 prior subgroup: Inc PAS

	Undisc. LY			QALYs			Costs			
	PFS	PPS	OS	PFS	PPS	Total	Drug	ConMed	Ongoing	Total
BORD	1.920	0.953	2.873	1.259	0.553	1.779	£27,007	£9,520	£5,504	£44,707
IXAL	2.168	5.007	7.175	1.415	2.547	3.932	£172,834	£21,145	£14,756	£211,951
Net	0.249	4.054	4.302	0.155	1.994	2.153	£145,828	£11,626	£9,252	£167,244
ICER										£77,678

The probabilistic modelling suggests mean net costs of £168k, mean net benefits of 2.13 QALYs and a cost effectiveness of £78,781 per QALY for IXA+LEN+DEX compared to BORT+DEX.

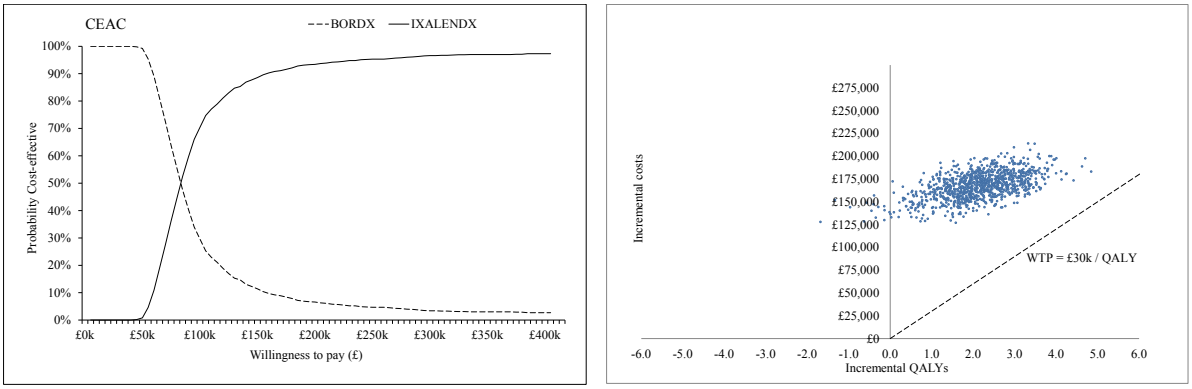

Figure 3: ERG revised company 1 prior group modelling: Probabilistic: Inc PAS

There is apparently no prospect of IXA+LEN+DEX being cost effective compared to BORD+DEX among the 1 prior subgroup at conventional willingness to pay thresholds.

ERG Analysis 2: 2+ prior subgroup and company TMM-1 curves

The ERG revisions to the company base case for the 2+ subgroup result in the following cost effectiveness estimates.

Table 7: ERG revised company base case: 2+ prior subgroup: Inc PAS

	Undisc. LY			QALYs			Costs			
	PFS	PPS	OS	PFS	PPS	Total	Drug	ConMed	Ongoing	Total
LEND	2.283	1.315	3.598	1.440	0.798	2.204	£74,027	£11,826	£8,484	£97,655
IXAL	3.535	1.776	5.311	2.174	1.033	3.174	£201,941	£16,753	£8,954	£231,377
Net	1.252	0.461	1.713	0.733	0.235	0.969	£127,914	£4,927	£471	£133,722
ICER										£138k

The probabilistic modelling suggests mean net costs of £134k, mean net benefits of 0.99 QALYs and a cost effectiveness of £136k per QALY for IXA+LEN+DEX compared to LEN+DEX.

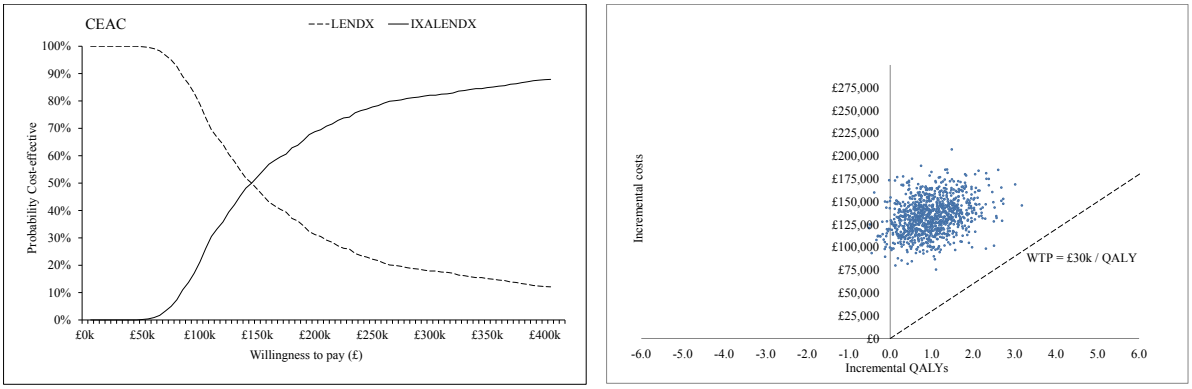

Figure 4: ERG revised company 2+ prior group modelling: Probabilistic: Inc PAS

There is apparently no prospect of IXA+LEN+DEX being cost effective compared to LEN+DEX among the 2+ prior subgroup at conventional willingness to pay thresholds.

ERG Analysis 3: 1 prior: IXA+LEN+DEX vs LEN+DEX and company TMM-1 curves

The ERG exploration of the cost effectiveness of IXA+LEN+DEX versus LEN+DEX for the 1 prior subgroup using the company parameterised curves results in the following cost effectiveness estimates. This uses the company parameterised curves for IXA+LEN+DEX and LEN+DEX based upon the 1 prior subgroup, and the associated OS hazard ratio of 0.89 for LEN+DEX versus IXA+LEN+DEX in favour of LEN+DEX.

Table 8: ERG revised base case: 1 prior subgroup: versus LEN+DEX: Inc PAS

	Undisc. LY			QALYs			Costs			
	PFS	PPS	OS	PFS	PPS	Total	Drug	ConMed	Ongoing	Total
LEND	2.033	6.000	8.033	1.330	3.025	4.326	£80,468	£23,319	£16,890	£123,801
IXAL	2.168	5.007	7.175	1.415	2.547	3.932	£172,834	£21,145	£14,756	£211,951
Net	0.135	-0.993	-0.858	0.085	-0.478	-0.394	£92,367	-£2,173	-£2,133	£88,150
ICER										Dom'ted

ERG Analysis 4: 1+ prior and ERG NMA: IXA+LEN+DEX vs BORT+DEX: Inc PAS

The ERG exploration of the cost effectiveness of IXA+LEN+DEX versus BORT+DEX for the 1 prior subgroup using the ERG NMA results for the 1+ prior group results in the following cost effectiveness estimates. Note that this retains the company parameterised curves for IXA+LEN+DEX and LEN+DEX, and the associated OS hazard ratio of 0.89 for LEN+DEX versus IXA+LEN+DEX.

Table 9: ERG revised base case: 1 prior subgroup: ERG NMA: Inc PAS

	Undisc. LY			QALYs			Costs			
	PFS	PPS	OS	PFS	PPS	Total	Drug	ConMed	Ongoing	Total
LEND	2.073	6.027	8.099	1.352	3.032	4.356	£27,181	£23,480	£16,865	£69,872
IXAL	2.168	5.007	7.175	1.415	2.547	3.932	£172,834	£21,145	£14,756	£211,951
Net	0.096	-1.020	-0.924	0.062	-0.485	-0.424	£145,654	-£2,335	-£2,109	£142,079
ICER										Dom'ted

Given the superior OS hazard ratio of 0.99 for BORT+DEX compared to LEN+DEX, this analysis slightly increases the QALY loss from IXA+LEN+DEX compared to the QALY loss of the ERG analysis 3 that compared IXA+LEN+DEX with LEN+DEX.

ERG Analysis 5: 2 prior subgroup and ERG TMM-1 curves

The ERG exploration of the cost effectiveness of IXA+LEN+DEX versus LEN+DEX for the 2 prior subgroup using the ERG 2 prior group parameterised curves results in the following cost effectiveness estimates.

Table 10: ERG revised base case: 2 prior subgroup: ERG parameterised curves: Inc PAS

	Undisc. LY			QALYs			Costs			
	PFS	PPS	OS	PFS	PPS	Total	Drug	ConMed	Ongoing	Total
LEND	2.488	3.974	6.462	1.537	2.086	3.592	£79,770	£19,300	£12,888	£115,334
IXAL	3.246	4.495	7.741	1.981	2.272	4.222	£193,889	£22,501	£13,105	£232,973
Net	0.758	0.521	1.279	0.444	0.185	0.631	£114,119	£3,200	£216	£117,639
ICER										£186k

ERG deterministic sensitivity analyses

The PAS inclusive results of the sensitivity analyses are as below.

Table 11: SA01: OS Curves: PAS inclusive

Analysis	ERG 1	ERG 2	ERG 3	ERG 4	ERG 5
Subgroup	1 prior	2+ prior	1 prior	1 prior	2 prior
Comparator	BORT+DEX	LEN+DEX	LEN+DEX	BORT+DEX	LEN+DEX
NMA	Comp 1+ prior	n.a.	n.a.	ERG 1+ prior	n.a.
Curves	Comp 1 prior	Comp 2+ prior	Comp 1 prior	Comp 1 prior	ERG 2 prior
Base case.	£77,678	£138k	Dom'ted	Dom'ted	£186k
Exponential	£72,579	£93,024	Dom'ted	Dom'ted	£186k
Weibull	£105k	£138k	Dom'ted	Dom'ted	£228k
Log Normal	£60,474	£120k	Dom'ted	Dom'ted	£256k
Log Logistic	£69,987	£131k	Dom'ted	Dom'ted	£244k
Gompertz	£166k	£243k	Dom'ted	Dom'ted	£290k
Gamma	£64,865	£117k	Dom'ted	Dom'ted	£290k

Table 12: SA02: PFS Curves: PAS inclusive

Analysis	ERG 1	ERG 2	ERG 3	ERG 4	ERG 5
Subgroup	1 prior	2+ prior	1 prior	1 prior	2 prior
Comparator	BORT+DEX	LEN+DEX	LEN+DEX	BORT+DEX	LEN+DEX
NMA	Comp 1+ prior	n.a.	n.a.	ERG 1+ prior	n.a.
Curves	Comp 1 prior	Comp 2+ prior	Comp 1 prior	Comp 1 prior	ERG 2 prior
Base case.	£77,678	£138k	Dom'ted	Dom'ted	£186k
Exponential	£77,488	£138k	Dom'ted	Dom'ted	£189k
Weibull	£77,775	£141k	Dom'ted	Dom'ted	£192k
Log Normal	£76,898	£138k	Dom'ted	Dom'ted	£187k
Log Logistic	£77,061	£139k	Dom'ted	Dom'ted	£188k
Gompertz	£78,056	£142k	Dom'ted	Dom'ted	£195k
Gamma	£77,678	£138k	Dom'ted	Dom'ted	£188k

Table 13: SA03: ToT Curves: PAS inclusive

Analysis	ERG 1	ERG 2	ERG 3	ERG 4	ERG 5
Subgroup	1 prior	2+ prior	1 prior	1 prior	2 prior
Comparator	BORT+DEX	LEN+DEX	LEN+DEX	BORT+DEX	LEN+DEX
NMA	Comp 1+ prior	n.a.	n.a.	ERG 1+ prior	n.a.
Curves	Comp 1 prior	Comp 2+ prior	Comp 1 prior	Comp 1 prior	ERG 2 prior
Base case.	£77,678	£138k	Dom'ted	Dom'ted	£186k
Exponential	£83,885	£138k	Dom'ted	Dom'ted	£186k
Weibull	£77,678	£142k	Dom'ted	Dom'ted	£200k
Log Normal	£106k	£203k	Dom'ted	Dom'ted	£336k
Log Logistic	£98,504	£190k	Dom'ted	Dom'ted	£308k
Gompertz	£73,182	£175k	Dom'ted	Dom'ted	£310k
Gamma	£77,118	£159k	Dom'ted	Dom'ted	£267k

Table 14: Sensitivity analyses SA04 to SA09: PAS inclusive

Analysis	ERG 1	ERG 2	ERG 3	ERG 4	ERG 5
Subgroup	1 prior	2+ prior	1 prior	1 prior	2 prior
Comparator	BORT+DEX	LEN+DEX	LEN+DEX	BORT+DEX	LEN+DEX
NMA	Comp 1+ prior	n.a.	n.a.	ERG 1+ prior	n.a.
Curves	Comp 1 prior	Comp 2+ prior	Comp 1 prior	Comp 1 prior	ERG 2 prior
Base case.	£77,678	£138k	Dom'ted	Dom'ted	£186k
SA04: ERG 1 prior	..	..	..	Dom'ted	..
SA05: IXAL HRs	£61,534	..	£358k	£634k	..
SA06a: TA171 Qol	£78,528	£127k	Dom'ted	Dom'ted	£173k
SA06b: TA338 Qol	£82,961	£134k	Dom'ted	Dom'ted	£180k
SA07: BORT 5wk	£78,271	..	Dom'ted	Dom'ted	..
SA08: no ToT, PFS	£87,665	£196k	Dom'ted	Dom'ted	£265k
SA09: PPS costs	£122k	£151k	Dom'ted	Dom'ted	£202k

ID807: Ixazomib for multiple myeloma: Addendum due to lenalidomide PAS

The PASLU has confirmed that the lenalidomide PAS where the lenalidomide company funds lenalidomide drug use after two years does not apply to the 1 prior subgroup. The 1 prior cost effectiveness estimates of the ERG need to be amended. This affects the ERG analyses 1, 3 and 4. Due to time pressures the ERG has only amended the cost effectiveness estimates inclusive of the ixazomib PAS.

Base case analyses

ERG Analysis 1: 1 prior and company NMA: IXA+LEN+DEX vs BORT+DEX

Table 01: ERG revised company base case: 1 prior subgroup: Inc PAS

	Undisc. LY			QALYs			Costs			
	PFS	PPS	OS	PFS	PPS	Total	Drug	ConMed	Ongoing	Total
BORD	1.920	0.953	2.873	1.259	0.553	1.779	£27,007	£9,520	£5,504	£44,707
IXAL	2.168	5.007	7.175	1.415	2.547	3.932	£199,616	£21,145	£14,756	£238,733
Net	0.249	4.054	4.302	0.155	1.994	2.153	£172,609	£11,626	£9,252	£194,026
ICER										£90,117

ERG Analysis 3: 1 prior: IXA+LEN+DEX vs LEN+DEX and company TMM-1 curves

Table 02: ERG revised base case: 1 prior subgroup: versus LEN+DEX: Inc PAS

	Undisc. LY			QALYs			Costs			
	PFS	PPS	OS	PFS	PPS	Total	Drug	ConMed	Ongoing	Total
LEND	2.033	6.000	8.033	1.330	3.025	4.326	£108,117	£23,319	£16,890	£151,450
IXAL	2.168	5.007	7.175	1.415	2.547	3.932	£199,616	£21,145	£14,756	£238,733
Net	0.135	-0.993	-0.858	0.085	-0.478	-0.394	£91,499	-£2,173	-£2,133	£87,283
ICER										Dom'ted

ERG Analysis 4: 1 prior and ERG NMA: IXA+LEN+DEX vs BORT+DEX: Inc PAS

Table 03: ERG revised base case: 1 prior subgroup: ERG NMA: Inc PAS

	Undisc. LY			QALYs			Costs			
	PFS	PPS	OS	PFS	PPS	Total	Drug	ConMed	Ongoing	Total
BORD	2.073	6.027	8.099	1.352	3.032	4.356	£27,181	£23,480	£16,865	£69,872
IXAL	2.168	5.007	7.175	1.415	2.547	3.932	£199,616	£21,145	£14,756	£238,733
Net	0.096	-1.020	-0.924	0.062	-0.485	-0.424	£172,436	-£2,335	-£2,109	£168,861
ICER										Dom'ted

Sensitivity analyses

Table 04: SA01: OS Curves: PAS inclusive

Analysis	ERG 1	ERG 3	ERG 4
Subgroup	1 prior	1 prior	1 prior
Comparator	BORT+DEX	LEN+DEX	BORT+DEX
NMA	Comp 1+ prior	n.a.	ERG 1+ prior
Curves	Comp 1 prior	Comp 1 prior	Comp 1 prior
Base case.	£90,117	Dom'ted	Dom'ted
Exponential	£84,111	Dom'ted	Dom'ted
Weibull	£122k	Dom'ted	Dom'ted
Log Normal	£69,846	Dom'ted	Dom'ted
Log Logistic	£81,064	Dom'ted	Dom'ted
Gompertz	£195k	Dom'ted	Dom'ted
Gamma	£75,018	Dom'ted	Dom'ted

Table 05: SA02: PFS Curves: PAS inclusive

Analysis	ERG 1	ERG 3	ERG 4
Subgroup	1 prior	1 prior	1 prior
Comparator	BORT+DEX	LEN+DEX	BORT+DEX
NMA	Comp 1+ prior	n.a.	ERG 1+ prior
Curves	Comp 1 prior	Comp 1 prior	Comp 1 prior
Base case.	£90,117	Dom'ted	Dom'ted
Exponential	£89,908	Dom'ted	Dom'ted
Weibull	£90,217	Dom'ted	Dom'ted
Log Normal	£89,283	Dom'ted	Dom'ted
Log Logistic	£89,451	Dom'ted	Dom'ted
Gompertz	£90,509	Dom'ted	Dom'ted
Gamma	£90,117	Dom'ted	Dom'ted

Table 06: SA03: ToT Curves: PAS inclusive

Analysis	ERG 1	ERG 3	ERG 4
Subgroup	1 prior	1 prior	1 prior
Comparator	BORT+DEX	LEN+DEX	BORT+DEX
NMA	Comp 1+ prior	n.a.	ERG 1+ prior
Curves	Comp 1 prior	Comp 1 prior	Comp 1 prior
Base case.	£90,117	Dom'ted	Dom'ted
Exponential	£103k	Dom'ted	Dom'ted
Weibull	£90,117	Dom'ted	Dom'ted
Log Normal	£148k	Dom'ted	Dom'ted
Log Logistic	£132k	Dom'ted	Dom'ted
Gompertz	£81,164	Dom'ted	Dom'ted
Gamma	£88,917	Dom'ted	Dom'ted

Table 07: Sensitivity analyses SA04 to SA09: PAS inclusive

Analysis	ERG 1	ERG 3	ERG 4
Subgroup	1 prior	1 prior	1 prior
Comparator	BORT+DEX	LEN+DEX	BORT+DEX
NMA	Comp 1+ prior	n.a.	ERG 1+ prior
Curves	Comp 1 prior	Comp 1 prior	Comp 1 prior
Base case.	£90,117	Dom'ted	Dom'ted
SA04: ERG 1 prior	..	..	Dom'ted
SA05: IXAL HRs	£71,068	£354k	£751k
SA06a: TA171 Qol	£91,103	Dom'ted	Dom'ted
SA06b: TA338 Qol	£96,246	Dom'ted	Dom'ted
SA07: BORT 5wk	£90,706	..	Dom'ted
SA08: no ToT, PFS	£107k	Dom'ted	Dom'ted
SA09: PPS costs	£135k	Dom'ted	Dom'ted

Additional scenario analyses

ERG OS NMA result

NICE has also requested that the ERG provide an estimate using the original company model corrected for the 5 month delay not being applied to the delayed exponential for BOR+DEX, removing the lenalidomide PAS from the calculations and applying the ERG NMA OS HR estimate. The sequential, cumulative effect of making these changes is outlined below.

Table 08: Corrected company model with ERG NMA OS HR

	Δ Cost	Δ QALYs	ICER
Original CS	£163k	2.336	£69,565
Correcting delayed exponential	£161k	2.191	£73,333
Removing lenalidomide PAS	£187k	2.191	£85,557
Applying the ERG NMA OS HR	£169k	-0.382	Dom'ted

Erratum for

Title: Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed refractory multiple myeloma

Produced by: Warwick Evidence

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Declared competing interests of the authors

The authors have no conflicts of interest.

Acknowledgements

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Ixazomib citrate in combination with lenalidomide and dexamethasone for relapsed refractory multiple myeloma: A Single Technology Appraisal. Warwick Evidence, 2017.

Contributions of authors: Xavier Armoiry (Senior Research Fellow) conducted the critique of clinical effectiveness evidence and co-ordinated the project; Ewen Cummins (Health Economist) conducted, reviewed and critiqued the cost-effectiveness evidence; Martin Connock (Senior Research Fellow) conducted the critique of clinical effectiveness evidence and undertook additional analyses; Alexander Tsertsvadze (Senior Research Fellow) conducted the critique of clinical effectiveness evidence and the NMA; G.J. Melendez-Torres (Assistant Professor) conducted the critique of clinical effectiveness evidence and the NMA; Rachel Court (Information specialist) and Pam Royle (Research Fellow) conducted the critique of the company searches; Karoline Munro conducted the critique of the background section and decision problem and contributed to the reporting of clinical effectiveness data; and Aileen Clarke (Professor of Public Health and Health Services Research) co-ordinated the project and provided comments on the report.

Word count: 65,667.

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

years in 2012 to 2014.[16] If one choses to express the value of a life year in monetary value, if one agreed with $150,000, and if one assumed that the average life expectancy is 85 years for 75 year old patients, the total value of life years lost would be $1,500,000. This calculation can be called into question at any point.

The company argues that high-risk subgroups should be identified according to NICE guidelines (CS, 48; NG35[17]), and states that IXA+LEN+DEX have demonstrated a consistently good performance in pre-specified subgroups, including amongst other things, patients with high-risk cytogenetic abnormalities (CS, 49). The CHMP however disagrees and states that "[i]t is not possible to identify a higher-risk subgroup that could benefit from treatment with ixazomib, especially based on post-hoc analysis and in view of non-compelling overall results. In addition, the results for the primary analysis and for sub-groups worsen from the first interim analysis to the second interim analysis and where the better results seen in high-risk patients appeared to be driven by patients with del(17) in the first interim analysis, but seemed driven by those with t(4;14) in the second interim analysis". [18] The CHMP states that no benefit can be observed for high-risk patients. This conclusion has not been revoked in the final decision by the EMA in November, in which they agree to grant marketing authorisation on the basis of the good toxicity profile but in expectation of more clinical data to support a positive benefit-risk balance.

2.2 Critique of company's overview of current service provision

The CS presents a treatment pathway for MM on page 56 and corresponding text on pages 56-57. The treatment pathway for first line is presented depending on patients are eligible or not for ASCT, and this is in line with current standards. In the pathway suggested by company, the importance of bortezomib for first line is highlighted and in text the company states that bortezomib retreatement is not recommended for second line. This apparently contradicts the postioning by the company of bortezomib-dexamethasone for second line. By definition, the use of bortezomib-dexamethasone for second line should only pertain to patients who did not receive bortezomib at first line. The ERG considers that the pathway should have better differentiated first line treatment depending on whether patients received bortezomib.

ixazomib must be combined with lenalidomide and dexamethasone. Therefore, we believe that, if ixazomib was to be recommended, the drug would be implicitly used in the situations where lenalidomide-dexamethasone is already used within the UK. Assuming bortezomib-dexamethasone to be the most relevant comparator for second line, a lenalidomide-dexamethasone based combination (used alone or with ixazomib) would have some advantages over bortezomib in terms in ease of use or better acceptance, but these would rely on the lenalidomide-dexamethasone based regimen, with or without ixazomib, which means that the advantages of an oral treatement advocated by the company do not come from ixazomib itself but from lenalidomide-dexamethasone.

3 Critique of company's definition of decision problem

3.2 Population

The population in the decision problem, and subsequent clinical evidence matches the population described in the final scope. The population of relevance includes patients with relapsed or refractory multiple myeloma (RRMM) who have had at least one prior therapy.

Our understanding is that the company has proposed the positioning of ixazomib as a second and third line treatment, which would exclude subsequent lines. Despite the exclusion of subsequent lines, the company has conducted clinical and cost-effectiveness analyses considering RRMM patients with at least one prior treatment. Although these analyses match the population described in the final scope, it does not exactly correspond to the population targeted by the company to benefit from ixazomib (i.e. second and third line).

Since we assume that the proposed positioning of ixazomib by the company is relevant to the current practice, we believe that the company would have better stated that the population in the decision problem is restricted to RRMM patients at second and third line. This would have been consistent to the choice of comparators in the decision problem where the company better differentiated between patients who have had 1 prior therapy to those who had 2 prior therapies.

4.4 Identified Studies

The main trial of the CS is the Tourmaline MM-1 study (1 publication from the main trial, [26] 1 publication from the China study,[29] plus unpublished data from the 2nd data cut IA2 (12th July 2015). The company also included this trial in their NMA (for discussion of the NMA see relevant section). The trial was funded by the Millennium Pharmaceuticals subsidiary of Takeda Pharmaceuticals.

The details of the trial were summarised and discussed in the CS on pp.81-110. The trial design was reported on p.81f. of the CS. The trial was an international, Phase III, randomised, double blind trial comparing IXA+LEN+DEX (4mg IXA on days 1, 8, 15 plus 25mg LEN on days 1-21, plus 40 DEX on days 1, 8, 15, 22) with LEN+DEX (placebo plus 25mg LEN on days 1-21, plus 40 DEX on days 1, 8, 15, 22) in 28 days cycles. 360 patients were randomly assigned to the IXA+LEN+DEX group, and 362 to the Placebo +LEN+DEX group. Randomisation was stratified by number of prior therapies (1 vs. 2 or 3), previous proteasome inhibitor treatment (naïve vs. exposed), and International Staging System disease stage (ISS I or II vs. III). Treatment continued until disease progression or unacceptable toxicity. Permitted concomitant medications were thromboprophylaxis according to American Society of Clinical Oncology (ASCO) guidelines, aspirin (81-325mg orally once daily), low-molecular weight heparin, prophylactic antiviral therapy as clinically indicated, myeloid growth factors, erythropoietin, red blood cells and platelet transfusions, standard anti-emetics as clinically indicated and prophylactic, topical, intravenous or oral antihistamines or steroids, bisphosphonates, CYP1A2 inhibitors. Strong CYP3A inducers were to be avoided and radiation therapy or anti-neoplastic treatment was not permitted (CS, 85).

Eligibility criteria were reported on p.82f. and in table 30 on p.83. The trial was designed to select patients with RRMM based on standard criteria and with measurable disease and an Eastern Cooperative oncology Group (ECOG) performance status between 0-2 (on a scale from 0-5), whilst excluding patients who were refractory to lenalidomide or proteasome inhibitor-based therapy. The trial included male and female patients who had 1-3 prior therapies and relapsed after previous treatment, both refractory and not refractory, and who had never responded to previous treatment. Patients were recruited in 147 centres in 26 countries, including 9 centres in the UK, which included 21 patients (CS, 84, table 31).

The median age of patients in both the IXA+LEN+DEX and the placebo group was 66 years, (38-91 in the IXA group and 30-89 in the placebo group). 53% of patients in the IXA group and 51% in the placebo group were over 65 years old. For both groups, the time since diagnosis was similar (median 44.2 months IXA vs. 42.2 months placebo). The number of

Overall, the company concludes a survival trend in favour of IXA+LEN+DEX for both ITT and the high-risk population. However, the CHMP did not agree with the company's conclusion for both ITT and for the high-risk population. On the contrary, the CHMP argues that the evidence the company provided is not substantial enough to draw conclusions for high-risk groups (EMA, 124).

4.10.1.3 Time to progression

In the 1st interim analysis, the median TTP for the IXA+LEN+DEX group is 21.4 months, for the LEN+DEX group 15.7 (HR 0.71, 95%CI 0.56-0.91;p=0.007). The 2nd interim analysis the results for IXA+LEN+DEX was 22.4 months and 17.6 months (Table 1). The ERG regrets that the company presented the HR for progression (0.79) without its 95%CI.

These results indicate that, like for PFS, the benefit of IXA on the risk of progression is reduced between the first and second interim analysis. The comparable HR for TTP and PFS, from both first and second interim analysis, confirm our statement that TTP can be considered as a good proxy for PFS (see section on NMA critique).

Table 1: Tourmaline entire ITT population Time to progression results (HR <1 favours IXA+LEN+DEX)

	IXA-LEN-DEX	LEN-DEX
Number of patients	360	362
1st interim analysis (median FUP 15 months)		
Number of progressions	114	145
Median TTP (months)	21.4	15.7
HR for progression (95%CI)	0.71 (0.56, 0.91)	
P value	0.007	
2nd interim analysis (median FUP 23 months)		
Number of progression	158	180
Median TTP (months)	22.4	17.6
HR for progression (95%CI)	0.79 (0.64, 0.98)	
P value	*	

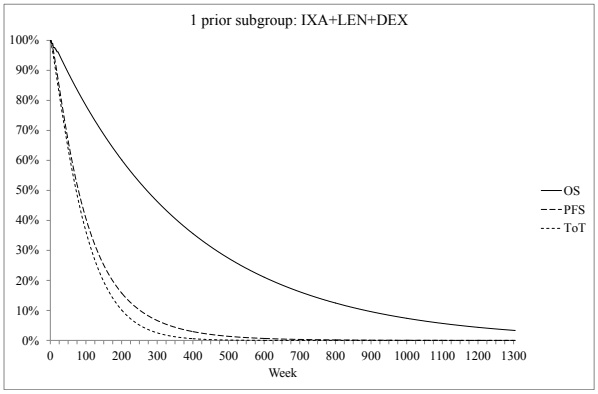
* P value not reported in the main CS

Table 2: Tourmaline 1 prior therapy Response rates (OR >1 favours IXA+LEN+DEX)

	IXA+LEN+DEX	LEN+DEX
Number of patients	212	213
1st interim analysis (median FUP 15 months)		
Overall response rate, n (%)	163 (76.9)	159 (74.6)
OR for OR rate (95%CI)	1.13 (0.72, 1.77)	
P value	NR	
very good response and complete response, n (%)	95 (44.8)	(43.7)
OR for VGPR + CR (95%CI)	1.05 (0.71, 1.54)	
P value	NR	
Complete response or better,n (%)	19 (9.0)	17 (8.0)
OR for CR or better (95% CI)	1.13 (0.57, 2.25)	
P value	NR	
2nd interim analysis (median FUP 23 months)		
Overall response rate, n (%)	164 (77.4)	166 (77.9)
OR for OR rate (95%CI)	0.97 (0.61, 1.53)	
P value	NR	
Very good response and complete response, n (%)	105 (49.5)	105 (49.3)
OR for VGPR + CR (95%CI)	-	
P value	NR	
Complete response or better,n (%)	26 (12.3)	27 (12.7)
OR for CR better (95% CI)	-	
P value	NR	

The results of the main trial do not show any benefit of IXA-LEN-DEX over LEN-DEX in terms of response rates. Initial insignificant benefits in PFS, TTP and OS seem to decrease from first to second interim analysis. It may even be argued that the triplet performs worse than the doublet.

Overall, the similarity between the IXA-LEN-DEX and LEN-DEX groups with 1 prior therapy supports the company's request to prioritise consideration of IXA-LEN-DEX for 3rd line positioning within the UK. The company did however provide a cost-effectiveness analysis of IXA-LEN-DEX vs. bortezomib plus dexamethasone in the 1 prior therapy group (i.e. at 2nd line) and requests that this positioning be considered as a secondary priority.



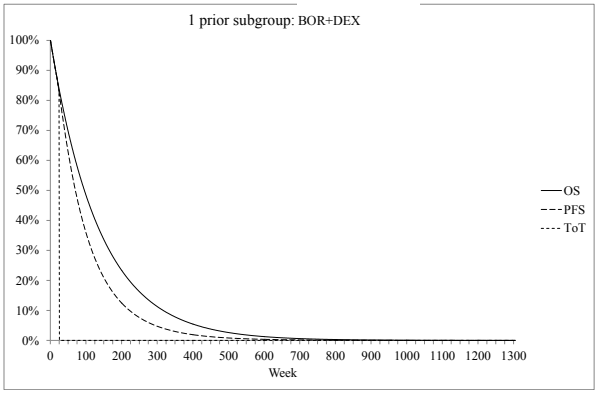
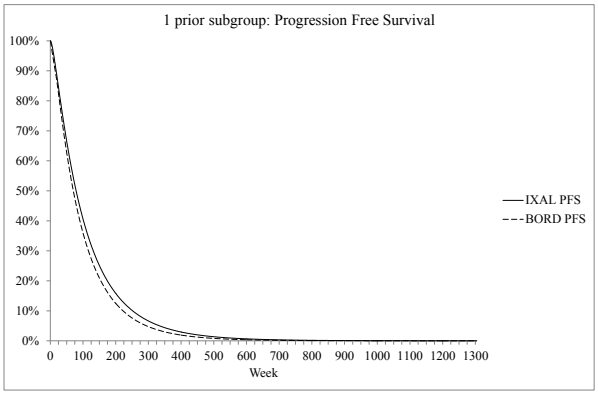


Figure 1: 1 Prior: Company base case curves

Immediately apparent from the above is the difference in terms of time on initial therapy, with IXA+LEN+DEX being much as per the PFS curve but BORT+DEX being restricted to 9 three week cycles to yield 27 weeks of treatment.

There is also only limited additional PPS survival subsequent to PFS survival for BORT+DEX but a great deal of additional PPS survival subsequent to PFS for IXA+LEN+DEX. IXA+LEN+DEX appears to have altered the course of the disease subsequent to progression compared to BORT+DEX.

The OS and the PFS curves modelled for each comparator can also be presented alongside one another.



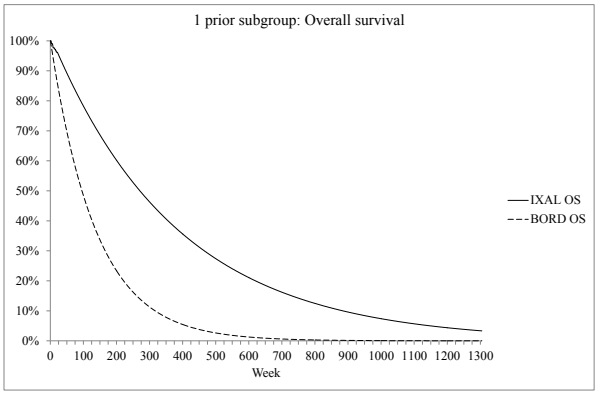


Figure 2: 1 Prior: Company base case OS and PFS curves[1]

[1] Within the tables and figures of the economics, in order to economise on space IXA+LEN+DEX is abbreviated to IXAL, LEN+DEX is abbreviated to LEND and BORT+DEX is abbreviated to BORD.

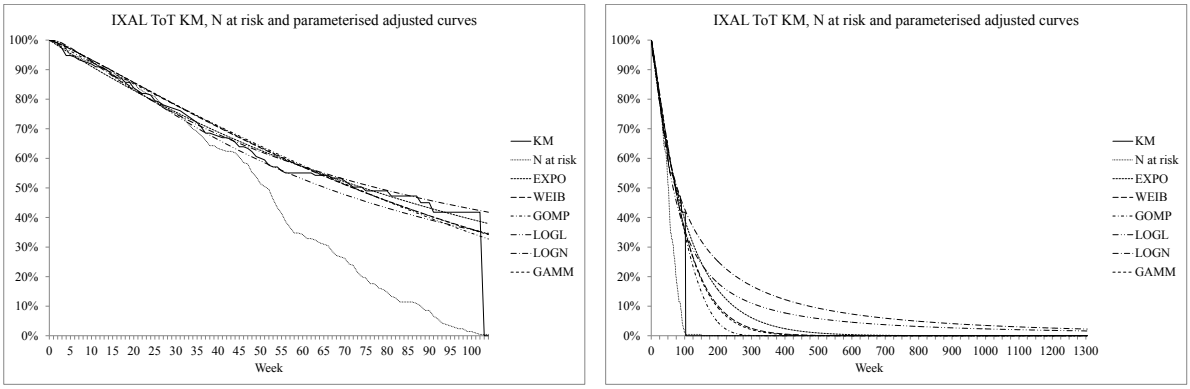
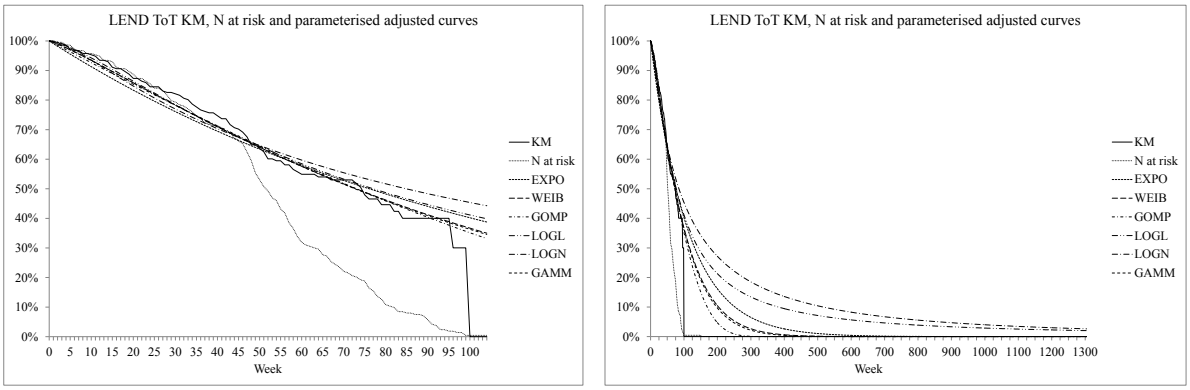


Figure 3: 1 Prior: IXA+LEN+DEX ToT KM, N at risk and adjusted parameterised curves

The graphs of the adjusted curves for LEN+DEX are as below.

Figure 4: 1 Prior: LEN+DEX ToT KM, N at risk and adjusted parameterised curves



The gompertz is the lowest curve for both IXA+LEN+DEX and LEN+DEX. The Weibull and the gamma are the pair of curves lying above this, and are little different from one another.

The BORT+DEX arm is assumed to have the same ToT curve as the LEN+DEX arm despite being estimated to have an inferior PFS curve to the LEN+DEX arm. In the absence of alternative data the more natural assumption might have been to apply the PFS hazard of 1.059 to the LEN+DEX ToT curve. BOR+ DEX is only administered for 8 three week cycles, which curtails its ToT curve to 24 weeks[2]. Note that the Weibull for IXA+LEN+DEX lies slightly below that for LEN+DEX.

[2] Or rather 25 weeks in the model given half cycle correction.

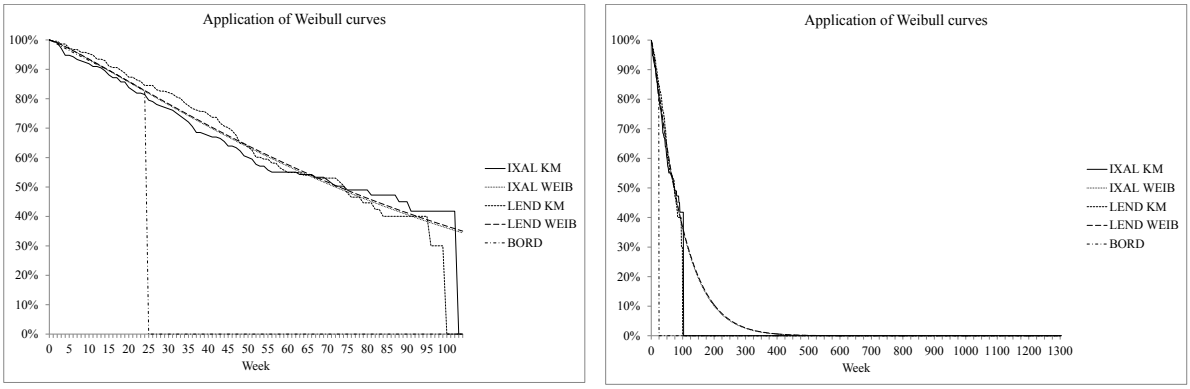


Figure 5: 1 Prior: Company base case ToT curves: Weibulls

5.2.6.10 Time on treatment (ToT): 2+ Prior subgroup

The economic model provides the following unadjusted and adjusted curves for the 1 prior subgroup, with the AIC and BIC values being taken from appendix 11 of the company submission and the company response to the ERG clarification questions.

Table 3: 2+ Prior: Unadjusted parameterised ToT curves

	Expo	Weib	Gomp	LogL	LogN	Gamm
IXAL Tx	-0.312	0.323	-0.308	0.368	0.393	0.349
Constant	-4.476	4.497	-4.377	4.113	4.153	4.407
Gamma		-0.044	-0.003			
Sigma				0.108	0.506	0.211
Kappa						0.680
AIC	1542.37	1544.05	1543.66	1543.55	1547.47	1545.33
BIC	1549.75	1555.13	1554.74	1554.64	1558.55	1560.11

Table 4: 2+ Prior: Adjusted parameterised ToT curves

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Friday 10 March 2017** using the below proforma 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 Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Regulatory opinion on high-risk sub-groups

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response to the factual accuracy check
Page 38 of ERG Report where it states: *The company argues that high-risk subgroups should be identified according to NICE guidelines (CS, 48; NG35[17]), and states that IXA+LEN+DEX have demonstrated a consistently good performance in pre-specified subgroups, including patients with high-risk cytogenetic abnormalities (CS, 49). The EMA however disagrees and states that "[i]t is not possible to identify a higher-risk subgroup that could benefit from treatment with ixazomib, ……..In addition, the results for the primary analysis.....but seemed driven by those with t(4;14) in the second interim analysis". [18] The EMA states that no benefit can be observed for high-risk patients. This conclusion has not been revoked in the final decision by the EMA in November, in which they agree to grant marketing authorisation on the*	Change "*good performance in pre-specified subgroups, including patients with high-risk cytogenetic abnormalities (CS, 49).*" to "*good performance in pre-specified subgroups, including amongst other things, patients with high-risk cytogenetic abnormalities (CS, 49).*" Change *"the EMA"* to *"the CHMP"* on the first two occasions it is used within this paragraph.	High-risk cytogenetics is outside of scope. The ERG wording implies that a higher-risk subgroup corresponds to high-risk cytogenetics patients but actually the CHMP comments relate to a *post hoc* pooled group of higher risk features, including ISS Stage 3 and a broader high risk cytogenetics group. These comments therefore do not reflect the high risk cytogenetics subgroup data included in the NICE clinical section. It was not EMA who gave these opinions, rather it was the CHMP which is an advisory committee within the EMA. Ixazomib never had a negative final decision from the EMA or disagreement from EMA on its efficacy.	We have revised as suggested

basis of the good toxicity profile but in expectation of more clinical data to support a positive benefit-risk balance.		EMA did not have to revoke any conclusions for high-risk patients as this subgroup was not separately considered, and ultimately EMA chose to grant ixazomib a conditional marketing authorisation based on the full ITT population from the TMM-1 trial.	

Issue 2 Panobinostat's place in the treatment pathway and its relevance as a comparator

Description of problem	**Description of proposed amendment**	**Justification for amendment**	ERG's response to the factual accuracy check
Page 39 of ERG Report where it states: *The company claims that Panobinostat in combination with Bortezomib and Dexametasone is recommended as 3rd line treatment, but not often used in clinical practice. The company concludes that Panobinostat is not a relevant comparator for 3rd line treatment. However, Panobinostat is recommended by NICE and is therefore one treatment option.[19] The company argues that clinical practice does require the option of a variety of different treatment*	Change *"The company claims that Panobinostat in combination with Bortezomib and Dexametasone is recommended as 3rd line treatment, but not often used in clinical practice."* to *"The company claims that Panobinostat in combination with Bortezomib and Dexametasone is recommended for 3rd line treatment onwards, but is not often used in 3rd line in UK clinical practice".*	As clarified at the end of this paragraph, the panobinostat-bortezomib-dexamethasone regimen (PVd) is recommended by NICE for patients who had 2 or more prior therapies (i.e. 3rd line onwards, and not just 3rd line as implied at the start). This is important because if IXA+LEN+DEX replaces LEN+DEX at 3rd line, then PVd can be used at 4th line and hence is not a comparator. The market share data shows little use of the panobinostat-bortezomib-dexamethasone	This is not a factual error. No ERG change required

options and flexibility in the treatment approach (CS, 17). In addition the company states that the triplet of panobinostat-bortezomib-dexamethasone and lenalidomide with dexamethasone are the only treatment options recommended by NICE for MM patients who had 2 or more prior therapies (CS 18).		regimen at 3rd line, again supporting that it is not a relevant comparator at 3rd line.	

Issue 3 Clarification re number of prior therapies received by patients in the TMM-1 study

Description of problem	**Description of proposed amendment**	**Justification for amendment**	ERG's response to the factual accuracy check
Page 42 of ERG Report where it states: *Our understanding is that the company has proposed the positioning of ixazomib as a second and third line treatment, which would exclude subsequent lines. Despite the exclusion of subsequent lines, the company has conducted clinical and cost-effectiveness analyses considering RRMM patients with at least one prior treatment (i.e. including 4th line and beyond). Although these*	Delete the following text within this section: *"(i.e. including 4th line and beyond)."*	The TMM-1 study recruited patients with RRMM who had received 1-3 prior lines of treatment (i.e. patients treated at 2nd, 3rd or 4th line). No patients treated beyond 4th line were included in this trial. Cost effectiveness analyses were based on the TMM-1 pivotal trial. Clinical and cost-effectiveness analyses considered RRMM patients who had received 1-3 prior treatments.	We have revised accordingly

analyses match the population described in the final scope, it does not exactly correspond to the population targeted by the company to benefit from ixazomib (i.e. second and third line).			

Issue 4 Justification for CDF consideration

Description of problem	**Description of proposed amendment**	**Justification for amendment**	ERG's response to the factual accuracy check
Page 47 of ERG Report where it states: *On page 29, the company considered that ixazomib could be a potential candidate to be recommended for use within the CDF for two years. This could offer the opportunity to collect clinical data such as more mature survival data. The ERG appreciates the interest of collecting data to provide real-world evidence on drugs that have*	Delete all of the following text within this section: *The ERG appreciates the interest of collecting data to provide real-world evidence on drugs that have only been evaluated through rigorous clinical trials. However, such a short period of data collection (2 years) is likely to be irrelevant with the scope of MM even at the stage of relapsed or refractory disease. Looking at the data from the TMM-1 trial26, although we acknowledge that a RCT may not exactly represent real-word practice, the median overall survival has not been reached for any of*	Nowhere in the submission does Takeda suggest that real world evidence collection within the CDF could directly be used to provide more mature OS data for ixazomib. Given the timescales involved, this could only be done using emerging data from the TMM-1 trial.	We disagree with the proposed amendment. As stated in our report, the Company indicated in the submission that the inclusion of IXA in the CDF could offer the opportunity to collect clinical data such as more mature survival data. We still consider that a 24 month-period would be insufficient to collect more clinical survival data. We have not revised the report.

only been evaluated through rigorous clinical trials. However, such a short period of data collection (2 years) is likely to be irrelevant with the scope of MM even at the stage of relapsed or refractory disease. Looking at the data from the TMM-1 trial26, although we acknowledge that a RCT may not exactly represent real-word practice, the median overall survival has not been reached for any of the included population (1 prior line and 2-3 prior lines) in either the IXA-LEN-DEX or LEN-DEX arms after a median follow-up of 23 months (second interim analysis). Consequently, the ERG considers that the inclusion of ixazomib within the CDF for 24 months would not enable the collection of mature overall survival data, unless the effectiveness of ixazomib in real-word setting is reduced compared to what was observed in the TMM-1 trial. A reduced effectiveness of ixazomib in real-life conditions cannot be excluded, given that the compliance of patients with their treatment might not be as good as	*the included population (1 prior line and 2-3 prior lines) in either the IXA-LEN-DEX or LEN-DEX arms after a median follow-up of 23 months (second interim analysis). Consequently, the ERG considers that the inclusion of ixazomib within the CDF for 24 months would not enable the collection of mature overall survival data, unless the effectiveness of ixazomib in real-word setting is reduced compared to what was observed in the TMM-1 trial. A reduced effectiveness of ixazomib in real-life conditions cannot be excluded, given that the compliance of patients with their treatment might not be as good as that observed in the main RCT.* The section should be rewritten as: *On page 29, the company considered that ixazomib could be a potential candidate to be recommended for use within the CDF for two years. This could offer the opportunity to collect clinical data such as more mature survival data from the ongoing TMM-1 trial. Based on the estimated timing of the final analysis of this trial, the ERG considers that the inclusion of ixazomib within the CDF for 24 months could potentially enable the collection of mature overall survival data.*		

that observed in the main RCT. On this basis, the ERG believes that mature overall survival data should be obtained from the TMM-1 trial once it becomes available.			

Issue 5 Stratification by International Staging System disease stage

Description of problem	**Description of proposed amendment**	**Justification for amendment**	ERG's response to the factual accuracy check
Page 52 of ERG Report where it states: *Randomisation was stratified by number of prior therapies (1 vs. 2 or 3), previous proteasome inhibitor treatment (naïve vs. exposed), and International Staging System disease stage (ISS I, II or III).*	Change to *"and International Staging System disease stage (ISS I or II vs. III)."*	The ISS stratification was ISS I or II vs. III.	We have revised this

Issue 6 Regulatory opinion for both ITT and the high-risk population

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response to the factual accuracy check
Page 79 of ERG Report where it states: *Overall, the company concludes a survival trend in favour of IXA+LEN+DEX for both ITT and the high-risk population. However, the EMA did not agree with the company's conclusion for both ITT and for the high-risk population. On the contrary, the EMA argues that the evidence the company provided is not substantial enough to draw conclusions for high-risk groups (EMA, 124).*	Change *"the EMA"* throughout this paragraph to *"the CHMP"* Revise the wording to reflect that CHMP did agree with the company's conclusion for the ITT population as it recommended a conditional licence for the full ITT population upon appeal.	It was not EMA who gave these opinions, rather it was the CHMP which is an advisory committee within the EMA. The final decision regarding the granting (or not) of a marketing authorisation is made by EMA. Ultimately, EMA chose to grant ixazomib a conditional marketing authorisation based on the full ITT population from the TMM-1 trial.	Strictly speaking, we agree that the final decision regarding the approval is made by the EMA following the opinion provided by the CHMP, though the CHMP is not just an advisory committee. We have revised accordingly.

Issue 7 Consideration of IXA-LEN-DEX for 2nd line vs. 3rd line positioning

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response to the factual accuracy check
Page 85 of ERG Report where it states: *Overall, the similarity between the IXA-LEN-DEX and LEN-DEX groups with 1 prior therapy*	Change to*:* *Overall, the similarity between the IXA-LEN-DEX and LEN-DEX groups with 1 prior therapy supports the company's request to prioritise consideration of IXA-LEN-DEX for*	Nowhere in the submission did Takeda request not to place IXA+LEN+DEX at 2nd line. However, we now request that priority be given to consideration	We have revised this.

supports the company's request not to place IXA-LEN-DEX at 2nd line within the UK. The company did however provide a cost-effectiveness analysis of IXA-LEN-DEX in the 1 prior therapy group.	*3rd line positioning within the UK. The company did however provide a cost-effectiveness analysis of IXA-LEN-DEX vs. bortezomib plus dexamethasone in the 1 prior therapy group (i.e. at 2nd line) and requests that this positioning be considered as a secondary priority.*	of IXA+LEN+DEX for 3rd line positioning; with 2nd line positioning being a secondary consideration. We did not provide an analysis of IXA-LEN-DEX vs LEN-DEX in 2nd line as LEN-DEX is not reimbursed.	

Issue 8 Consideration of IXA-LEN-DEX for 2nd line vs. 3rd line positioning

Description of problem	**Description of proposed amendment**	**Justification for amendment**	ERG's response to the factual accuracy check
Page 151 of ERG Report presents a graph labelled "BOR+LEN+DEX"	Change to*:* *BOR+DEX*	Assume this is a typo as BOR+LEN+DEX is not considered in the submission.	We have revised this.

Issue 9 Consideration of IXA-LEN-DEX for 2nd line vs. 3rd line positioning

Description of problem	**Description of proposed amendment**	**Justification for amendment**	ERG's response to the factual accuracy check
Page 151 of ERG Report where it states: *Immediately apparent from the above is the difference in terms of*	Change to*:* *Immediately apparent from the above is the difference in terms of time on initial therapy, with IXA+LEN+DEX being much as per the*	Nine cycles of three weeks in length equates to 27 weeks of treatment.	We have revised this.

time on initial therapy, with IXA+LEN+DEX being much as per the PFS curve but BORT+DEX being restricted to 9 three week cycles to yield 24 weeks of treatment.	*PFS curve but BORT+DEX being restricted to 9 three week cycles to yield 27 weeks of treatment.*		

Issue 10 Consideration of IXA-LEN-DEX for 2nd line vs. 3rd line positioning

Description of problem	**Description of proposed amendment**	**Justification for amendment**	ERG's response to the factual accuracy check
Page 170-171 of ERG Report where it states: *BOR+LEN_DEX is only administered for 8 three week cycles, which curtails its ToT curve to 24 weeks.*	Change to*:* *BOR+DEX is only administered for 8 three week cycles, which curtails its ToT curve to 24 weeks.*	Assume this is a typo as BOR+LEN+DEX is not considered in the submission.	We have revised this.

(please cut and paste further tables as necessary)