Single Technology Appraisal

Elranatamab for treating relapsed and refractory multiple myeloma after 3 or more treatments [ID4026]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Elranatamab for treating relapsed and refractory multiple myeloma after 3 or more treatments [ID4026]

Contents:

The following documents are made available to stakeholders:

1. Comments on the Draft Guidance from Pfizer:

a. Company draft guidance response
b. Company draft guidance response appendix
c. Company draft guidance response addendum – comparison with selinexor
d. Company draft guidance response addendum appendix – indirect treatment comparison report selinexor
e. Company factual accuracy check of EAG critique of company draft guidance response
f. Company factual accuracy check of EAG critique of company draft guidance response addendum – model changes
g. Company factual accuracy check appendix – indirect treatment comparison report panobinostat

2. Consultee and commentator comments on the Draft Guidance from:

a. Myeloma UK
b. Myeloma UK Haematological Malignancy Research Network data
c. Bristol-Myers Squibb Pharmaceuticals Ltd
d. Johnson & Johnson Innovative Medicine

3. External Assessment Group critique of company response to the Draft Guidance:

a. EAG factual accuracy check response
b. EAG critique post factual accuracy check
c. EAG critique appendix – comparison with selinexor

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

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Pfizer Ltd

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Pfizer Ltd: Pharmaceutical company and marketing authorisation holder
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Pfizer Ltd: Pharmaceutical company and marketing authorisation holder
Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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Summary	Pfizer wishes to thank NICE for the opportunity to consult on substantive concerns that we have based upon the appraisal and recommendation of elranatamab for treating relapsed and refractory multiple myeloma (RRMM) after 3 or more treatments. We are not contesting those within the recommendation but have concerns for those who have been excluded from it. The Company is particularly concerned by the lack of justification for the restriction applied within the recommendation; the impact it has on patients, clinical research and the treatment pathway; and its inconsistency with previous decisions made by NICE for treatments in multiple myeloma. As will be further explained, Pfizer considers that the Draft Guidance decision is unfair, inequitable, unreasonable, and unsustainable in its conclusion based on the evidence presented within this appraisal and other comparable appraisal outcomes. The company requests that: • The committee align the recommendation to the elranatamab label indication, as an option for: treating relapsed and refractory multiple myeloma in adults after 3 or more treatments (including an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody) when the myeloma has progressed on their last treatment. • The POM+DEX optimisation is removed. We consider that the recommendation would be applicable for use within managed access. In addition, the Company would like to remind the committee that elranatamab is being considered for use within the Cancer Drugs Fund (CDF). A commercial access agreement (CAA) has been agreed to manage the risk during the time of data collection and elranatamab will be fully re-evaluated upon its exit. The areas of concern are described further in the document and summarised below. Where relevant we have cross referenced with the original submission and provided additional evidence. **1. Line of Treatment (LOT) recommendation is inappropriate: The evidence presented within the Company submission is not based on LOT but on class exposure/refractoriness which is consistent with the label indication and current clinical management. We request that the reference to LOT is removed from the recommendation.** a) The previously submitted clinical and cost evidence (for both intervention and comparator) is based upon class exposure and refractoriness not lines of treatment. b) Evidence presented shows that class exposure and refractoriness align more closely with outcomes and recommendations based on LOT are out of step with clinical practice.

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	c) Patients in MagnetisMM-3 were exposed and refractory to 3 classes of treatment (as per the label) but spanned multiple lines of treatment with less heavily treated patients responding better than more refractory patients. This is consistent with other published data for bispecific antibodies (BsAbs). d) UK clinicians have confirmed that MagnetisMM-3 is generalisable to the label and the population they expect to treat in the UK. **2. Line of treatment (LOT) recommendation is inconsistent: The current recommendation is not aligned across two current appraisals despite the same approach to the decision problem. The decision is not justified within Draft Guidance and does not reflect the evidence presented.** a) It is unclear why the recommendation within Draft Guidance for teclistamab (ID6333), another bispecific antibody being evaluated for the same disease and population differs from the recommendation for elranatamab. (1)The company can find no rationale to justify the different recommendations based on submitted evidence to date. The company emphasises the importance of ensuring guidance is clear and clinically meaningful (useful and useable) and does not create clinical uncertainty. b) To further reassure the committee we have presented additional validation using a published unanchored matching-adjusted indirect comparison (MAIC) of the relative efficacy of elranatamab versus teclistimab which supports the need for consistent decision making. **3. The POM+DEX restriction is inappropriate: A restriction based on patients where *pomalidomide plus dexamethasone would otherwise be offered*, is not in line with the submitted evidence.** a) MagnetisMM-3 included 81% of patients with prior POM exposure. Those patients with POM exposure (POM exposed) had comparable responses with the overall cohort A on which the current recommendation is based. b) The EAG agree that known differences in the populations between MagnetisMM-3 and the comparator source for POM+DEX, MM-003 (inc. prior POM exposure) are more likely to bias comparative treatment effect estimates against elranatamab. c) Furthermore, to provide confidence to the Committee the Company have also applied the accepted POM+DEX efficacy in ID6333 and applied within our cost effectiveness model along with the Committee's preferred assumptions. Results from this UK real world evidence source suggest there are negative incremental costs associated with elranatamab and resultant positive net health benefit of 3.27.

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	4. The POM+DEX restriction is inappropriate: POM+DEX is the most relevant, plausible and feasible comparator in TCE RRMM. a) The company still considers POM+DEX to be the most relevant, plausible and feasible comparator in this appraisal. The company believes a comparison with POM+DEX is generalisable to the entire eligible population in line with the marketing authorisation as it represents the only commonly used treatment in TCE RRMM in the UK. b) To further reassure the Committee, we have presented additional external clinical validation evidence. The real-world evidence from Costa et al which includes an adjusted indirect treatment comparison to a comparator of physician choice treatments support the clinical efficacy of elranatamab in a triple class exposed (TCE) relapsed refractory multiple myeloma (RRMM) population beyond a single comparator. c) In addition, the Draft Guidance does not highlight any alternative comparators based on the NICE scope. Furthermore, clinical experts do not identify any other relevant appropriate comparators. d) However, despite significant limitations, to further reassure the Committee we have also provided a comparison with PANO+BORT+DEX that is used in a very small number of patients often where no other alternatives exist, due to its toxicity and requirement for attenuated dosing, which nonetheless shows negative incremental costs and a net health benefit of 1.38. **5. POM+DEX restriction is inconsistent: The Company is unclear why the recommendation aligned to the choice of comparator is inconsistent with prior appraisals.** a) The Recommendation is inconsistent with prior appraisals in TCE RRMM; TA783(2), ID4067 [formerly TA658])(3), and ID2701.(4). In these appraisals NICE concluded that POM+DEX was the only relevant comparator and did not apply any restrictions related to POM+DEX in their recommendations. b) The company is not aware of any other appraisals where the Committee has specifically limited a recommendation to use in patients for whom the identified comparator would otherwise be offered without any consideration of generalisability. If there are examples, we expect these to be in the significant minority especially for oncology treatments. **6. The POM+DEX restriction is inequitable and will have significant impact on patients and their carers.** *a)* The impact of this restriction on patients with RRMM cannot be underestimated. The Draft Guidance acknowledges the *"psychological benefit of knowing another treatment option is available in case of relapse",* as well as the *"substantial impact multiple myeloma has on*

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	survival" and "the unmet need for effective treatments…, who have already had several treatments" (Draft Guidance, pg. 5). b) This is a patient population with a poor prognosis and estimated survival of just 11.1 months compared to 24.6 months median overall survival (MagnetisMM-3) (5) c) Patients treated for RRMM will, due to their disease biology and/or comorbidities, have already received pomalidomide containing regimens, have significant unmet need, but will not be eligible for elranatamab. Examples include, but not exclusive to, those at the end of the current treatment pathway or those who are intolerant to steroid containing regimens. The Draft Guidance recognises this group would specifically benefit from the option of receiving elranatamab due to not requiring combination with steroids (Draft Guidance pg. 6). d) Restricting elranatamab for patients where *"pomalidomide plus dexamethasone would otherwise be offered"* is inequitable, leaving patients behind who would benefit from treatment. This is supported by comments from patient groups such as the Director of Research and Advocacy, Myeloma UK who stated that *"Patients must not be unfairly left behind when new effective treatments are approved."(6)* **7. The POM+DEX restriction risks undermining clinical decision making and patient choice. Its inclusion makes the guidance less useful and useable for clinicians and patients.** a) This restriction would make clinical decision making more challenging within the treatment pathway. By restricting it to a specific comparator the guidance could cease to be relevant with future pathway changes denying patients an effective and cost-effective treatment. In the long-term clinicians might wish to avoid using pomalidomide-containing regimens prior to elranatamab and instead reserve potentially efficacious treatments for subsequent use, to ensure patients can still access elranatamab (or other BsAb treatments). **8. The POM+DEX restriction risks undermining future clinical research in the UK.** a) The company has recently received a letter of withdrawal from a research site for a future study of elranatamab citing the POM+DEX restriction in the Draft Guidance for their reasoning explaining that their interpretation would make these patients ineligible for elranatamab on trial exit. One further site has indicated an intention to follow.

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Triple classed exposed relapsed refractory multiple myeloma (TCE RRMM)	**1. Line of Treatment (LOT) recommendation is inappropriate: The evidence presented within the Company submission is not based on LOT but on class exposure/refractoriness which is consistent with the label indication and current clinical management. We request that the reference to LOT is removed from the recommendation.** During the appraisal, we provided extensive information in relation to both the complexity of the multiple myeloma (MM) landscape and the expected positioning for elranatamab. Table 1 and Section B.1.1 (See Document B of the Company submission) clearly states our submission covers the technology's full marketing authorisation for this indication. This is validated in the Evidence Assessment Group (EAG) report (Table 3, page 7). There are several combination treatments (including immune mediated inflammatory disease (IMiD), protease inhibitor (PI) and anti-CD38 monoclonal antibody (mAb) classes of treatments) being used across, and increasingly earlier, in the treatment pathway. This has changed the onset of refractoriness whereby patients are exposed and refractory to these (multiple) therapies earlier in the treatment pathway, and this trend is expected to continue.(7-9) Figures 3 and 4 of the company submission display multiple routes that transplant-eligible and transplant-ineligible patients can take to become exposed and refractory to treatments from multiple classes, therefore becoming eligible for treatment with elranatamab, in the current treatment pathway (See Section B.1.3.3 in Document B of the Company submission). These figures are not exhaustive but demonstrate the complexity of the current pathway and the many possible routes through which patients may become eligible for elranatamab based on its label indication. Furthermore, evidence suggests that class-refractoriness maps more closely to outcomes.(10) (See Section B.1.3.1 and B.1.3.3. in Document B of the Company submission) MagnetisMM-3 clinical evidence shows the impact of treating those patients as early as possible. The subgroup of less heavily treated patients had better PFS and complete response rate than patients who were more exposed to prior treatments, Table 1, Figure 6 and Figure 7 in Appendix). This is consistent with other published data for BsAbs.(11) Recommendations based on LOT are out of step with clinical practice. We have engaged several clinicians who confirm treatment decisions are based on exposure/refractoriness, not based on lines of treatment (Clinical validation in original submission (7) and Appendix Section 4). This is due to multiple combinations of treatment becoming available earlier in the pathway and the onset of refractoriness across multiple classes of medicines (i.e., PI, IMiD, anti-CD38 mAb) moves to earlier in the treatment pathway. Patients' ineligible today based on LOT, might quickly become eligible per licensed indication, as this "shift" continues over time as more patients become TCE RRMM earlier in the pathway. However, patient potential to benefit, the cost effectiveness of treating these patients, and relevance of the evidence are the same. This is inequitable and unsustainable and unintentionally forces the treatment pathway to the disadvantage of patients.

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	Patients in MagnetisMM-3 were exposed and refractory to 3 classes of treatment (as per the label) but spanned multiple lines of treatment. UK clinicians have stated that the MagnetisMM-3 population is in line with the population they would expect to treat with elranatamab in the UK, given the UK approved label .(7, 12, 13) The clinical and cost-effectiveness estimates presented by the Company are based on class exposure/refractoriness not on LOT. The Company maintains the clinical generalisability of the submitted evidence applies across the entire eligible patient population in line with its marketing authorisation. The Company asks the Committee to consider it in this context as an option for treating relapsed and refractory multiple myeloma in adults after 3 or more treatments (including an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 antibody) when the myeloma has progressed on their last treatment.

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Inconsistency with a directly comparable appraisal	**2. Line of treatment (LOT) recommendation is inconsistent: The current recommendation is not aligned across two current appraisals despite the same approach to the decision problem. The decision is not justified within Draft Guidance and does not reflect the evidence presented.** The company are unclear why the recommendation within Draft Guidance for teclistamab, another bispecific antibody being evaluated for the same disease and population differs from the recommendation for elranatamab. This difference is in reference to having had "3 or more treatments" (ID6333), compared with our appraisal where the recommendation referred to "3 or more lines of treatment". Comparable evidence was submitted for the two respective appraisals.(14, 15) After reviewing both Draft Guidance' we can find no rationale to justify the different recommendations. We assume this is due to. a) Inadvertent inconsistent decision across committees, or b) Evidence that supports this differential recommendation or c) That "treatments" and "lines of treatment" are considered interchangeable by NICE. We ask that NICE and the committee provides clarity, transparency and ensures consistency in decision-making on this point. The company emphasises the importance of ensuring guidance is clear and clinically meaningful to clinicians in practice and does not create clinical uncertainty. While we acknowledge that teclistamb is not a named comparator in the scope, we would like to highlight recent publication *Mol et al* supports the alignment in decision making. An unanchored matching-adjusted indirect comparison (MAIC) was conducted to assess the relative efficacy of elranatamab versus teclistimab.(16). Key baseline characteristics were adjusted to be comparable between the two trials. In the MAIC, elranatamab demonstrated significantly better objective response rate (See Table 3 in Appendix) and progression-free survival (PFS) (Figure 14 in Appendix) than teclistamab, and numerically better complete response (Table 3 in Appendix), duration of response (Figure 13 in Appendix), and overall survival (OS) (Figure 15 in Appendix). As discussed previously the evidence presented by the Company in its submission is aligned to the approved label indication. We ask that the committee considers that elranatamab is recommended as an option for treating relapsed and refractory multiple myeloma in adults after 3 or more treatments (IMiD, PI and an anti-CD38 mAb) when the myeloma has progressed on their last treatment.

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The POM+DEX restriction is inappropriate	**3. The POM+DEX restriction is inappropriate: A restriction based on patients where *pomalidomide plus dexamethasone would otherwise be offered*, is not in line with the submitted evidence.** The committee recommendation states; *Elranatamab is recommended with managed access as an option for treating relapsed and refractory multiple myeloma in adults after 3 or more lines of treatment (including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody) when the myeloma has progressed on the last treatment. It is only recommended if:* - *pomalidomide plus dexamethasone would otherwise be offered, and* - *the conditions in the managed access agreement for elranatamab are followed.* The recommendation paragraph 1.1 of the Draft Guidance (also reflected at paragraph 3.16), limiting use to patients for whom pomalidomide plus dexamethasone would otherwise be offered, constitutes a restriction on use relative to the licensed indication. No clear explanation for the stated restriction is provided in the Draft Guidance and we welcome the committee discussion and clear guidance on this. The impact of the committee recommendation is demonstrated by the current elranatamab Blueteq form (Criteria 7). *"I confirm that the patient has NOT received treatment with any pomalidomide-containing regimen and also set out below which line of myeloma therapy elranatamab is being used for"* *"Note: the only comparator for elranatamab chosen by the company and accepted by NICE was pomalidomide plus dexamethasone. NICE has concluded that elranatamab is clinically and cost effective only when compared against pomalidomide plus dexamethasone, hence the need for patients accessing elranatamab not to have been treated with any pomalidomide-containing regimen."* MagnetisMM-3 included 81% of patients with prior POM exposure (Company submission. B.2.9.1, B.2.9.3.1, and B.3.7, and the EAG assessment report pg. 27, 55, 76). Therefore, the clinical evidence for elranatamab is based on a cohort where the majority of patients had prior pomalidomide exposure. The EAG agreed with the company that known differences in the populations between MagnetisMM-3 and the comparator source for POM+DEX, MM-003 (inc. prior POM exposure) are more likely to bias comparative treatment effect estimates against elranatamab (EAG Assessment report pg. 55, 56). This is supported by additional data presented in Table 2 and Figure 11 and Figure 12 in Appendix which shows that patients in MagnetisMM-3 with POM exposure (POM exposed) showed comparable results to the overall cohort (Cohort A, Table 2). Clinicians confirm that these results align with expectation, as POM exposed patients are more heavily pre-treated/refractory so will have less responsive disease (Appendix Section 4). Since the current recommendation (and ICER) is also aligned to the overall cohort A then a restriction based on prior POM is not

appropriate as it biases against elranatamab. Therefore, in the context of discussions to date, the Committee have already accepted the generalisability of the Company submission data regardless of POM exposure, because it has accepted that data in patients with 81% prior POM exposure is generalisable to a patient population without prior POM exposure.

To further reassure the Committee, we present additional evidence showing that the comparison with POM+DEX in the Company submission is conservative. The company explored the impact of using UK real world evidence use of POM+DEX accepted in ID6333 within the cost effectiveness model.

Results using the Committee preferred assumptions and Company net price discount (incl. CAA confidential additional rebate*) of [redacted] suggest there are negative incremental costs associated with elranatamab and resultant net health benefit of 2.99 (Table 1) in comparison with Company base case. This provides the Committee with further confidence in elranatamab's cost effectiveness.

Table 1: Cost-effectiveness results scenario using SACT POM+DEX efficacy from appraisal ID6333 and EAG base case setting.

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Elranatamab	[redacted]	[redacted]			
POM+DEX (SACT)			[redacted]	[redacted]	Dominant (net health benefit = 3.27)

Key: DEX, dexamethasone; EAG, evidence assessment group; ICER, incremental cost effectiveness ratio; POM, pomalidomide; QALY, quality adjusted life year; SACT, systemic anti-cancer therapy.
Source: TBC

[redacted]

4. The POM+DEX restriction is inappropriate: POM+DEX is the most relevant, plausible and feasible comparator in TCE RRMM.

The statement on page 1 of the Draft Guidance that "the company asked for elranatamab to only be considered as an alternative to pomalidomide plus dexamethasone" is factually incorrect. The company provided extensive evidence in the submission that supports POM+DEX as the most relevant comparator and this is generalisable to the entire eligible patient population (See Section B.1.1. in Document B of the Company submission). We believe it entirely appropriate that within our submission we compared only with pomalidomide and dexamethasone.

The complexity of the MM treatment pathway and the resulting choice of comparator was fully explored within our submission. We considered POM+DEX to represent the only frequently used treatment in TCE RRMM in the NHS and

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	therefore the most relevant comparator (See Sections B.1.1, B.1.3.1, B.1.3.3, B.1.3.3.3, B.1.3.3.4, and B.3.3 [Figure 2] in Document B of the Company submission). Advice from clinical experts has repeatedly agreed with this choice of comparator and is further reinforced from recent clinical validation (Appendix Section 4). From discussions with clinicians, the Company estimated around 80-85% of patients in the relevant population receive POM+DEX (See the CQ Response page 13).(7) We note that in the submission for ID6333 a similar figure of 90% was estimated for patients with TCE RRMM (See Section B.1.1 in Document B of the ID6333 submission [Table 1]). Paragraph 6.2.3 of NICE's Manual defines the comparators for an appraisal, stating that these will *"normally be guided by established practice in the NHS".* The comparator technology or technologies then form the basis for assessment of clinical and cost effectiveness of the technology under consideration. A frequent consideration during committee deliberations is the generalisability of a comparison made, specifically if an alternative comparator is deemed relevant. Neither in the committee discussion or the Draft Guidance has an alternative comparison been highlighted as relevant. Furthermore, there was no discussion of the generalisability. To further reassure the Committee, we present clinical external validation evidence showing the relative effectiveness of elranatamab versus POM+DEX, is comparable with the relative effectiveness versus a real-world basket of treatments based on physicians' choice. This reinforces that the current ICER for POM+DEX is generalisable to a TCE RRMM population beyond a single comparator. Elranatamab was associated with a significantly higher objective response rate (risk ratios, 1.88–2.25), significantly longer progression-free survival (hazard ratios [HRs], 0.37–0.57), and, across most analyses, significantly longer overall survival (HRs,0.46–0.66) versus physician choice of treatment (PCT).(17) Whilst this study is in a US based population and the basket of treatments are not generalisable to the UK, the clinical outcomes are similar to that observed in MM-003 (data source for POM+DEX in Company submission) that showed ORR 31%, median PFS of 4 months [95% CI 3.6,4.7] and median OS of 12.7 months [95% CI 10.4,15.5]. These results reaffirm what has been previously published with respect to the outcomes of a TCE RRMM population. The observed ORR (~30%) for physician's choice therapies was consistent with that of previously published studies.(9, 16, 18-21) Similarly, the observed median PFS and OS were approximately 4 and 12 months, which is also consistent with what has been reported in prior studies.(9, 16, 19-22) The observation that these clinical outcomes are aligned provides confidence that the clinical and cost-effective estimates considered in this appraisal are generalisable to TCE RRMM patients, irrespective of the comparator. However, the company stands by its original submission that POM+DEX is the relevant, plausible and generalisable comparator in this appraisal.

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	During the submission process two alternative medicines were mentioned as potential comparators, IXA+LEN+DEX and PANO+BORT+DEX, but these treatments were also disregarded (with clinical agreement) and reasons provided in the Company submission. The EAG report agrees with the company rationale for excluding IXA+LEN+DEX, but also received clinical advice that suggests this could be considered as a comparator at third line but, as outlined below, the Company believes this would not be relevant for a TCE population and this is further supported by clinical opinion (Appendix Section 4). PANO+BORT+DEX was mentioned by the CDF lead as a potential option as this is also reimbursed in this population(23) (24). However, the Company also deems this not to be a relevant comparator and is further outlined below and is supported by clinical opinion (Appendix Section 4). • IXA+LEN+DEX: given the recent approval of daratumumab in combination with lenalidomide and dexamethasone as first-line therapy in transplant ineligible patients (ID4014) and lenalidomide maintenance following autologous stem cell transplant (ASCT) (TA680), and the remainder of patients being likely to receive LEN+DEX or CAR+LEN+DEX nearly all patients will then be LEN refractory. Therefore, current treatments received after TCE would not include IXA+LEN+DEX. Whilst patients who are exposed to LEN but not refractory could receive IXA+LEN+DEX, this will be a small cohort and may not be appropriate, as patients can only be exposed and not refractory to LEN if they have stopped LEN early within a combination, which is suggestive of intolerance or adverse event. This is supported by the company's clinical validation and supported by clinical experts at the first ACM (clinical validation from company submission(7); (Appendix Section 4). • PANO+BORT+DEX (TA380) is no longer a relevant comparator in this setting in the UK due to toxic adverse events and lack of efficacy, as confirmed through Committee conclusions in TA658 and TA783(25, 26) Additionally, the evidence on which NICE recommended PANO+BORT+DEX is not reflective of the real world context in which it is used i.e. where there are no other treatment options available. This RRMM population would include those patients re-treated with a PI (i.e., bortezomib), which is associated with poorer outcomes(27). Analysis of the SACT database confirms BORT-based regimens accounted for more than half of all first line regimens(28) and clinical advice confirm they would expect worse outcomes in this population. This is due to the level of refractoriness and, to mitigate toxicity, PANO+BORT+DEX is often used in attenuated dosing.(29) In addition, there are a number of challenges in providing robust comparative efficacy assessments versus PANO+BORT+DEX because neither the available RWE nor the relevant PANORAMA trials align with the population in MagnetisMM-3; • Patients enrolled in the PANO+BORT+DEX clinical trials will generally have disease that is less refractory and easier to treat than the patients

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	enrolled in MagnetisMM-3 (30-32). This was confirmed in consultancies with 2 practicing UK clinicians (Appendix Section 4). • Clinicians confirm that PANO+BORT+DEX is not used often owing to its toxicity profile and low efficacy. If used this is often using attenuated dosing to address the issue of toxicity as described above. • Real world evidence analysis of systemic anticancer therapy (SACT) showed 3.9% of patients receiving this combination at 3L, 7.5% at 4L, then 14.3% at 5L (33). However, it is important to note that there were methodological limitations with this study due to restrictions on analyses of CDF drugs at the time of analyses. This resulted in the exclusion of 26% of all eligible patients with MM and 77% of all eligible TCE patients from analyses of treatments and clinical outcomes. • Existing UK real world evidence of PANO+BORT+DEX is in a cohort of patients that are not reported as TCE and therefore do not align with the decision problem and elranatamab's marketing authorisation. Despite fewer prior lines of therapy and either not reporting CD38 exposure (27) or minimal exposed (29, 34) , these studies demonstrated minimal activity of this combination in RRMM, with median progression free survival ranging from 3.4 to 4.2 months and median overall survival from 9.5 to 10 months. The company stands by its original submission that POM+DEX is the relevant, plausible and generalisable comparator in this appraisal. However, despite limitations outlined above the company have conducted an unanchored matching adjusted indirect comparison (MAIC) with PANO+BORT+DEX. Further detail is provided in the Appendix section 3. PANORAMA-2 has been selected to inform the unanchored MAIC as this trial includes the most comparable population to elranatamab according to baseline characteristics including median lines of prior treatments.(32). The company believes a comparison between trial versus trial is more robust as trials typically have fitter patients and produce more favourable results when compared to RWE. However, as patients in PANORAMA-2 were not TCE RRMM, efficacy outcomes from this trial will provide upper bound estimates of efficacy outcomes, given that true TCE RRMM patients will have worse outcomes. Full results are presented in Appendix Section 3. Using the Company net price discount (incl. Commercial Access Agreement (CAA) confidential additional rebate*) of [redacted] suggest there are negative incremental costs associated with elranatamab and resultant net health benefit of 1.38 (Table 2) This evidence, taken together, demonstrates that elranatamab is a clinical and cost-effective use of NHS resources, POM+DEX is the relevant comparator that is generisable to patients with TCE RRMM and therefore the restriction for POM+DEX should be removed. **Table 2:** [redacted]

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	<table><tr><th>Technologies</th><th>Total costs (£)</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th></tr><tr><td>Elranatamab</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td></tr><tr><td>PANO+ BORT+DEX</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>Dominant (net health benefit = 1.38)</td></tr></table> ICER, Incremental cost effectiveness ratio; MAIC, matching adjusted indirect comparison; PANO, panobinostat; QALY, quality adjusted life year. [redacted]
The POM + DEX restriction is inconsistent	**5. POM+DEX restriction is inconsistent: The Company is unclear why the recommendation aligned to the choice of comparator is inconsistent with prior appraisals.** The Company evaluated NICE's decision making in previous appraisals for patients being treated in TCE RRMM (Company Submission. B.1.1, B.1.3.3.3 and B.1.3.3.4). In two previous guidance documents NICE concluded that POM+DEX is the only relevant comparator in this position for multiple myeloma. - Final Guidance (FG) from TA783 for daratumumab (DARA) monotherapy, published on 13 April 2022, concludes (page 9) that *"After 3 previous lines of treatment, pomalidomide plus dexamethasone is the only relevant comparator."*(2) In this appraisal the company provided a comparison against PANO+BORT+DEX but it was not deemed relevant, with the FG citing clinicians as saying that it *"is rarely used after 3 previous lines of treatment because of toxicity and perceived poor clinical efficacy".* Furthermore, the committee only took the comparison with POM+DEX in its final decision making. - In the appraisal consultation document (ACD, page 6) for ID2701 for belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies (5L+ MM) published on 9 May 2023 the committee conclude *"After 3 previous lines of treatment, pomalidomide plus dexamethasone is the only relevant comparator."(4)* Although there was discussion within the appraisal meeting around other treatments, those explored (PANO+BORT+DEX and chemotherapy combinations) were discounted due to limited use and toxicity. - In a further TA, ID4067 (review of TA658) for isatuximab (ISA) with POM+DEX, notably the Final Draft Guidance (FDG) was published on the same day as elranatamab.(3) *"The committee concluded that both pomalidomide plus dexamethasone and daratumumab monotherapy were relevant comparators"* given that daratumumab monotherapy had

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	exited the Cancer Drugs Fund (CDF). Whilst we understand that DARA monotherapy was deemed a relevant comparator in ID4067, the EAG agreed with our rationale that it is not a relevant comparator for the elranatamab appraisal as patients must have been exposed to anti CD38 mAb therapy to be eligible. There is no discussion of PANO+BORT+DEX in the Draft Guidance. - We would also highlight that ID4067 (review of TA658) and TA783 recommendations were made by the same committee as elranatamab – committee B (ID2701 committee D).(2, 3) - In addition, an ongoing appraisal for teclistimab (ID6333) with the comparable decision problem, the draft guidance also states that *"The committee concluded that pomalidomide plus dexamethasone is the most appropriate comparator for this evaluation"*.(14) The company is not aware of any other appraisal where the Committee has specifically limited a recommendation to use in patients for whom the identified comparator would otherwise be offered without any consideration of generalisability. To the Company's knowledge, there is no precedent for this decision for adopting a different approach in the current appraisal or for deviating from NICE's established procedures and practice. If there are examples, the Company expects this to be in the significant minority especially for oncology medicines. Whilst all of the above appraisals concluded the relevance of POM+DEX, none have restrictions of use to only where the comparator was used. Given the past precedence and the lack of a justification for the POM+DEX restriction in the Draft Guidance, we request the Committee removes the POM+DEX restriction.
The impact on Patients has been underestimated	**6. The POM+DEX restriction recommended by the NICE Committee is inequitable and will have significant impact on patients and their carers.** The impact of this restriction on patients with RRMM cannot be underestimated. The Draft Guidance acknowledges the *"psychological benefit of knowing another treatment option is available in case of relapse"* (Draft Guidance. Page 5). Restricting elranatamab for patients where *"pomalidomide plus dexamethasone would otherwise be offered"* is inequitable, leaving patients behind who would benefit from treatment and create the potential for challenges to clinical decision making and reduced patient choice in the longer term. This is supported by comments from patient groups such as the Director of Research and Advocacy, Myeloma UK who stated that *"Patients must not be unfairly left behind when new effective treatments are approved."(6)* Patients treated for RRMM will, due to their disease biology and/or comorbidities, have already received pomalidomide containing regimens, have significant unmet need, but will not be eligible for elranatamab. And yet there is clear evidence from MagnetisMM-3 that these patients could benefit from elranatamab, which is the first funded bispecific antibody (BsAb) in the UK. The NICE committee have recognised the *"substantial impact multiple myeloma has on survival"* and *"the unmet need for effective treatments…, who have already had several treatments"* and this is the case for patients regardless of whether they have previously received pomalidomide (Draft Guidance pg.5). This is a

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	patient population with a poor prognosis and estimated survival of just 11.1 months. In the pivotal study MagnetisMM-3 (MM-3), RRMM patients being treated with elranatamab had a median overall survival (OS) of 24.6 months.(5) There are specific groups that could be particularly impacted by the current restriction. • Those patients who have already come to the end of the current treatment pathway having received POM+DEX and have limited or no treatment options left (Appendix Section 4 and original clinical validation for company submission(7)). • High risk patients are often recruited into clinical trials to access either an experimental combination or a control arm that is not available on the NHS. These patients may therefore become exposed to pomalidomide in an early line of therapy (i.e., DARA+POM+DEX MagnetisMM-5), therefore limiting future elranatamab access (35). Whilst we understand NHSE intentions are that these patients would still have access, this is not clear within the guidance. • Similarly, high risk patients were treated with POM+DEX in early lines of therapy during the COVID-19 pandemic as a way of limiting the infection risk of exposure to hospitals (36) (37). Because of the POM restriction, these patients could be denied access. • Patients who are intolerant to POM (or indeed are class-intolerant to IMiDs) will be unfairly disadvantaged by the POM restriction. Patients who are TCE at fourth line would be expected to be lenalidomide refractory. Therefore, if these patients are unable to receive POM, they would have no effective options at fourth line. • Patients who are or become intolerant to steroids. Most regimens include long-term corticosteroids, the negative impact of which has been highlighted in interviews with UK TCE RRMM patients.(38) Steroid side effects were the most referenced toxicities, with their use being associated with fatigue, insomnia, and dramatic mood swings that even damaged relationships.(38) Severe toxicities including thrombosis, immunosuppression with subsequent infections, gastrointestinal bleeding and psychosis can also occur.(39, 40) The Draft Guidance references one patient expert who "*explained that prolonged steroid treatment can be physically and mentally tough on people with multiple myeloma and their families"* (Draft Guidance, page 6). Elranatamab would provide a steroid sparing treatment option for these patients. The company requests that the committee considers the substantial impact of its current recommendation on patients and removes the POM+DEX restriction.
The impact on NHS clinical decision making has been underestimated	**7. The POM+DEX restriction risks undermining clinical decision making and patient choice. Its inclusion makes the guidance less useful and useable for clinicians and patients.** The company also wishes to highlight the risk of creating additional complexity in clinical decision making within the treatment pathway in the longer term whereby clinicians might wish to avoid using POM-containing regimens prior to

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	elranatamab and instead reserve potentially efficacious treatments for later lines, to ensure patients can still access elranatamab (or other BsAb treatments). We are aware of efforts to make pomalidomide-containing regimens available earlier in the treatment pathway in the future (POM+BORT+DEX or belantamab plus POM+DEX). We are concerned that if this restriction remains in place, there is a risk health care decision making will be undermined and reduce patient choice as the pathway evolves. This situation would serve neither patient nor healthcare system and is unsustainable. The company requests that the committee considers the impact of its current recommendation on optimal clinical decision making and removes the POM+DEX restriction.
The impact on future clinical Research has been underestimated	**8. The POM+DEX restriction risks undermining future clinical research in the UK.** The company has recently received a letter of withdrawal from a research site for a future study of elranatamab citing the POM+DEX restriction in the DG for their reasoning explaining that their interpretation would make these patients ineligible for elranatamab on trial exit. One further site has indicated an intention to follow due to the considerable uncertainty. We have raised this with NHS England (NHSE) as it has the potential to impact across multiple trials and treatments both now and in the future. While assurances have been given to us, there is little publicly available to reassure patients and clinicians. The guidance document does not address this specifically, and we are concerned this creates uncertainty that may impact current and future clinical trials in the UK. Several studies include treatments currently not recommended by NICE but are used in clinical trials i.e., ID6211(41), TA658(42), TA726(43), and TA602.(44) A search on clinicaltrials.org suggests there are 23 studies in the UK that have POM+DEX containing regimens as a comparator/treatment (10 recruiting, 7 active not recruiting. 6 completed, 3 terminated). These all include patients that once relapsed would not be eligible for elranatamab. The company requests that the committee considers the impact of its current recommendation on the uncertainty created by the lack of clarification in the guidance document and the resulting impact on clinical research.
Factual Accuracy	Draft Guidance, page 3: *For this evaluation, the company asked for elranatamab to only be considered as an alternative to pomalidomide plus dexamethasone.* • The statement at page 1 of the FDG that *"the company asked for elranatamab to only be considered as an alternative to pomalidomide plus dexamethasone"* is factually incorrect. The company has provided extensive evidence in the company submission that supports POM+DEX as the only relevant comparator (See Section B.1.1. in Document B of the

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	Company submission). We believe it entirely appropriate that within our submission we compared only with pomalidomide and dexamethasone. The company asks that this statement be removed. Draft Guidance, page 8: *The committee was aware of recently published real-world evidence for elranatamab, Costa et al. 2024, but it noted that the company had not provided data from this study in its submission.* • Please note this data was only made available after submission, please amend to reflect this. Also, to help the Committee, the data from Costa *et al*, has been included above in response to this comment in the DG.

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Insert extra rows as needed

Checklist for submitting comments

Use this comment form and submit it as a Word document (not a PDF).
Complete the disclosure about links with, or funding from, the tobacco industry.
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Appendix

Additional Scenario Evidence – Draft Guidance Consultation ID4026

Abbreviation	Definition
ASCT	Autologous stem cell transplant
BORT	Bortezomib
CRS	Cytokine release syndrome
CR	Complete response
Cyclo	Cyclophosphamide
DARA	Daratumumab
DEX	Dexamethasone
IMiD	Immunomodulatory drug
ISA	Isatuximab
IVIG	Intravenous immunoglobulin
IXA	Ixazomib
LEN	Lenalidomide
MAIC	Matching-adjusted indirect comparison
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PI	Proteasome inhibitor
POM	Pomalidomide
TCE	Triple-class exposed
TCR	Triple-class refractory

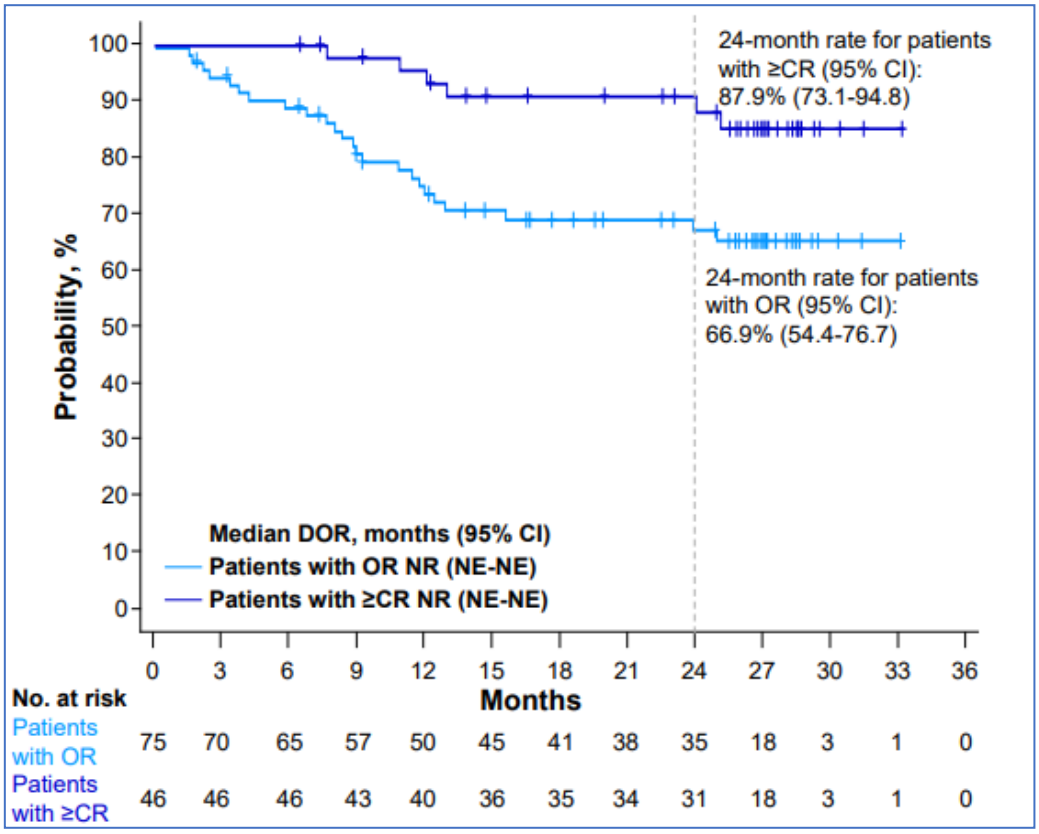
Contents

1. MagnetisMM-3 28-month data-cut

Following the Company submission, additional 28-month data from the MagnetisMM-3 trial is now available.

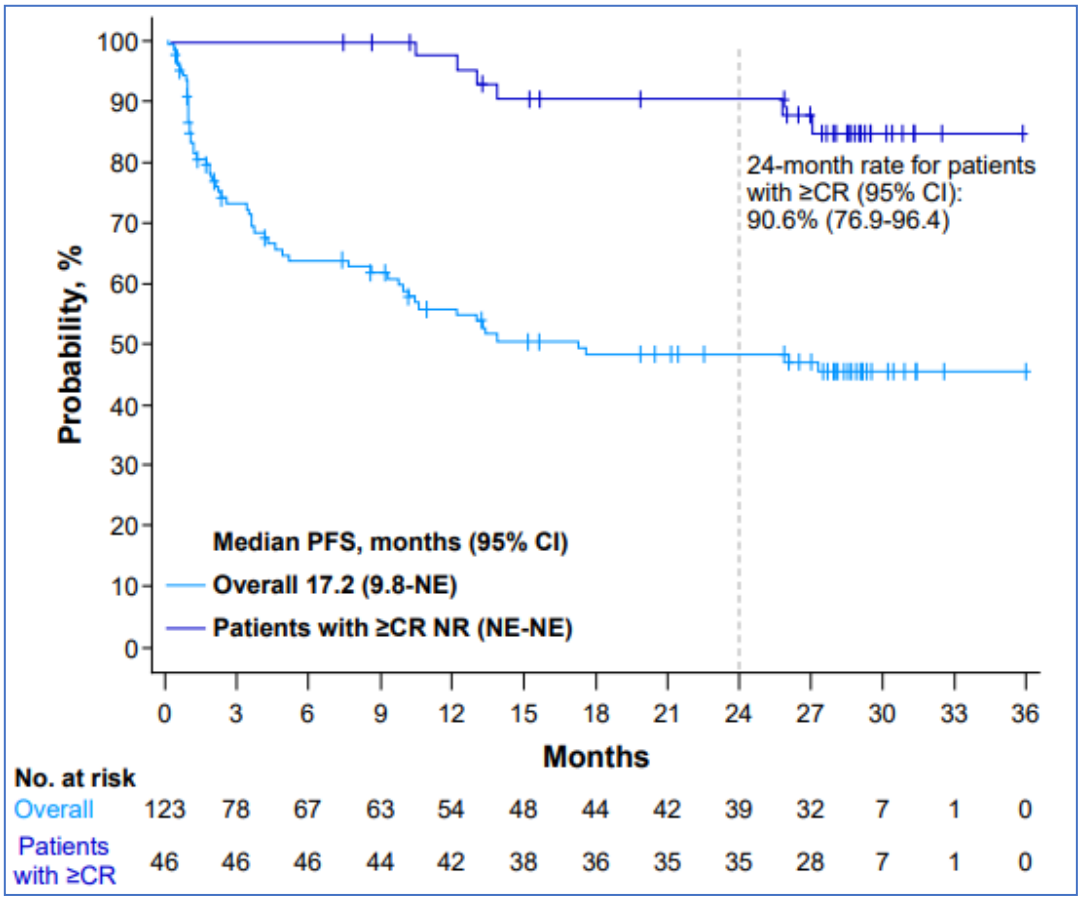
1.1. Updated efficacy data

Figure 1: Duration of response at 28 months in the MagnetisMM-3 trial



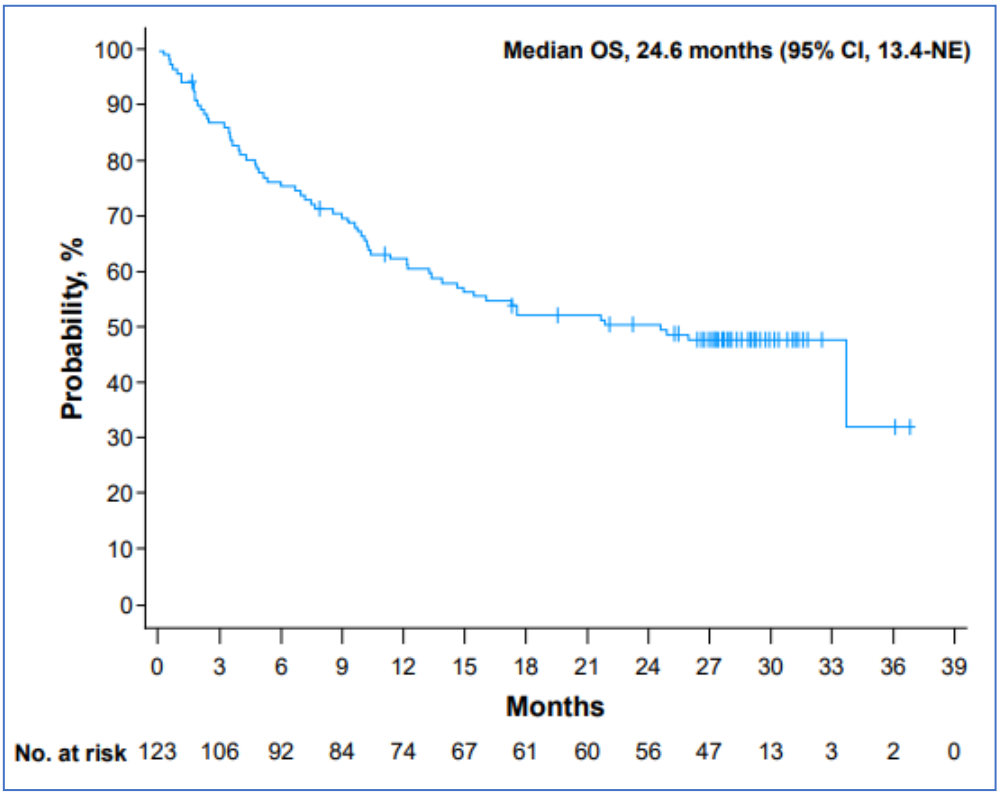
Key: CI, confidence interval; CR, complete response; DOR, duration of response; NE, not estimable; NR, not reached; OR, objective response; PFS, progression-free survival.
Source: MagnestisMM-3 28 months data-cut.(1)

Figure 2: Progression free survival at 28 months in the MagnetisMM-3 trial



Key: CI, confidence interval; CR, complete response; NE, not estimable; NR, not reached; PFS, progression-free survival.
Source: MagnestisMM-3 28 months data-cut.(1)

Figure 3: Overall survival at 28 months in the MagnetisMM-3 trial

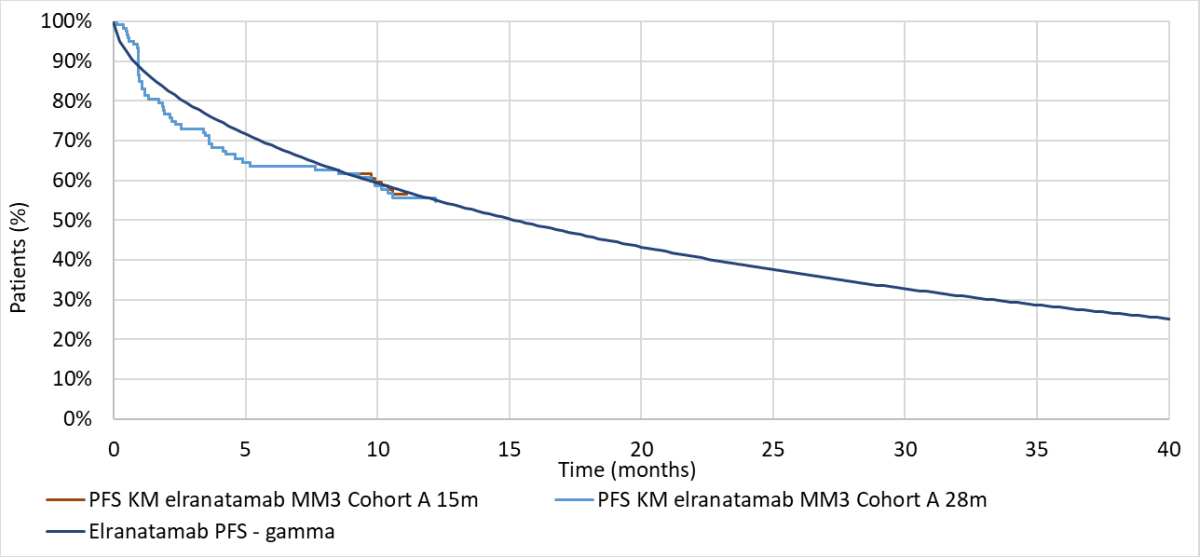


Key: CI, confidence interval; NE, not estimable; OS, overall survival.
Source: MagnestisMM-3 28 months data-cut.(1)

1.2. Committee preferred extrapolations

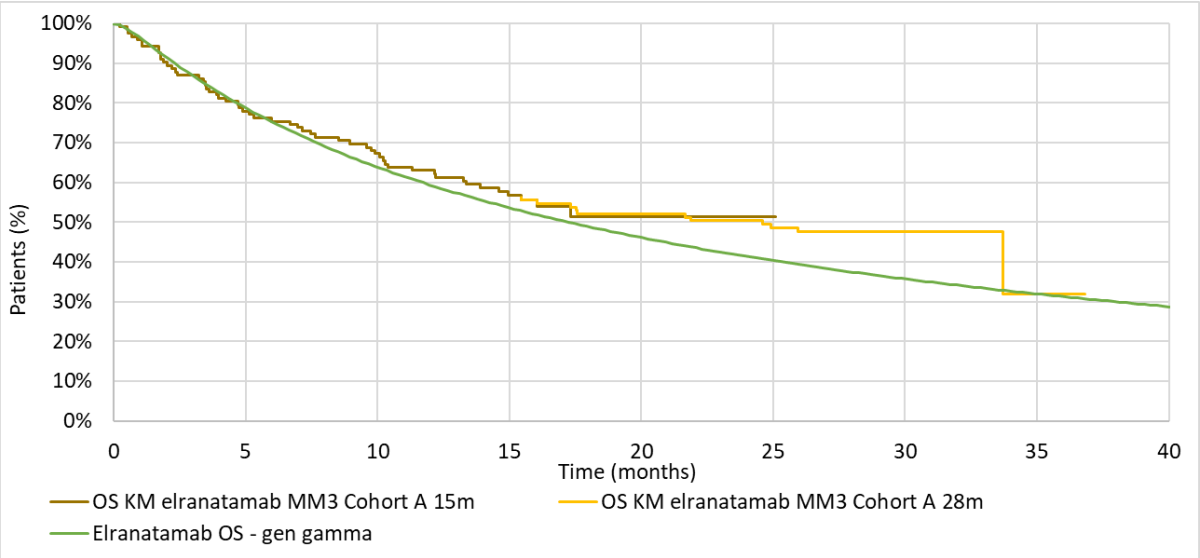
Kaplan-Meier plots of progression-free survival and overall survival with committee preferred extrapolations at 15-months and 28-months from the MagnetisMM-3 trial are presented below.

Figure 4: Kaplan Meier data progression-free survival (15 months) with committee preferred extrapolation (Gamma) overlayed with 28 month data cut.



Key: KM, Kaplan-Meier; m, months; MM3, MagnetisMM-3; PFS, progression-free survival.
Source: Pfizer. MagnetisMM-3: 28 month data-cut. 2024.(1)

Figure 5: Kaplan-Meier of overall survival at 15 months with committee preferred extrapolation (Gen Gamma) overlayed with 28 month data



Key: KM, Kaplan-Meier; m, months; MM3, MagnetisMM-3; OS, overall survival.
Source: Pfizer. MagnetisMM-3: 28 month data-cut. 2024.(1)

1.3. Subgroup analysis by number of prior lines of therapy

Table 1: Summary of best overall response by BICR (Safety Analysis Set - Cohort A participants with 2–3 prior lines versus ≥ 4 prior lines)

	Cohort A	**2–3 (n = [redacted])**	**≥ 4 (n = [redacted])**
Best overall response[a], n (%)			
Stringent complete response	20 (16.3)	[redacted]	[redacted]
Complete response	26 (21.1)	[redacted]	[redacted]
Very good partial response	23 (18.7)	[redacted]	[redacted]
Partial response	6 (4.9)	[redacted]	[redacted]
Minimal response	[redacted]	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]	[redacted]
ORR (sCR+CR+VGPR+PR), n (%) (95% CI[b]; p-value)	75 (61) (51.8,69.6)	[redacted]	[redacted]
CRR (sCR+CR), n (%) (95% CI[b])	46 (37.4) (28.8,46.6)	[redacted]	[redacted]

VGPR or better (sCR+CR+VGPR), n (%) **(95% CI[b])**	[redacted]	[redacted]	[redacted]
CBR (sCR+CR+VGPR+PR+MR), n (%) **(95% CI[b])**	[redacted]	[redacted]	[redacted]
Patients still on treatment without progression and confirmed response	[redacted]	[redacted]	[redacted]
Responders still on treatment without progression and confirmed VGPR	[redacted]	[redacted]	[redacted]
Responders still on treatment without progression and confirmed CR	[redacted]	[redacted]	[redacted]

Key: BICR, blinded independent central review; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; CRR, complete response rate; MR, minimal response; ORR, objective response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Notes: For Cohort A: 1-sided efficacy boundary p-value ≤ 0.0202 (≥ 48 responders) for H0: ORR ≤ 30. [a] Responses defined per the modified IMWG criteria 2016.(2) [b] Clopper–Pearson method was used.

Source: CSR Table 14.2.1.1.8 PF-06863135. Data cut-off: 26 March 2024.(1)

Figure 6: Progression-free survival by BICR – Kaplan-Meier plot (Safety Analysis Set – Cohort

A participants with 2–3 prior lines versus ≥ 4 prior lines)

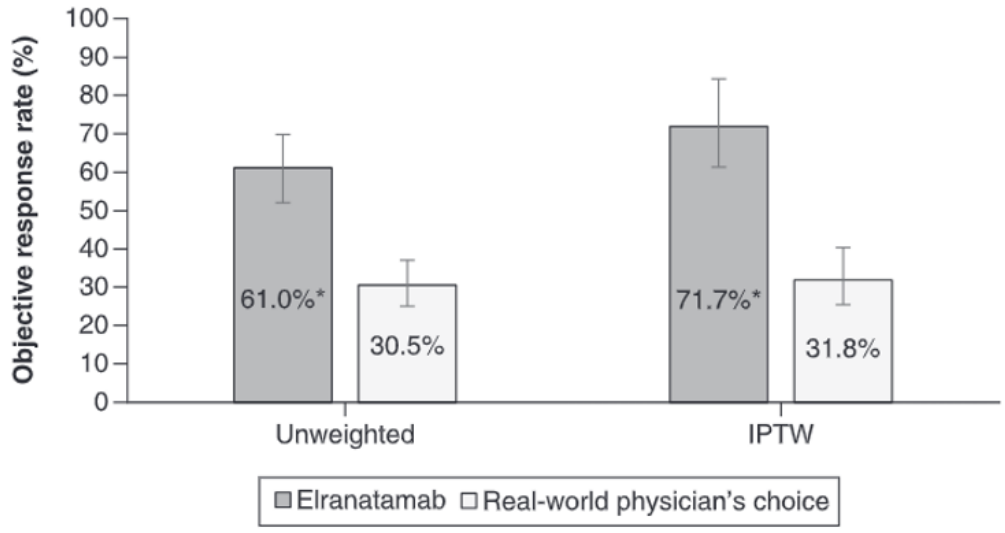
Key: BICR, blinded independent central review; CI, confidence interval; NE, not evaluable; PFS, progression-free survival.
Source: CSR Figure 14.2.3.1.1 PF-06863135. Data cut-off: 26 March 2024.(1)

Figure 7: Kaplan-Meier plot of overall survival - (Safety Analysis Set – Cohort A participants with 2–3 prior lines versus ≥ 4 prior lines)

Key: CI, confidence interval; NE, not evaluable; OS, overall survival.
Source: CSR Figure 14.2.7.2 PF-06863135. Data cut-off: 26 March 2024.(1)

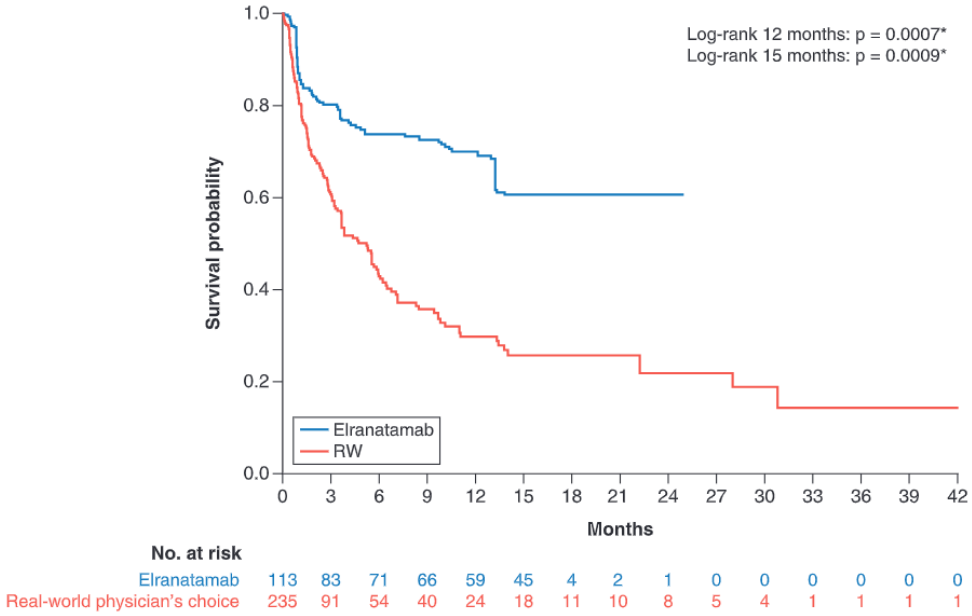
1.4. Subgroup analysis: MagnetisMM-3 and real-world physician' choice

Figure 8: Objective response rate differences between elranatamab in MagentisMM-3 and real-world physicians' choice (COTA Health Database)



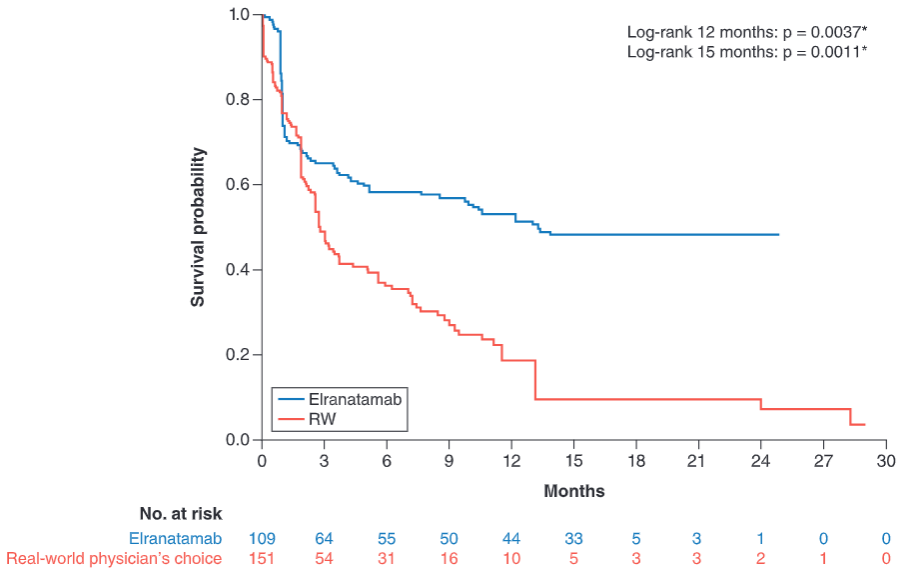
Key: IPTW, inverse probability of treatment weighted.
Notes: * p < 0.05.
Source: (3)

Figure 9: Progression-free survival differences between elranatamab in MagnetisMM-3 and real-world physician's choice in the COTA database, after applying multiple imputation and IPT weighting.



Key: IPT, inverse probability of treatment; RW, real-world.
Notes: * p < 0.05.
Source: (3)

Figure 10: Overall survival differences between elranatamab in MagnetisMM-3 and real-world physician's choice in the COTA database, after applying multiple imputation and IPT weighting.



Key: IPT, inverse probability of treatment; RW, real-world.
Notes: * $p < 0.05$.
Source: (3)

1.5. Subgroup analysis by pomalidomide exposure

Table 2: Summary of best overall response by BICR (Cohort A participants in Safety Analysis Set – prior pomalidomide-exposed versus prior pomalidomide-naïve

		Cohort A (n = 123)	POM exposed (n = 100)	POM naïve (n = 23)
Best overall response[a], n (%)				
Stringent complete response		20 (16.3)	[redacted]	[redacted]
Complete response		26 (21.1)	[redacted]	[redacted]
Very good partial response		23 (18.7)	[redacted]	[redacted]
Partial response		6 (4.9)	[redacted]	[redacted]
Minimal response		[redacted]	[redacted]	[redacted]
Stable disease		[redacted]	[redacted]	[redacted]
Progressive disease		[redacted]	[redacted]	[redacted]

Not evaluable		[redacted]	[redacted]	[redacted]
ORR (sCR+CR+VGPR+PR), n (%) **(95% CI[b]; p-value)**		75 (61) (51.8,69.6)	[redacted]	[redacted]
CRR (sCR+CR), n (%) **(95% CI[b])**		46 (37.4) (28.8,46.6)	[redacted]	[redacted]
VGPR or better (sCR+CR+VGPR), n (%) **(95% CI[b])**		[redacted]	[redacted]	[redacted]
CBR (sCR+CR+VGPR+PR+MR), n (%) **(95% CI[b])**		[redacted]	[redacted]	[redacted]
Patients still on treatment without progression and confirmed response		[redacted]	[redacted]	[redacted]
Responders still on treatment without progression and confirmed VGPR		[redacted]	[redacted]	[redacted]
Responders still on treatment without progression and confirmed CR		[redacted]	[redacted]	[redacted]

Key: BICR, blinded independent central review; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; CRR, complete response rate; MR, minimal response; ORR, objective response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Notes: For Cohort A: 1-sided efficacy boundary p-value ≤ 0.0202 (≥ 48 responders) for H0: ORR ≤ 30. [a] Responses defined per the modified IMWG criteria 2016.(2) [b] Clopper–Pearson method was used.

Source: CSR Table 14.2.1.1.10 PF-06863135. Data cut-off: 26 March 2024.(1)

Figure 11: Progression-free survival by BICR - Kaplan-Meier plot (Cohort A participants in Safety Analysis Set - prior pomalidomide-exposed versus prior pomalidomide-naïve)

Key: BICR, blinded independent central review; CI, confidence interval; NE, not estimable; PFS, progression-free survival.
Source: CSR Figure 14.2.3.1.4 PF-06863135. Data cut-off: 26 March 2024.(1)

Figure 12: Kaplan-Meier plot of overall survival (Cohort A participants in Safety Analysis Set - prior pomalidomide-exposed versus prior pomalidomide-naïve)

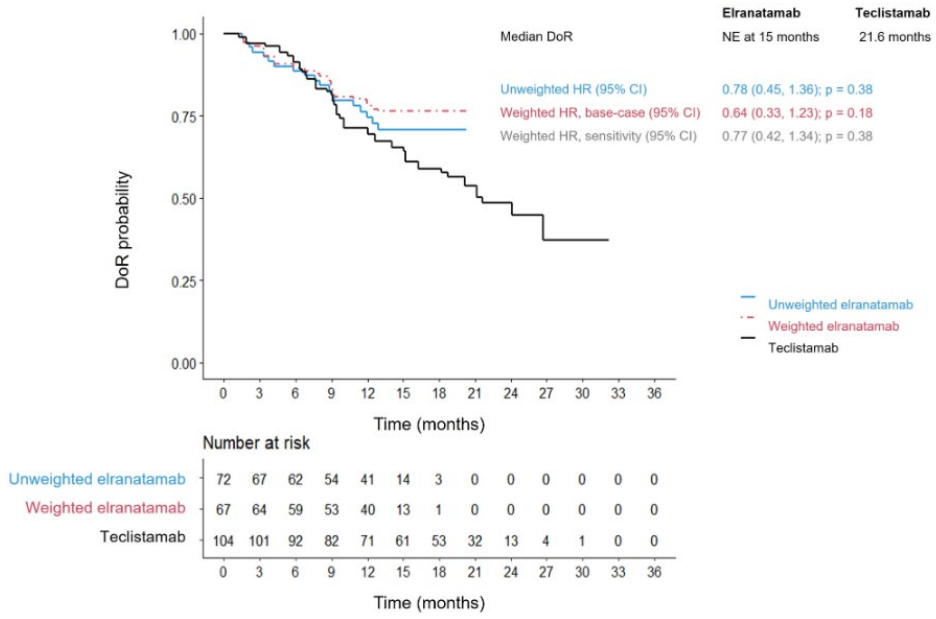
Key: CI, confidence interval; NE, not estimable; OS, overall survival.
Source: CSR Figure 14.2.7.4 PF-06863135. Data cut-off: 26 March 2024.(1)

2. *Matching-adjusted indirect comparison versus teclistimab*

Table 3: ORR and ≥ CR for elranatamab versus teclistamab (naïve, base case adjusted, and sensitivity analysis results)

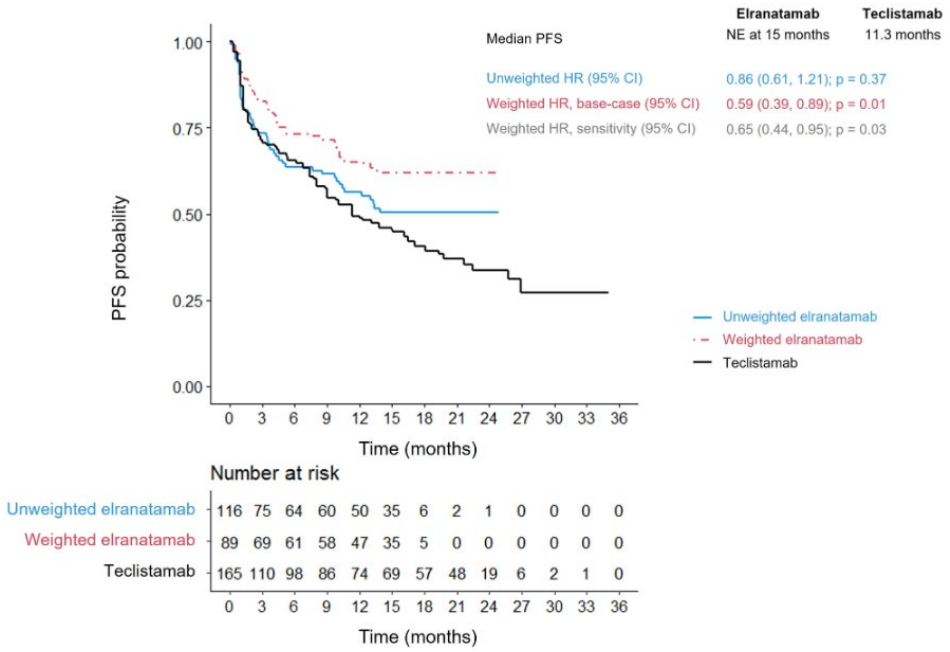
Analysis	Elranatamab	Teclistimab	ESS (n)	Rate difference (95% CI)	Odds ratio (95% CI)
ORR					
Naïve comparison	62.1%	63.0%	116	-0.96 (-12.46,10.54)	0.96 (0.59,1.57)
Base case	75.3%	63.0%	75	12.30 (0.70,23.90)	1.79 (1.01,3.19)
Sensitivity analysis	75.5%	63.0%	89	12.44 (1.28,23.60)	1.80 (1.04,3.14)
≥ CR rate					
Naïve comparison	36.2%	39.4%	116	-3.19 (-14.68.8.31)	0.87 (0.53,1.43)
Base case	43.0%	39.4%	75	3.63 (-9.08,16.33)	1.16 (0.69,1.96)
Sensitivity analysis	43.1%	39.4%	89	3.70 (-8.50,15.89)	1.16 (0.70,1.93)
Key: CI, confidence interval; CR, complete response, ESS, effective sample size; ORR, objective response rate **Source:** Pfizer Data on File, 2023.(4)					

Figure 13: DoR results for elranatamab in Cohort A of MagnetisMM-3 versus teclistamab in MajesTEC-1



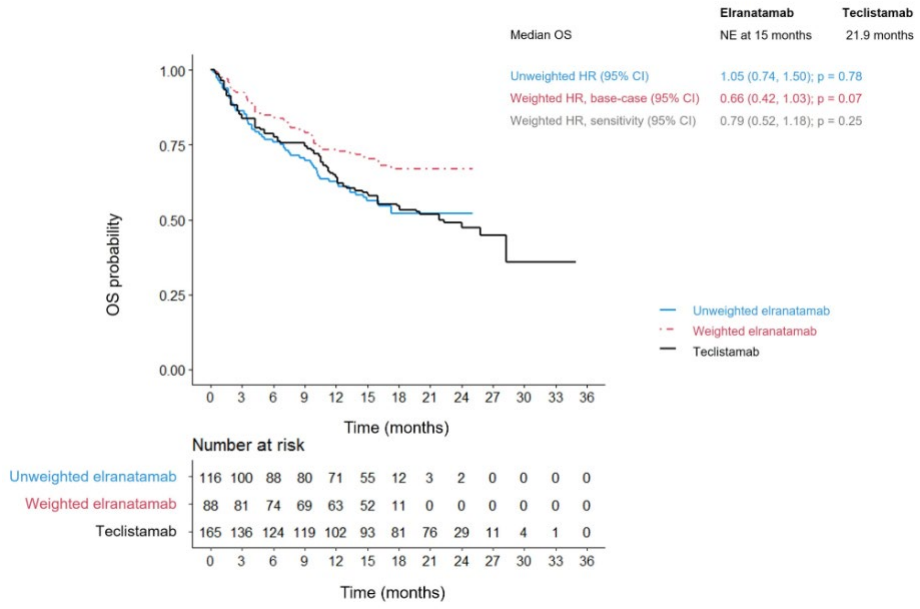
Key: CI, confidence interval; DoR, duration of response; HR, hazard ration; NE, not estimable.
Notes: While DoR is only captured among patients with a response, the MAIC weighs all patients (regardless of response).
Source: Mol et al. 2024 (5)

Figure 14: PFS results for elranatamab in Cohort A of MagnetisMM-3 versus teclistamab in MajesTEC-1



Key: CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival.
Source: Mol et al. 2024 (5)

Figure 15: OS results for elranatamab in Cohort A of MagnetisMM-3 versus teclistamab in MajesTEC-1



Key: CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.
Source: Mol et al. 2024 (5)

3. *Matching-adjusted indirect comparison versus PANO+BORT+DEX*

As detailed in the company submission, the approach taken by the company within the submission is based upon POM+DEX being the most relevant comparator. The company stands by our original approach but provides an alternative scenario for the Committee to consider: a matching adjusted indirect comparison versus panobinostat with bortezomib plus dexamethasone (PANO+BORT+DEX).

Available clinical trial data for PANO+BORT+DEX were either published before the introduction of anti-CD38 mAbs, excluded patient's refractory to anti-CD38 mAbs, or began recruiting before the introduction of anti-CD38 mAbs so included very limited data, no data were available in the relevant patient population. Thus, it is likely that patients enrolled in the PANO+BORT+DEX clinical trials will generally have disease that is less refractory and easier to treat than the patients enrolled in MagnetisMM-3 – the pivotal study for elranatamab. This was confirmed in consultancies with 2 practicing UK clinicians. Furthermore, clinicians confirm that PANO+BORT+DEX is not used often owing to its toxicity profile and low efficacy. This is confirmed in an analysis of systemic anticancer therapy (SACT) which showed 3.9% of patients receiving this combination at 3L, 7.5% at 4L, then 14.3% at 5L. (6)

Existing UK real world evidence of PANO+BORT+DEX is in a cohort of patients that are not reported as TCE and therefore do not align with the decision problem and elranatamab's marketing authorization. Despite fewer prior lines of therapy and either not reporting CD38 exposure (7) or minimal exposed (8) (9), these studies demonstrated minimal activity of this combination in RRMM, with median progression free survival ranging from 3.4 to 4.2 months and median overall survival from 9.5 to 10 months.

This poses a challenge for providing robust comparative efficacy assessments because neither the available RWE study nor the PANORMA trials align with the population in MagnetisMM-3. Please note due to time constraints we were not able to conduct a full systematic literature review to identify the relevant MAIC comparator trial for PANO+BORT+DEX.

PANORAMA-2 has been selected to inform the unanchored MAIC as this trial includes the most comparable population to elranatamab according to baseline characteristics including median lines of prior treatments. (10) The company also believes a comparison between trial versus trial is more robust as trials typically have fitter patients and produce more favourable results when compared to RWE. This analysis has been used as efficacy data for the PANO+BORT+DEX in the scenario economic analysis presented below. However, as patients in PANORAMA-2 were not TCE RRMM, efficacy outcomes from this trial will provide upper bound estimates of efficacy outcomes, given that true TCE RRMM patients will have worse outcomes.

3.1. Method

To explore how best to provide an indirect comparison between elranatamab and PANO+BORT+DEX, the company sought to explore key differences between trials that might need to be considered.

There are key differences in the patient populations between the MagnetisMM-3 and PANORAMA-2. The PANORMA-2 trial included patients with RRMM who had failed at least two previous treatments with BORT and LEN, no patients reported to be anti-CD38 mAb exposed or refractory, as this trial was conducted prior to the availability of anti-CD38 mAbs. In MagnetisMM-3, 96.7% of patients were TCR and were 42.3% penta-class refractory. PANORAMA-2 excluded patients who were previously treated with POM, while MagnetisMM-3 did not. Differences in the proportion of previous exposure to POM (81% of patients in MagnetisMM-3 were treated with POM) was identified as a considerable limitation in adjustment, as adjusting for this in the MAIC could lead to a very small sample size.

Table 4 provides an overview of the baseline characteristics of patients enrolled in the MagnetisMM-3 and PANORMA-2 rials, based on the list of identified prognostic variables (PVs) and treatment effect modifiers (EMs). Out of the identified PVs and EMs, high-risk cytogenetics, extramedullary disease, penta-exposed and penta-refractory reported in the PANORMA-2 data and therefore adjustment could not be made for them in the MAIC. The exclusion of high-risk cytogenetics and

extramedullary disease leads to bias of the results, as these variables were identified as key PV/EMs based on clinical opinion.

Table 4: Patient characteristics at baseline for studies considered for MAIC

		Elranatamab: MagnetisMM-3 (n = 123)	Pan-VD: PANORAMA-2 (n = 55)
Age	≥65 years	80 (65%)	21 (38%)
Sex	Male	68 (55%)	29 (53%)
Time since initial diagnosis, median years		6.1	4.6[2]
ISS disease stage	Stage I	35 (28%)	18 (33%)
	Stage II	47 (38%)	23 (42%)
	Stage III	24 (20%)	13 (24%)
High-risk cytogenetics[3]		31 (25%)	14 (26%)
Previous line of therapy	Median	5	4
ECOG status	0	45 (37%)	26 (47%)
	1	71 (58%)	25 (46%)
	2	7 (6%)	4 (7%)
Type of MM	IgG	65 (53%)	35 (64%)
	Non-IgG	45 (37%)	13 (24%)

1: Only includes characteristics which will be adjusted for in the MAIC

2: Reported in months, converted into years for comparison with MagnetisMM-3

3: Defined as del(17p), t(4;14), or t(14;16), which is similar to the definition in MagnetisMM-3.

A comparative summary of the outcomes from Panorama-2 versus MagnetisMM-3 is summarised in Table 5.

Table 5: Summary of outcomes used for clinical studies considered for MAIC

	MagnetisMM-3 Cohort A (n = 123)	PANORAMA-2 (n = 55)
OS	Median OS at 15-months: Not reached (95% CI: 13.9, NE)	Median OS: not reached Median follow up: 8.3 months
PFS	Median PFS at 15-months: Not reached (95% CI: 9.9, NE)	Median PFS: PANO+BORT+DEX: 5.4 months
Key: CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; ISA, isatuximab; NE, not evaluable; OS, overall survival; PFS, progression-free survival; POM, pomalidomide. **Source**: Lesokhin et al. 2023(11); Miguel et al. 2013.(12)		

There was heterogeneity across MagnetisMM-3 and PANORAMA-2 with regard to trial design and patient populations, including: 1) lack of relevance owing to the low use of PANO+BOR+DEX in the NHS; 2) Non-aligned trial populations, with a less heavily pre-treated cohort and no anti-CD38mAb exposure in Panorama-2; AND 3) differing POM exposure between Panorama-2 and MagnetisMM-3. We expand on these reasons below.

Firstly, PANO+BORT+DEX is not used in the UK except as a treatment of last resort due to its toxicity. Clinicians unanimously confirm this in validation interviews, and this has been confirmed through prior committee decisions. This is also confirmed using real world evidence which confirms limited use of PANO+BORT+DEX in the UK (6).

Secondly, patients in PANORAMA-2 were not previously treated with anti-CD38 therapies, while this was an inclusion criterion for MagnetisMM-3. As such patients in MagnetisMM-3 have a poorer prognosis than the population of PANORMA-2. These differences cannot be adjusted in a MAIC and may cause bias, where patients in PANORAMA-2 were not TCE RRMM.

Finally, patients previously treated with PANO were excluded from PANORAMA-2, while in MagnetisMM-3, 2.4% of patients were treated with PANO previously. These differences cannot be adjusted in a MAIC and may also lead to bias. While 81% of patients in MagnetisMM-3 were POM exposed, POM exposure was not reported in Panorama-2 as it was run prior to the introduction of POM. Here, too, these would lead to efficacy outcomes from this trial will provide upper bound estimates of efficacy outcomes, given that true TCE RRMM patients will have worse outcomes.

Proportional Hazards were assessed in the MAIC. A key assumption of the Cox model is that the hazard curves for the groups of observations should be proportional and cannot cross. This is tested in the MAIC, to assure that the proportional hazard assumption holds.

The final list of prognostic variables (PVs) and effect modifiers (EMs) is presented in Table 6. Base case Adjusted for the full list of the identified PVs/EMs where available, and the sensitivity analysis imputed the missing baseline patient characteristics for elranatamab to increase the effective sample size (ESS). For each baseline variable with missing data for elranatamab, it was imputed by a random sample based on the available observations in the MagnetisMM-3

Table 6: Prognostic variables and effect modifiers identified based on the SLR and clinical opinion

	PFS	**OS**
Prognostic variables and effect modifiers	Age Median time since initial diagnosis ISS or R-ISS High-risk cytogenetics Extramedullary disease Prior lines of therapy ECOG status Creatinine clearance Refractory/exposure status (penta-exposed; penta-refractory) Type of MM (IgG, IgA, IgD, light-chain)	Age Sex Median time since initial diagnosis ISS or R-ISS High-risk cytogenetics Extramedullary disease Prior lines of therapy ECOG status Creatinine clearance Refractory/exposure status (penta-exposed; penta-refractory) Type of MM (IgG, IgA, IgD, light-chain)
Key: ECOG, Eastern Cooperative Oncology Group; EM, effect modifiers; OS, overall survival; PFS, progression-free survival; PV, Prognostic variables; R-ISS, Revised International Staging System. **Note:** R-ISS was prioritised as a PV/EM if it was reported in the comparator's trial.		

For the unanchored MAIC, MagnetisMM-3 data were reweighted to the aggregated data from PANORAMA-2, based on the identified PVs and EMs (Table 6). The adjusted PVs and EMs in this analysis were age (> 75 years), sex, median time since initial diagnosis, ISS disease stage, number of prior lines (> 2 lines), ECOG status, and creatinine clearance. Weights were generated so that the distributions of

these variables for elranatamab were the same as those reported for PANO+BORT+DEX in the PANORAMA-2 study.

3.2. Results

Table 7: Unanchored MAIC: Results of the unanchored MAIC adjusting for MagnetisMM-3 versus PANORAMA-2 for PFS and OS

Outcome and analysis	ESS	Weighted HR (95%CI)	p-value
PFS:			
Naïve comparison	[redacted]	[redacted]	[redacted]
Base case	[redacted]	[redacted]	[redacted]
SA (imputation base case)	[redacted]	[redacted]	[redacted]
OS:			
Naïve comparison	[redacted]	[redacted]	[redacted]
Base case	[redacted]	[redacted]	[redacted]
SA (Imputation with base case)	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; ELRA, elranatamab; ESS, effective sample size; HR, hazard ratio; OS, overall survival; PanVd, panobinostat, bortezomib, dexamethasone

Figure 16 presents the Kaplan–Meier curves from the unanchored MAIC of PFS for MagnetisMM-3 versus PANORAMA-2. Elranatamab treatment led to significant improvements in PFS compared to PANO+BOR+DEX. These results are observed despite the inability of the MAIC to fully account for differences in each cohort's exposure to prior therapies – a bias that would likely lead to the treatment benefit of elranatamab being underestimated.

Figure 16: Kaplan–Meier of PFS for the unanchored MAIC: MagnetisMM-3 vs. PANORAMA-2

Figure 17 presents the Kaplan–Meier curves from the naïve comparison and the unanchored MAIC of OS for MagnetisMM-3 versus PANORAMA-2.

Figure 17: Kaplan–Meier of OS for the unanchored MAIC: MagnetisMM-3 versus PANORAMA-2

Key: ELRA = elranatamab; KM = Kaplan-Meier; OS = overall survival; PanVd =panobinostat, bortezomib, dexamethasone.

In summary, every attempt has been made to provide a robust MAIC for the comparison of elranatamab to PANO+BORT+DEX from the PANORAMA-2 trial, despite limitations in the comparability of the populations, data availability, maturity, and heterogeneity. However, the MAIC analyses suggest that elranatamab provides longer PFS and OS compared to PANO+BORT+DEX.

3.3. Economic Analysis with comparator: PANO+BORT+DEX via an unanchored matching adjusted indirect comparison.

As outlined above, the chosen comparator is PANO+BORT+DEX which is modelled as per its marketing authorisation and licensed dosing regimen until the end of the TTD period.

The treatment dosing is as follows:

- Dexamethasone 20 mg orally, given on the days of and after bortezomib was administered
- Panobinostat 20 mg orally 3 times per week
- Bortezomib 1.3 mg/m2 IV on Days 1, 4 , 8 and 11 of the first 8 3-week cycles; 1.3 mg/m2 IV QW for the subsequent treatment cycles

The comparator in the model base case is consistent with the NICE scope(13) for the evaluation of elranatamab in RRMM, but the company believes this is an inappropriate comparator as it has limited use in the UK and often as a drug of last resort due to its toxicity. The most appropriate comparator is POM+DEX as outlined in the CS and described in the company DG response.

PANO+BORT+DEX progression-free survival

The base case HR of [redacted] was applied to the elranatamab PFS curve in order to estimate PFS in the PAN+BORT+DEX model arm. The resulting landmark survival probabilities for PANO+BORT+DEX are detailed in Table 8.

Table 8: Survival landmarks for PFS, PANO+BORT+DEX (PANORAMA-2) – adjusted for excess mortality

	Proportion of patients progression-free at:					
	6 months	1-year	2-years	5-years	10-years	25-years
MAIC HR applied to elranatamab PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: MAIC, matching-adjusted indirect comparisons; PFS, progression-free survival.						

PANO+BORT+DEX overall survival

As detailed above, the HR derived from the MAIC of [redacted] is subject to several limitations. When including the HR from the MAIC in the economic model, the median OS for PANO+BORT+DEX is estimated at [redacted] months. The landmark survival estimates using this HR are reported in Table 9.

Clinical advice to the company was that OS for PANO+BORT+DEX is expected to be much lower than that of elranatamab owing to the reasons presented in 3.1. Additionally, real-world evidence in UK cohorts median OS for PANO+BORT+DEX treated patients has been observed estimated at 9.5 months (95% CI 5.0-14.9 months) (9), and 10 months (7). This suggests that, due to uncertainty in the MAIC relating to the age of the study, the immaturity of PANORAMA-2 OS data and the misalignment of PANORAMA-2 to a TCE cohort, the MAIC overestimates PANO+BORT+DEX OS by approximately [redacted] Therefore, an adjustment to the HR was explored to bring estimates of PANO+BORT+DEX OS into line with clinical opinion, observed data and modelled PFS. The landmark survival estimates using this adjusted HR are also reported in Table 9.

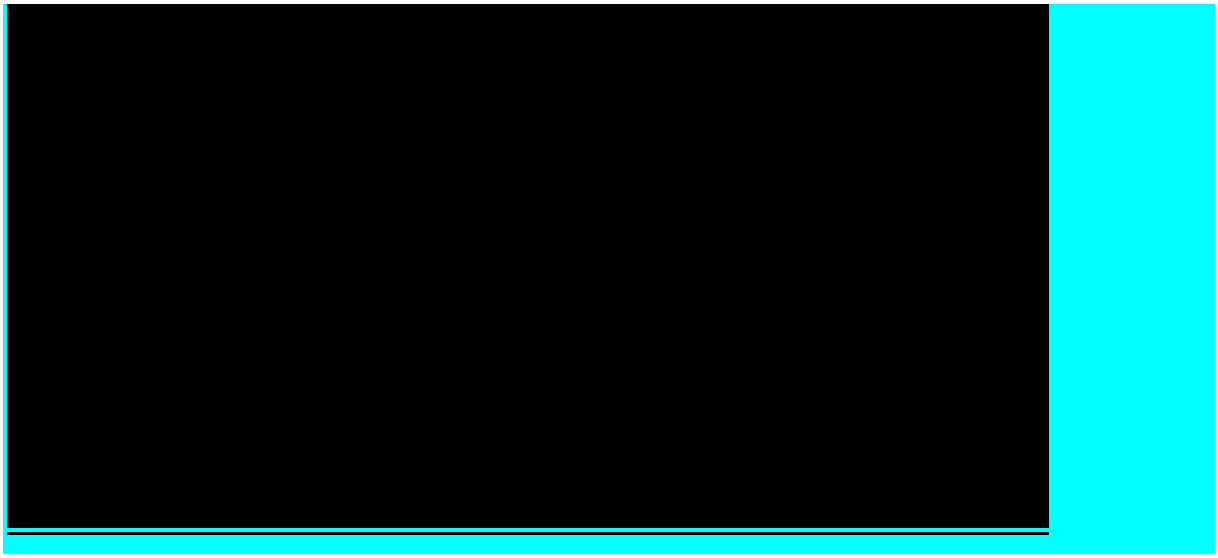
Table 9: Survival landmarks for OS, PANO+BORT+DEX (MAIC PANORAMA-2) – adjusted for excess mortality

Distribution	6 months	10 months	1-year	2-years	5-years	10-years	25-years
MAIC base-case HR applied to elranatamab OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adjusted HR applied to elranatamab OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: HR, Hazard ratio; OS Overall Survival							

The base case OS and PFS comparison for elranatamab versus PANO+BORT+DEX are presented here.

Figure 18: Base case: Elranatamab Cohort A curve compared with PANO+BORT+DEX PANORAMA-2 PFS curve – adjusted for excess mortality


[redacted]

Key: MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; PANO+BORT+DEX, panobinostat, bortezomib and dexamethasone.

Error! Reference source not found.**Figure 19Figure 19: Base case: Elranatamab Cohort A curve**

compared with PANO+BORT+DEX PANORAMA-2 OS curve – adjusted for excess mortality

Key: MAIC, matching-adjusted indirect comparison; OS, overall survival; PANO+BORT+DEX, panobinostat + bortezomib + dexamethasone.

As TTD data were not available from PANORAMA-2, the median treatment duration and median PFS reported in Maouche et al. (2022) were used to create a ratio of modelled PFS to modelled TTD. This approach generated a median TTD of 4.6 months.

4. Clinical validation

Two interviews were conducted to further validate the statements provided in the response to the NICE draft guidance for elranatamab for the treatment of relapsed, refractory multiple myeloma [ID4026].

Video calls took place on the 6th of August 2024 with the following attendees:

- 13:00-14:00 BST discussion: Dr. Jaimal Kothari| Consultant Haematologist | Oxford University Hospitals
- 14:00-15:00 BST discussion: Dr. Neil Rabin | Consultant Haematologist | University College Hospital

Topics discussed included the treatment algorithm in multiple myeloma patients; comparators in TCE RRMM patients, and validity of indirect treatment comparisons presented in the response to the draft guidance.

Treatment pathway

- Both clinicians agreed that, in an ideal world, treatment strategies would be based on exposure and refractoriness status of patients. However, lines of treatments are used according to NICE guidance, limiting clinician autonomy and their ability to optimise treatment for RRMM patients. Dr. Rabin further stated that NICE's pathways has not kept up with the changes in MM treatment and eligibility populations, hindering the ability of clinicians to offer personalised treatments.
- Elranatamab's trial is based on PI and IMiD exposure, which would logically make the therapy positioned in third line rather than fourth.
- Both clinicians reiterated the issue of the "third line gap". Dr. Rabin explained that lines of treatments create holes in the treatment pathways where patients who become TCE at third line are not eligible for better therapies until they are considered to be 4th line. In turn, less efficacious treatments, such as CYCLO+DEX, are provided in 3rd line to bridge lines, which is harmful to patients and not in their best interests.
- Dr. Rabin added that unmet needs also existed in 4th and 5th line where limited treatment options are available (e.g. selinexor which marginally extends survival and PANO which has high associated toxicities)
- Dr. Kothari also emphasised that there is a high unmet need for high-risk patients (about 20% of the population), who die within two years. Earlier access to treatment is required for those patients, and more flexibility in using certain therapy and combination regimens upfront would help. For example, having a BCMA (i.e. elranatamab and/or teclistimab) available for use at third line would benefit those patients.
- Clinicians agreed that patients are becoming refractory to more drugs earlier, as more therapies are being approved and treatment strategies look to offer the more efficacious treatments earlier on in the pathway. This means that, according to the label, a growing proportion of patients would be eligible for elranatamab earlier in the pathway but are unable to access the therapy owing to restrictions by lines of treatment, which forces the use of potentially harmful and ineffective drugs as bridging therapies.

Comparators

- Both clinicians agreed that IXA+LEN+DEX and LEN+DEX are not relevant comparators in fourth line. Most patients would receive LEN in 2nd line, or 3rd line if they had not received it yet. Dr. Kothari reiterated that it is not a relevant comparator for TCE RRMM population, and Dr. Rabin confirmed that the population who is LEN sensitive in 3rd line is small and decreasing, and these patient would not be eligible for IXA+LEN+DEX or LEN+DEX in 3rd and 4th line.
- Dr. Rabin further noted that some patients who are LEN exposed but not LEN refractory, may be eligible for IXA+LEN+DEX, but this is a very small population.
- Clinicians agreed that POM+DEX would be used ahead of PANO+BORT+DEX, excepting rare situations in which a POM naive patient is suitable for PANO and is not refractory to BORT
- Clinicians agreed that PANO was very toxic and is rarely given in 4th line. Dr. Kothari added that, rather than PANO, they may use Cyclo in combination with BORT+DEX
- Considering the above, and the fact that CDF treatments and newly approved therapies (e.g. Selinexor) are not considered relevant comparators by NICE, both clinicians agreed that POM+DEX was the most relevant comparator for elranatamab.

Restriction of POM+DEX in draft guidance

- When asked for their opinion on the POM+DEX restriction included in the draft guidance, both clinicians agreed that it was detrimental to patients.
- Dr. Kothari stated that the recommendation was illogical based on the clinical trial data and the label, and highlighted that it would further restrict treatment sequencing and lead to suboptimal treatment strategies.
- Dr. Rabin explained that there are many POM-exposed patients who would be suitable to receive elranatamab but who cannot receive it with this restriction.

The guidance does make sense for a POM-naïve population. However, 81% of patients were POM exposed in the MagnetisMM-3 trial.

- Both clinicians did not understand the rationale for this restriction, and stated that the option to offer elranatamab earlier would benefit patients, and avoid exposing them to other less efficacious treatments and their associated toxicities.
- When presented with the MagnetisMM-3 trial subgroup analysis showing outcomes for POM exposed and POM naïve patients, Dr. Rabin agreed that POM naïve patients still get a meaningful outcome despite limited patient numbers in that group. He explained that the POM naive curve was representative of what would be expected, i.e. POM naive patients would do better, as they are less refractory and less pre-treated. He also added that POM exposed patients will likely be both LEN and POM refractory.

PANO+BOR+DEX vs. Elranatamab MAIC

- Both clinicians strongly agreed that PANORAMA-2 was not generalizable to a TCE RRMM population in current clinical practice given differences in anti-CD38 exposure, IMiD choice available at the time of the trial (pre- 2013); and PI refractoriness.
- Dr. Rabin agreed that PANORAMA 2 remained more relevant than PANORAMA 1 given the PI and LEN refractoriness status of patients.
- Both clinicians agreed that, if TCE RRMM NHS cohort were given PANO+ BORT+DEX, they would expect to see worst outcomes than those in PANORAMA-2, meaning that comparison with elranatamab would be show a very conservative effect of elranatamab's efficacy.
- When presented with the MAIC results, including the PFS and OS KM curves for the weighted and unweighted Elranatamab data against PANO+BOR+DEX, both clinicians agreed with the direction of the results for PFS but said it was very hard to comment on the differences given the limitations and associated uncertainties of the indirect comparisons.
- Both clinicians were unable to explain the OS results, and would expect an inferior outcome for PANO+BORT+DEX (OS ~ <9 months)

Teclistimab vs. Elranatamab MAIC

- Both clinicians agreed with the relevance of performing a MAIC with elranatamab and teclistimab.
- When presented with the MAIC results, Dr. Kothari stated that the superior median PFS of elranatamab is well documented, and there will be a focus on the rationale behind why that is the case.
- Dr. Rabin added that, while you are comparing two BCMA in similar populations, it is still difficult to interpret the difference given limitations in the data (i.e. small patient numbers, differences in prior / subsequent therapies), and both teclistimab and elranatamab would be considered equivalent without further data on efficacy. Dr Kothari also agreed that is hard to make a statement on whether the difference is clinically meaningful, and the analysis should be interpreted cautiously.
- Both clinicians agreed that elranatamab had a more favorable dosing schedule than teclistimab. Dr. Kothari reiterated that a reduced administration burden on patients should not be underestimated.

COTA Real World study

- Both clinicians agreed that the study COTA's baseline demographics are relatively similar to TCE RRMM patients in the UK.
- COTA patients, however, are less refractory and would be easier to treat, making the comparison with elranatamab conservative.
- Dr. Rabin caveated that the US would have different therapies available and prior / subsequent therapies received may effect results, which should be interpreted with caution.

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Elranatamab for treating relapsed and refractory multiple myeloma after 3 or more treatments [ID4026]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 9 August 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Pfizer Ltd

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Pfizer Ltd: Pharmaceutical company and marketing authorisation holder
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Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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Addendum	Following the second appraisal for teclistimab in relapsed refractory multiple myeloma (ID6333) please find enclosed an addendum summarising the cost effectiveness of elranatamab against Selinexor plus dexamethasone (SEL+DEX). **Background** At the second appraisal meeting for teclistimab (ID6333) on the 3rd September 2024 the committee and expert discussion identified three comparators of interest that would allow the committee to evaluate whether the optimisation to only recommend treatment where pomalidomide plus dexamethasone (POM+DEX) is unsuitable could be removed. The three comparators of interest were POM+DEX representing 70%of the eligible population, Panobinostat plus bortezomib plus dexamethasone (PANO+BORT+DEX) representing 20% and SEL+DEX representing 10% respectively. To date the Cmpany have provided cost effectiveness results against POM+DEX and PANO+BORT+DEX. Prior to the committee meeting on the 3rd September the Compaby had no reason to consider SEL+DEX as a relevant comparator in later lines. This is based on the following. 1. SEL+DEX was not in the original scope for the elranatamab appraisal. 2. SEL+DEX was approved in April 2024 (Final Draft Guidance) after elranatamab's first appraisal committee meeting on the 14th March 2024. 3. In all our clinical discussions and validations SEL+DEX has not been mentioned as a potential comparator. In addition, the EAG in their assessment did not identify SEL+DEX as a potential or relevant comparator. The company stands by its original submission that POM+DEX is the relevant, plausible and generalisable comparator in this appraisal. However, given the circumstances the Company wants to provide as much relevant information to the committee to make a decision which is consistent with the information provided as part of ID6333. To further reassure the Committee, we present additional evidence, a matching indirect treatment comparison with SEL+DEX. A summary of results for overall survival and progression free survival are below and a full report is available as supporting reference. The STORM trial [NCT02336815] was selected as the relevant trial. [1] The median OS in STORM was 8.6 months (95% CI 6.2, 11.3) and the median PFS was 3.7 months (95% CI 3.0, 5.3).[1] **Summary Results: MAIC of elranatamab (Cohort A) versus selinexor plus dexamethasone (STORM).** In the base case, the identified PVs and EMs listed in the accompanying full report were adjusted in the analysis. These include age (≥75 years), sex, time from initial diagnosis, R-ISS disease stage, high-risk cytogenetics, median number of prior lines, ECOG status, creatinine clearance, penta-drug refractory status, and type of myeloma. Weights were generated based on the identified PVs and EMs so that the distributions of these two variables for elranatamab were the same as those reported for selinexor plus dexamethasone in the STORM study.

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Table 1 provides the HRs for OS. The OS of elranatamab was significantly longer than SEL+DEX in both the naïve analysis and following MAIC adjustments. The HR of elranatamab compared with SEL+DEX was [redacted] before weighting and [redacted] after weighting. The sensitivity analysis results were consistent with the base case results.

Table 1: Hazard ratios of OS: elranatamab vs. selinexor plus dexamethasone

Scenario	*ESS*	*HR (95% CI)*	*p-value*
Naïve comparison	**123**	[redacted]	**0.000**
Base case	**47**	[redacted]	**0.022**
Sensitivity analysis (imputation)	**54**	[redacted]	**0.046**

Note: All numbers in bold were identified to be statistically significant at the specified threshold.

Abbreviations: CI = confidence interval; ESS = effective sample size; HR = hazard ratio; OS = overall survival

Figure 1 shows the KM curves of OS for elranatamab (unweighted and weighted) and selinexor plus dexamethasone.

Figure 1: KM curve of OS – elranatamab vs. selinexor plus dexamethasone

[redacted]

Abbreviations: KM = Kaplan-Meier; OS = overall survival; tx = treatment

Progression-free survival

In the base case, the identified PVs and EMs shown in Table 3.2 that were available in STORM data were adjusted. These include age (≥75 years), time from initial diagnosis, ISS disease stage, high-risk cytogenetics, median number of prior lines,

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ECOG status, creatinine clearance, penta-drug refractory status, and type of myeloma.

Weights were generated so that the distributions of the variables for elranatamab were the same as those reported for SEL+DEX in the STORM study.

Table 2 provides the HRs for PFS. The PFS of elranatamab was significantly longer than selinexor plus dexamethasone, both with and without MAIC adjustments. The HR of elranatamab compared with SEL+DEX was [redacted] before weighting and [redacted] after weighting. The results of the sensitivity analysis were consistent with the base case results.

Table 2 Hazard ratios of PFS: elranatamab vs. selinexor plus dexamethasone

Scenario	*ESS*	*HR (95% CI)*	*p-value*
Naïve comparison	**123**	[redacted]	**0.001**
Base case	**47**	[redacted]	**0.009**
Sensitivity analysis (imputation)	**54**	[redacted]	**0.015**

Note: All numbers in bold were identified to be statistically significant at the specified threshold.

Abbreviations: CI = confidence interval; ESS = effective sample size; HR = hazard ratio; PFS = progression-free survival

Figure 2 shows the KM curves of PFS for elranatamab (unweighted and weighted) and SEL+DEX.

Figure 2 KM curve of PFS - elranatamab vs. selinexor plus dexamethasone

[redacted]

Abbreviations: KM = Kaplan-Meier; PFS = progression =-free survival; tx = treatment

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Cost effectiveness Results: MAIC of elranatamab (Cohort A) versus selinexor plus dexamethasone (STORM).

Results using the Committee preferred assumptions and Company net price discount (incl. CAA confidential additional rebate*) of [redacted] suggest there are negative incremental costs associated with elranatamab and resultant net health benefit of 1.73 (Table 3). This provides the Committee with further confidence in elranatamab's cost effectiveness.

Table 3: Cost-effectiveness results scenario from a MAIC versus comparator SEL+DEX.

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Elranatamab	[redacted]	[redacted]			
SEL+DEX	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (net health benefit = 1.73)

Key: DEX, dexamethasone; EAG, evidence assessment group; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; SEL, Selinexor.

Table 4 explores the relative cost effectiveness of elranatamab using the Committee preferred assumptions and Company net price discount (incl. CAA confidential additional rebate*) at varying comparator net price patient access scheme (PAS) discounts.

Table 4: Relative cost effectiveness of elranatamab at varying comparator net price PAS discounts.

Technologies	PAS Discount %	ICER (£/QALY)
Elranatamab vs. SEL+DEX	5%	Dominant
	10%	449
	15%	2,401
	20%	4,354
	25%	6,306
	30%	8,259
	35%	10,211
	40%	12,164
	45%	14,116
	50%	16,065
	55%	18,017
	60%	19,970
	65%	21,922
	70%	23,875
	75%	25,827
	80%	27,780

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		85%	29,732
		90%	31,685

Key: DEX, dexamethasone; EAG, evidence assessment group; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; SEL, Selinexor.

[redacted]

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Insert extra rows as needed

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Elranatamab

Indirect Treatment Comparison Report: Selinexor plus Dexamethasone

Matching-adjusted indirect treatment comparison (MAIC) of elranatamab versus approved therapies for the treatment of patients with multiple myeloma who are exposed or refractory to at least one proteasome inhibitor, one immunomodulatory drug, and one anti-CD38 monoclonal antibody

Study Information

Title	Matching-adjusted indirect treatment comparison (MAIC) of elranatamab versus approved therapies for the treatment of patients with multiple myeloma who are exposed or refractory to at least one proteasome inhibitor, one immunomodulatory drug, and one anti-CD38 monoclonal antibody
Date	1 September 2023
Active substance	Elranatamab (ELREXFIO®)
Comparators	Selinexor (Xpovio®) plus dexamethasone
Research question and objectives	What is the relative treatment effect of elranatamab compared with relevant comparators in patients with triple-class exposed (TCE) / refractory (TCR) multiple myeloma (MM)?
Author	Pfizer Ltd

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1.1. Compatibility assessment

1.1.1. Trial design

The STORM trial ([NCT02336815]) was a phase 2b, single-arm, multicenter, open-label study of selinexor plus dexamethasone.[1] Overall, the design of the pivotal trials of elranatamab (MagnetisMM-3) and selinexor plus dexamethasone (STORM) was similar (see Table 1.1).

Table 1.1: Study design features: MagnetisMM-3 (elranatamab) vs. STORM (selinexor plus dexamethasone)

	MagnetisMM-3 (elranatamab) (Cohort A)[2]	**STORM[1] (selinexor + dexamethasone)**
Trial number	NCT04649359	NCT02336815
Trial design	Single-arm, phase 2, open-label	Single-arm, phase 2, open-label
Enrolment	n = 123	n = 122
Treatment arm	Elranatamab monotherapy	Selinexor plus low-dose dexamethasone
Primary endpoint	ORR	ORR
Secondary endpoints	DOR, CRR, DOCR, OS, PFS, TTR, MRD negativity rate	DOR, CB, PFS, OS
Patient population	Patients with TCR MM	Patients with TCR MM

Abbreviations: CB = clinical benefit; CRR = complete response rate; DOCR = duration of complete response; DOR = duration of response; MRD = minimal residual disease; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SC = subcutaneous; TCR = triple-class refractory; TTR = time to response; QW = every week

1.1.2. Key inclusion and exclusion criteria

Table 1.1.2 provides an overview of the selected key inclusion and exclusion criteria of MagnetisMM-3 and STORM. Of the main inclusion and exclusion criteria, the majority were similar between the two studies.

There was a minor difference in the eligibility criteria between the two studies regarding the definition of TCR status. TCR was defined in STORM as patients who were refractory at least one IMiD, one PI, and daratumumab, whereas in MagnetisMM-3, TCR was defined as refractory to any anti-CD38 mAb, as well as one IMiD and one PI. However, since daratumumab represents the vast majority of anti-CD38 mAbs used in RRMM,[3-5] the difference in the TCR definitions between the two trials was considered small.[1] In the MagnetisMM-3 trial, approximately 92% of patients had previously been treated with daratumumab and almost all patients were refractory to an anti-CD38 mAb.

Table 1.2: Main trial inclusion and exclusion criteria: MagnetisMM-3 (elranatamab) vs. STORM (selinexor plus dexamethasone)

	MagnetisMM-3[2], elranatamab (Cohort A)	STORM[1], selinexor + dexamethasone
Inclusion Criteria		
1	Age ≥18 years	Age ≥ 18 years
2	Prior diagnosis of MM as per IMWG criteria	Measurable disease based on IMWG criteria
3	Measurable disease of MM as per IMWG criteria	Previously received ≥3 anti-MM regimens including: an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab, and a glucocorticoid
4	Refractory to at least one IMiD, at least one PI, and one anti-CD38 mAb	Refractory to glucocorticoids, PIs, IMiD, and daratumumab
5	Relapsed or refractory to last anti-MM regimen	Refractory to most recent anti-MM regimen
6	ECOG performance score ≤2	ECOG performance status ≤2
Exclusion Criteria		
1	Prior BCMA-directed therapy	Active smoldering MM
2	Stem cell transplant within 12 weeks prior to enrolment	Prior exposure to a SINE compound

Abbreviations: BCMA = B-cell maturation antigen; ECOG = Eastern Cooperative Oncology Group; IMiD = immunomodulatory drug; IMWG =International Myeloma Working Group; mAb = monoclonal antibody; MM = multiple myeloma; PI = proteasome inhibitor; SINE = selective inhibitors of nuclear export

1.1.3. Patient characteristics

Table 1.1.3 presents an overview of the baseline patient characteristics of the identified PVs and EMs (Table 3.2) enrolled in the MagnetisMM-3 and STORM clinical trials.

Extramedullary disease was not reported in the STORM data and was therefore not included in the MAIC. This was considered as one of the main limitations of this MAIC, as extramedullary disease was identified as a PV in the SLR and clinical opinion.

Table 1.3: Baseline characteristics of patients: MagnetisMM-3 (elranatamab) vs. STORM (selinexor plus dexamethasone)

		MagnetisMM-3[2, 6], elranatamab (Cohort A) (n = 123)	STORM[1, 7, 8], selinexor + dexamethasone (n =122)
Age	Median	68	65
	>75 years	21 (17%)	18 (15%)
Sex	Male	68 (55%)	71 (58%)
Time from initial diagnosis (median, years)		6.1	6.6
R-ISS disease stage	Stage I	28 (23%)	20 (16%)
	Stage II	68 (55%)	78 (64%)
	Stage III	19 (15%)	23 (19%)
High-risk	del(17p)/p53	19 (15%)	32 (26%)

		MagnetisMM-3[2, 6], elranatamab (Cohort A) (n = 123)	STORM[1, 7, 8], selinexor + dexamethasone (n =122)
cytogenetics	t(4;14)	10 (8%)	17 (14%)
	t(14;16)	2 (2%)	5 (4%)
Number of previous treatment regimens, median		5	7
ECOG status	0	45 (37%)	36 (30%)
	≥1	78 (63%)	71 (58%)
Creatinine clearance (mL/min)	≥60	72 (59%)	82 (67%)
Penta-drug refractory status		52 (42%)	83 (68%)
Type of myeloma	IgG	65 (53%)	82 (67%)
	Non-IgG	20 (16%)	18 (15%)

Note: The percentage was rounded to whole numbers, and as such, the sum of each subcategory may not exactly equal 100% (i.e., ISS disease stage for STORM)

The baseline characteristics R-ISS disease stage, creatinine clearance, and type of myeloma have missing data in MagnetisMM-3 patient-level data. STORM reports missing baseline characteristics for ISS disease stage, ECOG, and creatinine clearance.

Only the patient characteristics that were identified PVs and EMs and were mutually reported in MagnetisMM-3 and STORM are shown in the table above.

Abbreviations: ECOG = Eastern Cooperative Oncology Group; R-ISS = Revised International Staging System

1.1.4. Outcome measures

Table 1.4 presents a comparison of the endpoint definition of OS and PFS used in MagnetisMM-3 and STORM. As the definitions of OS and PFS were similar between the two trials, they were able to be compared as endpoints in the indirect comparative analysis.

The median OS in STORM was 8.6 months (95% CI 6.2, 11.3) and the median PFS was 3.7 months (95% CI 3.0, 5.3).[1]

Table 1.4: Endpoint definitions - comparison between MagnetisMM-3 (elranatamab) and STORM (selinexor plus dexamethasone)

Endpoint	MagnetisMM-3[2]	STORM[1]
OS	Time from the date of first dose until death due to any cause	Duration from start of study treatment to death from any cause
PFS	Time from the date of first dose until confirmed PD per IMWG criteria or death due to any cause	Duration from start of study treatments to time of PD or death from any cause

Abbreviations: IMWG = International Myeloma Working Group; OS = overall survival; PD = progressive disease; PFS = progression-free survival

1.2. Results

The following section outlines the results for the MAIC of elranatamab (Cohort A) versus selinexor plus dexamethasone (STORM).

1.2.1. Overall survival

In the base case, the identified PVs and EMs listed in Appendix A were adjusted in the analysis. These include age (≥75 years), sex, time from initial diagnosis, R-ISS disease stage, high-risk cytogenetics, median number of prior lines, ECOG status, creatinine clearance, penta-drug refractory status, and type of myeloma.

Weights were generated based on the identified PVs and EMs so that the distributions of these two variables for elranatamab were the same as those reported for selinexor plus dexamethasone in the STORM study.

Table 1.5 provides the HRs for OS. The OS of elranatamab was significantly longer than selinexor plus dexamethasone in both the naïve analysis and following MAIC adjustments. The HR of elranatamab compared with selinexor plus dexamethasone was [redacted] before weighting and [redacted] after weighting. The sensitivity analysis results were consistent with the base case results.

Table 1.5: Hazard ratios of OS: elranatamab vs. selinexor plus dexamethasone

Scenario	ESS	HR (95% CI)	p-value
Naïve comparison	**123**	[redacted]	**0.000**
Base case	**47**	[redacted]	**0.022**
Sensitivity analysis (imputation)	**54**	[redacted]	**0.046**

Note: All numbers in bold were identified to be statistically significant at the specified threshold.

Abbreviations: CI = confidence interval; ESS = effective sample size; HR = hazard ratio; OS = overall survival

Figure 1.1 shows the KM curves of OS for elranatamab (unweighted and weighted) and selinexor plus dexamethasone.

Figure 1.1: KM curve of OS – elranatamab vs. selinexor plus dexamethasone

Abbreviations: KM = Kaplan-Meier; OS = overall survival; tx = treatment

1.2.2. Progression-free survival

In the base case, the identified PVs and EMs shown in Table 3.2 that were available in STORM data were adjusted. These include age (≥75 years), time from initial diagnosis, ISS disease stage, high-risk cytogenetics, median number of prior lines, ECOG status, creatinine clearance, penta-drug refractory status, and type of myeloma.

Weights were generated so that the distributions of the variables for elranatamab were the same as those reported for selinexor plus dexamethasone in the STORM study.

Table 1.6 provides the HRs for PFS. The PFS of elranatamab was significantly longer than selinexor plus dexamethasone, both with and without MAIC adjustments. The HR of elranatamab compared with selinexor plus dexamethasone was [redacted] before weighting and [redacted] after weighting. The results of the sensitivity analysis were consistent with the base case results.

Table 1.6: Hazard ratios of PFS: elranatamab vs. selinexor plus dexamethasone

Scenario	ESS	HR (95% CI)	p-value
Naïve comparison	**123**	[redacted]	**0.001**
Base case	**47**	[redacted]	**0.009**
Sensitivity analysis (imputation)	**54**	[redacted]	**0.015**

Note: All numbers in bold were identified to be statistically significant at the specified threshold.

Abbreviations: CI = confidence interval; ESS = effective sample size; HR = hazard ratio; PFS = progression-free survival

Figure 1.2 shows the KM curves of PFS for elranatamab (unweighted and weighted) and selinexor plus dexamethasone.

Figure 1.2: KM curve of PFS - elranatamab vs. selinexor plus dexamethasone

Abbreviations: KM = Kaplan-Meier; PFS = progression =-free survival; tx = treatment

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3. APPENDIX A

3.1. Statistical Methods

Identifying prognostic variables and effect modifiers

Prognostic variables (PVs) are variables which are significantly associated with the outcome of interest; effect modifiers (EMs) are variables which modify the relationship between treatment and outcomes of interest.[9] Because MagnetisMM-3 is a single-arm trial, it was not possible to assess EMs based on its clinical data. Therefore, additional EMs (and PVs) were identified through literature reviews and were validated by clinicians.

To identify potential PVs to adjust for in the comparative analyses, several steps were taken. First, univariate Cox proportional hazard models were performed to identify any potential PVs for time-to-event outcomes, and univariate logistic models were performed to identify any potential PVs for binary response outcomes based on the MagnetisMM-3 data. Any variables which exhibited a p-value of equal or less than 0.05 was included for further consideration as a key prognostic variable.

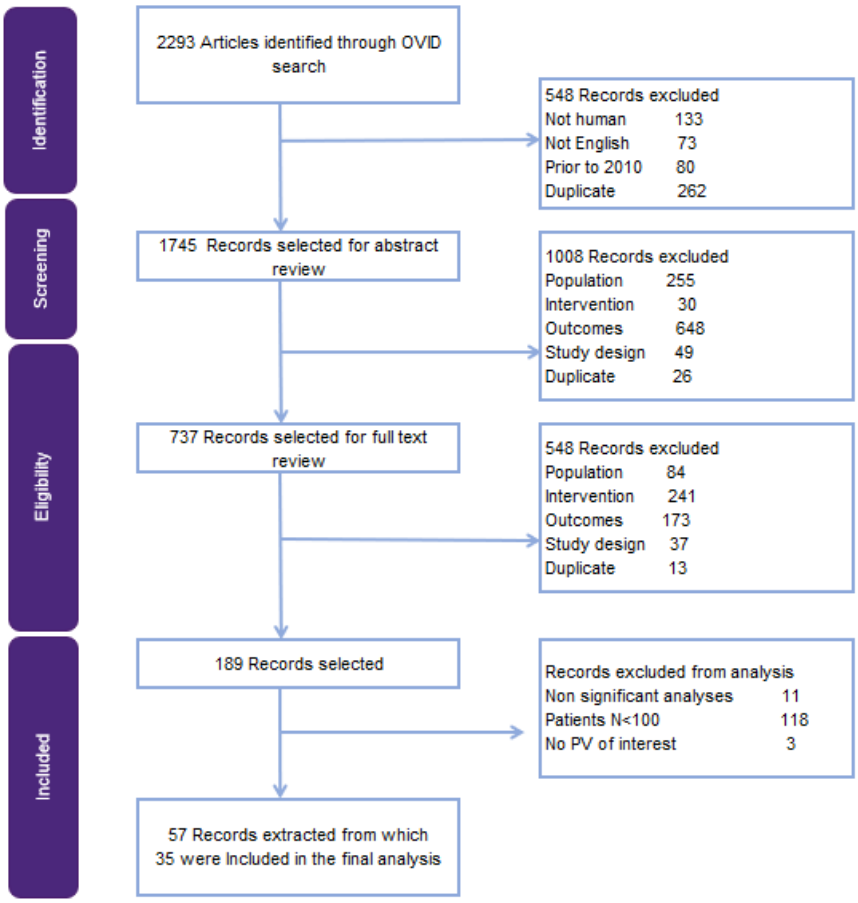
Additional PVs and EMs were identified through a SLR conducted in June 2021 in RRMM, a review of the recent clinical trials in TCE/R MM, and a review of recently published indirect treatment comparisons in TCE/R MM. The PICOS is shown in Table 3.1.

Table 3.1: PICOS statement

Category	Inclusion criteria
Patient population	Patients diagnosed with relapsed or refractory multiple myeloma (RRMM) in any line
Intervention and comparators	Bortezomib, lenalidomide, carfilzomib, ixazomib, daratumumab, pomalidomide, panobinostat, elotuzumab, selinexor, melflufen, vorinostat, isatuximab, bendamustin, TJ202/MOR202 (felzartamab), encorafenib, binimetinib, pembrolizumab, nivolumab, erdafitinib, RAPA-201, belantamab mafodotin, idecabtagene vicleucel, ciltacabtagene autoleucel, CAR-T
Outcomes measures	• Overall survival (OS) • Progression-free survival (PFS) • Response rates (ORR/CR/sCR/VGPR) • Time to Progression (TTP), duration of response (DOR) • Minimal Residual Disease (MRD) • Other time-to-event measurements (event-free survival, time-to-next treatment, treatment-free survival, duration of response) • Patient reported outcomes (PRO) (EORTC-QLQ C30, MY20, FACT) • Utility values (EQ-5D, SF-36, VAS, etc.) • Safety (SAE, Grade 3/4 AE, special interest AE)
Study design	• Real world evidence (prospective, observational, longitudinal, retrospective) • Indirect treatment comparisons • Systematic reviews, meta-analyses and indirect comparisons • Pooled Analyses (for cross-checking only)

Figure shows the PRISMA diagram of the SLR. Thirty-five studies with multivariate analyses were extracted and analyzed, which 22 studies with univariate analyses were extracted.

Figure 3.1: PRISMA diagram



The SLR identified two categories for PVs and EMs: 'likely' and 'potential' PVs and EMs. We only carried the 'likely' PVs and EMs into the MAIC for adjustment.

- 'Likely' PVs and EMs were defined if the variables were reported in 3 or more studies which support the association between the variable and outcome

'Potential' PVs and EMs were defined if the variable were reported in less than 3 studies with conflicting evidence to support an association between the variable and the outcomes

These were subsequently confirmed through clinical expert opinion. The final list of PVs and EMs is presented below.

Table 3.2: Prognostic variables and effect modifiers identified based on the SLR and clinical opinion

	OS	PFS
Prognostic variables and effect modifiers	• Age • Sex • Time since initial diagnosis • R-ISS or ISS (where available) • High-risk cytogenetics • Extramedullary disease • Number of prior lines of therapy • ECOG performance status • Creatinine clearance • Refractory/exposure status (penta-exposed; penta-refractory status) • Type of MM (IgG, IgA, IgD, light-chain)	• Age • Time since initial diagnosis • R-ISS or ISS (where available) • High-risk cytogenetics • Extramedullary disease • Number of prior lines of therapy • ECOG performance status • Creatinine clearance • Refractory/exposure status (penta-exposed; penta-refractory status) • Type of MM (IgG, IgA, IgD, light-chain)

Key: ECOG, Eastern Cooperative Oncology Group; EM, effect modifiers; OS, overall survival; PFS, progression-free survival; PV, Prognostic variables; R-ISS, Revised International Staging System.
Note: R-ISS was prioritised as a PV/EM if it was reported in the comparator's trial.

4. APPENDIX B

4.1. Log cumulative hazard plots and Schoenfeld residual plots for Cohort A

In this section, the log cumulative hazard plots and the Schoenfeld[10] residual plots are presented for the MAIC analyses of elranatamab (Cohort A) versus Selinexor plus dexamethasone. Log cumulative hazard plots show the relationship of logarithm of time versus the determined log cumulative hazard. If the two curves presented are deemed to be parallel, it can be presumed that the proportional hazards assumption holds. Schoenfeld residual plots show the relationship between time and the residuals and are used to further test for proportional hazards. If the residuals show a non-random pattern in a Schoenfeld residual plot, the PH assumption has been violated. Both the Schoenfeld residual plots and the log-cumulative hazard plots were used to determine whether the PH assumption held.

Figure 4.1: Log cumulative hazard plot: elranatamab vs. selinexor plus dexamethasone (OS)

Figure 4.2: Schoenfeld residual plot: elranatamab vs. selinexor plus dexamethasone (OS)

Figure 4.3: Log cumulative hazard plot: elranatamab vs. selinexor plus dexamethasone (PFS)

Figure 4.4: Schoenfeld residual plot: elranatamab vs. selinexor plus dexamethasone (PFS)

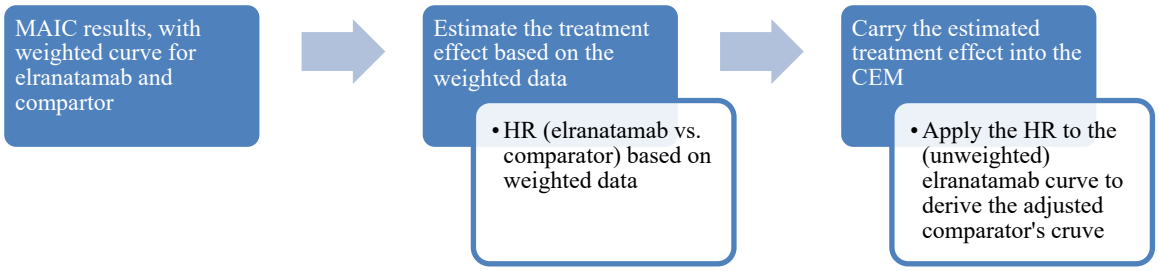
4.2. Approach for comparators where the proportional hazards does not hold

For the PFS comparison there is a presumption that the PH assumption does not hold. Therefore, the HRs derived from the MAICs could not be applied directly within the health economic models. An alternative approach (here after referred to "MAIC adjusted curve") is described below:

- Instead of measuring treatment effect via HRs, the treatment effects of elranatamab were estimated on the parameters of each survival distribution (e.g., shape and scale) based on the weighted data from MAIC
- In the health economic model, the treatment effects of elranatamab were subtracted from the unweighted parameters of the elranatamab parametric fits (e.g., shape and scale) to derive the adjusted parameters of the comparator's fits (e.g., adjusted shape and scale)
- The adjusted parameters of the comparator's fits were used to derive the extrapolation of the OS and PFS curves.

Figure 4.2.1 shows the classic method of applying the HR directly when the PH assumption does hold. Figure 4.2.2 shows the proposed MAIC adjusted curve method. In the normal HR approach, the treatment effect of elranatamab is measured by the HR.[9, 11] In the MAIC adjusted curve approach, the treatment effect of elranatamab is captured by the impact on the parameters of the survival distribution (e.g., shape and scale), instead of the HR. When the treatment effect is captured on the parameters of the parametric fits (e.g., both shape and scale), the PH assumption does not need to hold as both shape and scale are allowed to change by treatment.

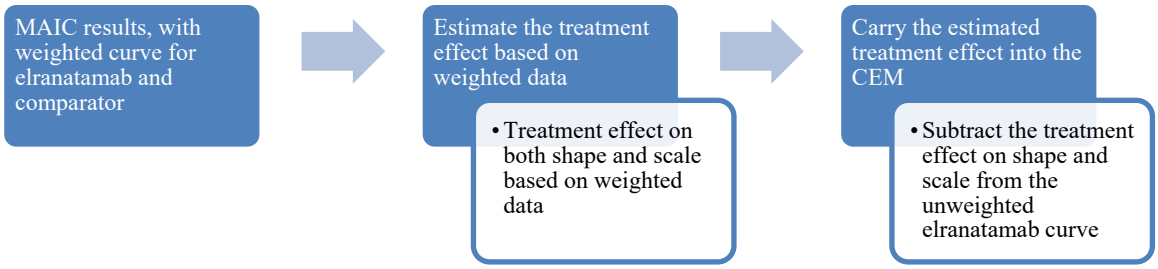
Figure 4.5: Normal HR approach.



Source: NICE DSU 18[9]

Abbreviations: CEM = cost-effectiveness model; HR = hazard ratio; MAIC = matching adjusted indirect comparison

Figure 4.6: MAIC adjusted curves method



Abbreviations: CEM = cost-effectiveness model; MAIC = matching adjusted indirect comparison

Table 4.1 show the treatment effect of Selinexor plus dexamethasone where the PH assumption did not hold for the comparison with elranatamab (Cohort A).

Table 4.1: Weighted treatment effect on shape and scale for selinexor plus dexamethasone PFS

Parametric distribution		Weighted treatment effect	Standard Error (SE)	New weighted parameters for selinexor plus dexamethasone
Weibull	shape	[redacted]	[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]
Log-normal	meanlog	[redacted]	[redacted]	[redacted]
	sdlog	[redacted]	[redacted]	[redacted]
Log-logistic	shape	[redacted]	[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]
Gompertz	shape	[redacted]	[redacted]	[redacted]
	rate	[redacted]	[redacted]	[redacted]
Generalized gamma	mu	[redacted]	[redacted]	[redacted]
	sigma	[redacted]	[redacted]	[redacted]
	Q	[redacted]	[redacted]	[redacted]
Gamma	shape	[redacted]	[redacted]	[redacted]
	rate	[redacted]	[redacted]	[redacted]

Abbreviations: PFS = progression-free survival; SE = standard error

Elranatamab for treating relapsed and refractory multiple myeloma after 3 or more treatments [ID4026]

Company response to EAG Critique of the draft guidance – Factual inaccuracies and comments

On the 13th September we received a copy of the EAG critique of the company's response to consultation on the draft guidance. The EAG critique highlighted a number of key points supporting the removal of the optimization where pomalidomide plus dexamethasone (POM+DEX) would otherwise be considered and the alignment of recommendations between this appraisal and ID6333[1]. This response should be read in conjunction with the EAG critique and Company draft guidance response plus additional addendum.

The Company would like to highlight the following inaccuracies and misinterpretations as well as updated scenarios. Further detail is presented in **Factual inaccuracies** and **Appendix A.**:

A. In the draft guidance response, the company have provided an alternative comparison to POM+DEX using data presented in ID6333. The company approach used the lognormal (for OS) and gompertz (for PFS), based on the publicly available information published for ID6333. **(FAC 1)**

B. The Company acknowledge that the subsequent treatments in RRMM are complex and, for those in later lines, there is no standard of care. The Company would raise a number of inaccuracies related to subsequent treatments and have therefore suggested a number of scenarios that would be considered representative and applied these across Tables 1-4 in **Appendix A** and described further in **FAC 2.**

   - PANO+BORT+DEX is not currently used in 3L despite its reimbursement by NICE. As outlined in our DG response this medicine is often used in later lines after POM+DEX[2]
   - For consistency, the Company believes that, given the comments raised at the second appraisal committee meeting (ACM) for ID6333 which identified SEL+DEX as a potential comparator, and the subsequent submission of a cost effectiveness analysis of elranatamab versus SEL+DEX, it is relevant to consider this comparator within the subsequent treatment baskets across all analysis.

C. As detailed in **FAC 3** for the (MM-003) adjustment of OS and PFS in the PANO+BORT+DEX comparison, Scenario 1 in **Table 2** and **Table 3** is incorrect and should be removed.

   - The company would like to clarify for the EAG that the MM-003 adjustment is specific for the comparison with POM+DEX, based on data from MM-003. There is no specific 'adjusted' data for the PANO+BORT+DEX comparison and in this scenario an adjusted HR is applied. Therefore, for the correct interpretation of the relative outcomes the comparison should be made using the unadjusted elranatamab data.

   - Consequently, related combined scenarios should also be removed (EAG preferred 1,2, and 4 along with 1,3, and 4). **Table 2** and **Table 3** include the combined scenarios 2+4 and 3+4.

D. As detailed in **FAC 4**, Table 2 and Table 3 of the EAG critique of the company DG response, where scenarios 2 and 3 replaced subsequent PANO+BORT+DEX with POM+DEX in the PANO+BORT+DEX arm and resulted in a higher ICER, there was an error in the model that means the results of these scenarios are incorrect.

   - When replacing PANO+BORT+DEX with POM+DEX in the PANO+BORT+DEX arm results in the ICER decreasing from £35,602 to £18,457 (**Table 2**) and from £37,892 to £20,747 (**Table 3**).

E. We welcome the EAG correcting the original base case economic evaluation versus POM+DEX. However, we are concerned that this is being raised as this is not part of the draft guidance consultation and we would urge some caution on re-opening discussions given that additional updates should also be considered. However, to provide reassurance for the committee, we have included updated POM-DEX subsequent treatment (**FAC 2**) and those related to ID6333 comparator source (**FAC 1)** scenario(s)/corrects, that results in further reduction of the ICER (Appendix, **Table 4** and **Table 5**).

F. In all scenarios the probabilistic ICERs are below the deterministic. The Company believes these should be considered for decision making. These illustrate the magnitude of direction to the deterministic ICERs.

Factual inaccuracies

EAG Critique Section Page Number	Factual Inaccuracy	Comment / Correction
FAC 1 Section 1: Page 5,6	*However, the company have not described their approach here transparently, and appear not to have used the preferred Gompertz OS curve that was agreed upon for POM+DEX in ID16333. They have instead used a lognormal curve. And whilst they have chosen a Gompertz curve for PFS, the selected curve does not appear to match the Gompertz PFS curve that was accepted in ID16333.*	We would like to explain the context to help the EAG understand as we believe the approach has been misinterpreted. Rather than a lack of transparency we would argue that there are many potential caveats that explain why the ID6333 POM+DEX curves and our version of the ID6333 POM+DEX curves don't match exactly. We respectively ask that this is considered and the EAG report updated accordingly. Firstly, the reason for the comparison is to show the lower decision risk in the elranatamab appraisal when compared with ID6333. In ID6333 a trial versus RWE was selected with minimal adjustment of critical confounding factors due to lack of available data. When this source of data is used in the appraisal of elranatamab, the ICER reduces significantly when compared with trial versus trial comparison (company base case). The argument is presented to support an alignment of recommendations as we believe the Company approach is more robust and therefore in this context is conservative. Given the EAG comments in the critique there is some alignment in believing this is a credible suggestion from the Company. Secondly, to enable this comparison the Company needed to digitise the curves from the published committee slides and papers. The company is limited by information that is available in the public domain and this might explain any discrepancy. In the EAG critique: page 11 draft guidance ID6333 "The company selected log-normal and Gompertz distributions to model both long-term overall survival and progression-free survival in the economic model for the teclistamab arm and the pomalidomide plus dexamethasone arm, respectively" Therefore, either the EAG potentially has information that isn't publicly available or this is an error as the committee papers clearly describe the preferred approach that are aligned with the company scenario as described below.[3] The company approach used the lognormal (for OS) and gompertz (for PFS), based on the publicly available information published for ID6333. The committee discussion mentions that the curves were adjusted to account for survival estimates derived from clinical judgments. As the exact mechanism of the adjustment was not published, we are unable to confirm if the adjustment included a change in curve. Note the curves are based on digitised data, so we would expect that they do not match exactly, to those presented in ID6333. Additionally, as we note above ,the ID6333 curves were adjusted to match survival estimates derived from clinical experts.[3] The curves that were presented by the company in response to the consultation on the draft guidance are unadjusted for clinical experts' judgement, however, in the model (on the model engine sheets) they are adjusted by the application of a time varying SMR which may somewhat explain the inconsistencies between the two appraisals.

FAC 2 **Section 2: Page 12**	Therefore, the EAG has assessed the impact of changing the distribution of subsequent therapy to remove PANO+BORT+DEX as a subsequent treatment option following PANO+BORT+DEX. Two alternative scenarios were considered: 1) Replacing PANO+BORT+DEX with POM+DEX (reflecting a subsequent treatment distribution that might be reasonable for those who receive PANO+BORT+DEX at third line, prior to being eligible for POM+DEX). 2) Replacing all subsequent treatment following PANO+BORT+DEX with cyclophosphamide (reflecting a subsequent treatment distribution for those who receive PANO+BORT+DEX as a comparator to elranatamab in later lines, having already received POM+DEX).	The Company understands the approach taken by the EAG. However, the Company would raise a number of inaccuracies. Firstly, PANO+BORT+DEX is not currently used in 3L despite its reimbursement by NICE. As outlined in our DG response this medicine is often used in later lines after POM+DEX[2]. Clinical experts confirm this is the case. An analysis of SACT data suggests the use is ~3%. We therefore argue that considering PANO+BORT+DEX at 3L is not reasonable and is most often used subsequent to POM+DEX in 5L+ or in a minority of patients in 4L. In addition, following the elranatamab appraisal committee meeting and despite being out of scope, SEL+DEX is being suggested as a comparator in this appraisal based on discussions in ID6333. The company do not believe this is an appropriate comparator, but we have provided the comparison to support committee decision making. However, the Company argue that this context should now be considered as part of any subsequent treatment basket for all potential comparators. The Company believes it would be unfair to not do so for consistency. The Company acknowledge that the subsequent treatments in RRMM are complex and, for those in later lines, there is no standard of care. The Company have therefore suggested a number of scenarios that would be considered representative of those identified (reimbursed) comparators within ID6333 and applied these across Tables 1-4 below in **Appendix A**. For the population of interest, ID6333 discussed POM+DEX (70%), PANO+BORT+DEX (20%) and SEL+DEX (10%). We would add that any subsequent lines for consideration would change the distribution of subsequent treatment baskets and we have represented this through the varying scenarios. Given the availability of these options we would argue that the use of CYCLO+DEX is minimal until it is used as a drug of last resort in later lines or as a bridging therapy for a short duration (as agreed by the CDF lead in ACM1).
FAC 3 **Section 2: Page 12, Table 2 and Table 3 (Scenario 1)**	The EAG also questions the company's decision to revert to parametric curves fitted to unadjusted MagnetisMM-3 cohort A data for elranatamab in their additional scenario. The committee may remember that the company used curves fitted to the MM-003 adjusted cohort A data in their base case against POM+DEX. For consistency, the EAG would prefer to retain these curves in the additional scenario. The EAG noted previously that the curves fitted to unadjusted cohort A data result in a more optimistic extrapolation of OS for elranatamab.	The company understands the EAG's motives for requesting the MM-003 adjusted cohort A data. However, the company would like to clarify for the EAG that the MM-003 adjustment is specific for the comparison with POM+DEX based on data from MM-003. There is no specific 'adjusted' data for the PANO+BORT+DEX comparison and in this scenario an MAIC-derived HR is applied. We have provided a copy of the MAIC report, which provides an overview of the analysis for the EAG's review. Note that in the analysis we have assumed the PH assumption holds for both PFS and OS, for consistency across endpoints and for simplicity. Apologies for our oversight in not providing this data. Therefore, for the correct interpretation of the relative outcomes, the comparison should be made using the unadjusted elranatamab data.

FAC 4 Section 2 Table 2 and 3, (Scenario 2)	2. Replace subsequent PANO+BORT+DEX treatment with POM+DEX in PANO+BORT+DEX arm	Please note that in Table 2 and Table 3 of the EAG critique of the company DG response, where scenarios 2 and 3 replaced subsequent PANO + BORT + DEX with POM+DEX in the PANO+BORT+DEX arm and resulted in a higher ICER, there was an error in the model that means the results of these scenarios are incorrect. When replacing PANO+BORT+DEX with POM+DEX in the PANO+BORT+DEX arm results in the ICER decreasing from £35,602 to £18,457 (**Table 2**) and from £37,892 to £20,747 (**Table 3**). The POM+DEX percentage was hard coded as 0 incorrectly in the parameters sheet of the model, resulting in changes to the POM+DEX percentage not being considered correctly. Please accept our apologies for this oversight which in part resulted in the incorrect EAG analyses.

Appendix A

Table 1. EAG corrected company base case against PANO+BORT+DEX

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)	% change from base case
Elranatamab	[redacted]	[redacted]				
PANO+ BORT+DEX	[redacted]	[redacted]	[redacted]	[redacted]	5,359*	NA
EAG Corrections (applied independently)						
Company base			[redacted]	[redacted]	£5,359	NA
1. Correction of PANO+BORT+DEX PFS and OS curves			[redacted]	[redacted]	£8,543	59.40%
2. Removal of RDI switch to 100% at 25 weeks to never++			[redacted]	[redacted]	Dominant	+246.65% NHB@30k
3. Subsequent treatment distribution for PANO+BORT+DEX switched from Elranatamab to PANO+BORT+DEX			[redacted]	[redacted]	£16,104	200.48%
4. Drug acquisition cost of PANO+BORT+DEX equals 0 from 48 weeks (no change to drug administration costs which are £0 from 48 weeks).			[redacted]	[redacted]	£16,403	206.05%
5. Assume only 1 3.5mg Bortezomib vials are used for subsequent treatment			[redacted]	[redacted]	£5,360	0.02%
EAG company corrected base case– [redacted] IVIG			[redacted]	[redacted]	£21,039	292.59%
EAG company corrected base case – 43.1% IVIG			[redacted]	[redacted]	£23,329	335.28%
**Company base case assumes 43.1% IVIG use; ++ the company corrected this themselves in an updated document following their initial response.*						

ICER, Incremental cost effectiveness ratio; MAIC, matching adjusted indirect comparison; PANO, panobinostat; QALY, quality adjusted life year.

Table 2. EAG cost-effectiveness scenarios of EAG corrected company base case against PANO+BORT+DEX – [redacted] IVIG

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (£/QALY)	% change from base case
Elranatamab	[redacted]	[redacted]				
PANO+ BORT+DEX			[redacted]	[redacted]	£21,039	NA
~~1. Retention of MM-003 adjusted Elranatamab PFS and OS curves~~			[redacted]	[redacted]	~~£26,093~~	~~24.03%~~
2. Replace subsequent PANO+BORT+DEX treatment with POM+DEX in PANO+BORT+DEX arm			[redacted]	[redacted]	£18,457	-12.27%
2.a Subsequent PANO+BORT+DEX • POM+DEX = 70% • SEL+DEX = 30%			[redacted]	[redacted]	£6,346	-69.83.78%
2.b Subsequent PANO+BORT+DEX • POM+DEX = 70% • SEL+DEX = 20% • CYCLO+DEX = 10%			[redacted]	[redacted]	£10,383	-50.65%
3. Replace subsequent PANO+BORT+DEX treatment with cyclophosphamide in PANO+BORT+DEX arms			[redacted]	[redacted]	£35,497	68.72%
3.a Subsequent PANO+BORT+DEX • SEL+DEX = 100%			[redacted]	[redacted]	Dominant (NHB=1.55)	+289.13% NHB@30k
3.b Subsequent PANO+BORT+DEX • SEL+DEX = 70% • CYCLO+DEX = 30%			[redacted]	[redacted]	£7,239	-65.59%
3.c Subsequent PANO+BORT+DEX • SEL+DEX = 50% • CYCLO+DEX = 50%			[redacted]	[redacted]	£15,313	-27.22%
4. Reduce subsequent treatment duration to mean Time-on-Treatment for POM+DEX (4.8 months)			[redacted]	[redacted]	£17,914	-14.85%
2+4			[redacted]	[redacted]	£16,344	-22.31%
3+4			[redacted]	[redacted]	£26,589	26.38%
COMPANY Preferred 2b and 4			[redacted]	[redacted]	£11,491	-45.38%
COMPANY Preferred 3b and 4			[redacted]	[redacted]	£9,604	-54.35%
Probabilistic results						
2+4			[redacted]	[redacted]	16,066	-23.63%
COMPANY Preferred 2b and 4			[redacted]	[redacted]	10,994	-47.74%

ICER, Incremental cost effectiveness ratio; MAIC, matching adjusted indirect comparison; PANO, panobinostat; QALY, quality adjusted life year.

Table 3. EAG cost-effectiveness scenarios of EAG corrected company base case against PANO+BORT+DEX – 43.1% IVIG

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (£/QALY)	% change from base case
Elranatamab	[redacted]	[redacted]				
PANO+ BORT+DEX	[redacted]	[redacted]	[redacted]	[redacted]	£23,329	NA
~~1. Retention of MM-003 adjusted Elranatamab PFS and OS curves~~			[redacted]	[redacted]	~~£28,824~~	~~23.56%~~
2. Replace subsequent PANO+BORT+DEX treatment with POM+DEX in PANO+BORT+DEX arm			[redacted]	[redacted]	£20,747	-11.01%
2.a Subsequent PANO+BORT+DEX • POM+DEX = 70% • SEL+DEX = 30%			[redacted]	[redacted]	£8,636	-62.98%
2.b Subsequent PANO+BORT+DEX • POM+DEX = 70% • SEL+DEX = 20% • CYCLO+DEX = 10%			[redacted]	[redacted]	£12,673	-45.68%
3. Replace subsequent PANO+BORT+DEX treatment with cyclophosphamide in PANO+BORT+DEX arms			[redacted]	[redacted]	£37,787	61.98%
3.a Subsequent PANO+BORT+DEX • SEL+DEX = 100%			[redacted]	[redacted]	Dominant (NHB=1.45)	+263.58% NHB@30k
3.b Subsequent PANO+BORT+DEX • SEL+DEX = 70% • CYCLO+DEX = 30%			[redacted]	[redacted]	£9,529	-59.15%
3.c Subsequent PANO+BORT+DEX • SEL+DEX = 50% • CYCLO+DEX = 50%			[redacted]	[redacted]	£17,603	-32.53%
4. Reduce subsequent treatment duration to mean Time-on-Treatment for POM+DEX (4.8 months)			[redacted]	[redacted]	£20,204	-24.54%
2+4			[redacted]	[redacted]	£18,634	-20.12%
3+4			[redacted]	[redacted]	£28,879	23.79%
COMPANY Preferred 2b and 4			[redacted]	[redacted]	£13,781	-40.93%
COMPANY Preferred 3b and 4			[redacted]	[redacted]	£11,894	-49.01%
Probabilistic Results						
2+4			[redacted]	[redacted]	£18,461	-20.87%
COMPANY Preferred 2b and 4			[redacted]	[redacted]	£13,314	-42.93%

ICER, Incremental cost effectiveness ratio; MAIC, matching adjusted indirect comparison; PANO, panobinostat; QALY, quality adjusted life year.

Table 4. Committee preferred assumptions against POM+DEX with corrected settings from company response to FAD

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (£/QALY)	% change from base case
Elranatamab ([redacted] IVIG)	[redacted]	[redacted]				
POM+DEX	[redacted]	[redacted]	[redacted]	[redacted]	£6,116	NA
Elranatamab (43.1% IVIG)	[redacted]	[redacted]				
POM+DEX	[redacted]	[redacted]	[redacted]	[redacted]	£8,472	NA
EAG corrections						
[redacted] IVIG						
1. Subsequent treatment distribution for POM+DEX switched from Elranatamab to POM+DEX			[redacted]	[redacted]	£17,320	183.18%
1 a. Subsequent POM+DEX plus • PANO+BORT+DEX = 70% • SEL+DEX = 30%			[redacted]	[redacted]	£4,760	-28.49%
1 b. Subsequent POM+DEX plus • PANO+BORT+DEX = 70% • SEL+DEX = 20% • CYCLO+DEX = 10%			[redacted]	[redacted]	£8,947	31.64%
2. Assume only 3.5mg Bortezomib vials are used for subsequent treatment			[redacted]	[redacted]	£6,117	0.02%
43.1% IVIG						
3. Subsequent treatment distribution for POM+DEX switched from Elranatamab to POM+DEX			[redacted]	[redacted]	£19,676	132.24%
3 a. Subsequent POM+DEX plus • PANO+BORT+DEX = 70% • SEL+DEX = 30%			[redacted]	[redacted]	£7,116	-19.06%
3 b. Subsequent POM+DEX plus • PANO+BORT+DEX = 70% • SEL+DEX = 20% • CYCLO+DEX = 10%			[redacted]	[redacted]	£11,303	25.05%
4 Assume only 3.5mg Bortezomib vials are used for subsequent treatment			[redacted]	[redacted]	£8,474	0.01%
EAG corrected committee preferred base case – 43.1% IVIG			[redacted]	[redacted]	£19,830	134.06%
COMPANY preferred base case – 43.1% IVIG 3 b+4.			[redacted]	[redacted]	£11,457	26.05%

ICER, Incremental cost effectiveness ratio; MAIC, matching adjusted indirect comparison; PANO, panobinostat; QALY, quality adjusted life year.

Table 5 EAG replicated scenarios for Elranatamab versus POM+DEX with Company preferred base case.

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (£/QALY)	% change from base case
Elranatamab ([redacted] IVIG)	[redacted]	[redacted]				
POM+DEX	[redacted]	[redacted]	[redacted]	[redacted]	£9,101	NA
Elranatamab ([redacted] IVIG)	[redacted]	[redacted]				
POM+DEX	[redacted]	[redacted]	[redacted]	[redacted]	£11,457	NA
Company Scenarios						
Committee preferred base case – [redacted] IVIG						
1. Alternative source of POM+DEX efficacy ID6333 (SACT)			[redacted]	[redacted]	Dominant (NHB=3.25)	+361% NHB@30k
Committee preferred base case – 43.01% **IVIG**						
2. Alternative source of POM+DEX efficacy ID6333 (SACT)			[redacted]	[redacted]	Dominant (NHB 2.72)	+340% NHB@30k

References

1. NICE Teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments: draft guidance consultation 2024 [updated July 2024. Available from: https://www.nice.org.uk/guidance/GID-TA11418/documents/draft-guidance.
2. Pfizer. Draft guidance stakeholder form. ID4026. August 9 2024
3. NICE Teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments (Review of TA869) [ID6333] Committee Papers 2024 [Available from: https://www.nice.org.uk/guidance/gid-ta11418/documents/committee-papers.

Company Corrections EAG Critique – Model Specification / Input Changes

The changes in table below provide a step-by-step guide to the company corrections in the model aligned with *Pfizer EAG Draft Guidance Critique response ID4026_FINAL[CIC].* The company do not contest the EAG corrections corresponding to table 1 in *ID4026_Elranatamab EAG critique of company DG response v1 020924VM [CON]*

For simplicity drop downs have been added to the Company submitted model and corrections 1-5 from table 1 (in *ID4026_Elranatamab EAG critique of company DG response v1 020924VM [CON]*) are described below.

Assumption / Scenario	**EAG Corrections: Table 1, EAG corrected company base case against PANO+BORT+DEX (Page 14)**
1. Correction of PANO+BORT+DEX PFS and OS curves	*Settings, cell E123* *Select, repair.*
2. IVIG: Proportion receiving IVIG	*Settings, cell E112* *Select, Patients who received IVIG in MagnetisMM-3 - 43.01% (53/123)*
3. Fix to the subsequent therapies drug costs	*Settings, cell E125* *Select, repair.*
4. Drug acquisition cost of PanoVD £0 from 48 weeks corrected	*Settings, cell E124* *Select, Assume £0 drug acquisition costs post week 48 for PanoVD*
5. Bortezomib minimum increments	*Settings, cell E126* *Select, 3.5mg*

Alongside this addendum, the Company have uploaded a model that aligns with Table 3: *EAG cost-effectiveness scenarios of EAG corrected company base case against PANO+BORT+DEX – 43.01% IVIG ICER of £23,329.* For clarity, this includes the corrections outlined in the table above.

- Note: This is the most conservative scenario presented by the EAG based on committee preferred assumptions and demonstrates the upper end of the ICERs.

Model File name:
ID4026 Elranatamab _RRMM_CEM_EAG_090824_v2.3_EAGCorrectedCompanybasePANOVd.

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (£/QALY)	% change from base case
Elranatamab	[redacted]	[redacted]				
PANO+ BORT+DEX	[redacted]	[redacted]	[redacted]	[redacted]	£23,329	NA

The table below outlines the changes to the model to replicate tables 2 and 3 in the most recent company response to the EAG critique (*Pfizer EAG Draft Guidance Critique response ID4026_FINAL[CIC]*)

- Note: To replicate the ICERs for IVIG use aligned to EAG preferred of [redacted] (Table 2 *Pfizer EAG Draft Guidance Critique response ID4026_FINAL[CIC]* change **cell E112 in the settings Tab** and repeat the steps in the table below.

Assumption / Scenario	Section in Company Response	Changes to model from company original base case
Company correction: 1. Retention of MM-003 adjusted Elranatamab PFS and OS curves	*FAC 3 Page 3, Table 3*	*Settings, cell E41* *Select Cohort A*
Company correction: 2. Replace subsequent PANO+BORT+DEX treatment with POM+DEX in PANO+BORT+DEX arm	*FAC 4 Page 4, Table 3*	*Parameters, cell F162* The POM+DEX percentage was hard coded as 0 incorrectly in the parameters sheet of the model, resulting in changes to the POM+DEX percentage not being considered correctly. <u>This is corrected in this version of the model.</u> Note: As parameters have been added to the updated model this corresponds to *cell F157* in the previous model that was submitted by the company as part of the DG response.
Company Scenario Subsequent Treatment: <u>Scenarios</u> **2a,** POM+DEX = 70%, SEL+DEX = 30% **2b,** POM+DEX = 70%, SEL+DEX = 20%, CYCLO+DEX = 10% **3a,** SEL+DEX = 100% **3b,** SEL+DEX = 70%, CYCLO+DEX = 30% **3c,** SEL+DEX = 50%, CYCLO+DEX = 50%	*FAC 2 Page 2* *Table 2,3* *Scenarios 2a, 2b, 3a, 3b, 3.c*	*Subsequent_treatment, cell G20 – G23* *Varying subsequent treatment basket aligned with company suggested scenarios. Inclusion of SEL+DEX in preference to CYCLO+DEX reduces the ICERs further*
4. Reduce subsequent treatment duration to mean Time-on-Treatment for POM+DEX (4.8 months)	*Table 2,3 scenario 4*	*Dosage, cell E82* *Change to 4.8 months*

Option: Comparison versus SEL+DEX

- Note: Company ICER vs SEL+DEX with EAG corrections (table 1), ICER is significantly below the comparison with PANO+BORT+DEX (Tables 3, Company draft guidance critique response).

Assumption / Scenario	Section in Company Response	Changes to model from company original base case
To assess the impact of: EAG cost-effectiveness scenarios of EAG corrected company base case versus SEL+DEX (IVIG 43.1%) This would allow the EAG corrections to be assessed alongside the Company submitted comparison with SEL+DEX.	*3.0 FORM - Draft guidance stakeholder comments form - Pfizer DG Response_Addendum[CIC]*	*Settings, cell E37* *Select MAIC vs.Selinexor+DEX* *Settings, cell E41* *Select cohort A* ICER is significantly below the comparison with PANO+BORT+DEX (Tables 3, Company draft guidance critique response). *Subsequent_treatment, cell G20 – G23* Any addition of POM+DEX to subs treatment basket reduces the ICER further.

Elranatamab

Indirect Treatment Comparison Report

Matching-adjusted indirect treatment comparison (MAIC) of elranatamab versus approved treatment(s) for the treatment of patients with relapsed or refractory multiple myeloma after at least 3 prior therapies

Study Information

Title	Matching-adjusted indirect treatment comparison (MAIC) of elranatamab versus approved therapies for the treatment of patients with relapsed or refractory multiple myeloma after at least 3 prior therapies
Date	13 August 2024
Active substance	Elranatamab (ELREXFIO®)
Comparator	Panobinostat in combination with bortezomib and dexamethasone
Research question and objectives	What is the relative treatment effect of elranatamab compared with the relevant treatment(s) for patients with relapsed or refractory multiple myeloma after at least 3 prior therapies?
Author	[redacted]

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EXECUTIVE SUMMARY

Multiple myeloma (MM) is the second most common hematologic cancer, with an estimated worldwide incidence of only 180,000 cases per year, with the highest share of cases located in North America, Western Europe, and Eastern Asia.[1] In the United Kingdom (UK), 5,951 new cases of MM are established each year.[2] The disease is characterized by monoclonal proliferation of bone marrow plasma cells, causing significant morbidity due to end-organ destruction.[3]

Almost all patients with MM will relapse or become refractory (RRMM) to treatment.[4] This is defined as being non-responsive while on salvage therapy or progressing within 60 days of their last therapy despite achieving minimal response or better at some point previously before.[5,6] As patients progress in their disease course, fewer treatment options are available to them, signifying a large unmet need.

Elranatamab (ELREXFIO®) is a Food and Drug Administration (FDA) approved bispecific antibody that binds to the B-cell maturation antigen (BCMA) on the surface of tumour MM cells, and the CD3 receptor on the surface of T-cells.[7] MagnetisMM-3 (NCT04649359) is an ongoing open-label, multicentre, non-randomized, phase 2 registrational study evaluating the efficacy and safety of elranatamab monotherapy in patients with MM who were exposed or refractory to at least one immunomodulatory drug (IMiD), one proteasome inhibitor (PI), and one anti-CD38 monoclonal antibody (mAb) (i.e., patients with triple-class exposed [TCE] or triple-class refractory [TCR] MM).[8,9] The trial included two cohorts: patients who had not previously received a BCMA-directed antibody-drug conjugate (ADC) or chimeric antigen receptor T-cell therapies ([CAR T-cell therapies] Cohort A), and patients who had previously received a BCMA-directed therapy (Cohort B). Median progression-free survival (PFS) by Blinded Independent Central Review (BICR) and median overall survival (OS) have not been reached at 15 months, and the respective rates at 15 months were 50.9% (95% CI 40.9, 60.0%) and 56.7% (95% CI 47.4, 65.1%). At the 14.7-month data cut, the objective response rate (ORR) was achieved in 61.0% of patients (95% CI 51.8, 69.6%), with a complete response (CR) seen in 35.0% (95% CI 26.6, 44.1%).[8,9]

To contextualize the clinical profile of elranatamab, an indirect treatment comparison (ITC) was conducted to compare the efficacy of elranatamab, as observed in MagnetisMM-3, with the efficacy of panobinostat in combination with bortezomib and dexamethasone (further referred to in this report as PanVd), from PANORAMA 2 trial.[10] The main analyses were run using the Cohort A patient population from MagnetisMM-3 (n = 123).

Given that MagnetisMM-3 is a single-arm trial and there may be potential differences in the baseline characteristics between MagnetisMM-3 and PANORAMA 2, unanchored matching adjusted indirect comparisons (MAICs) was conducted between elranatamab and PanVd. The key outcomes presented in this report are OS (defined in MagnetisMM-3 as the time from the date of first dose until death due to any cause) and PFS (defined as the time from the date of first dose until confirmed progressed disease [PD] per International Myeloma Working Group [IMWG] criteria or death due to any cause).

MAIC-adjusted results indicated that elranatamab was associated with numerically longer OS compared with PanVd based on the PANORAMA 2 trial, though the statistical significance was not reached.

Regarding the PFS endpoint, elranatamab was associated with significantly longer PFS after MAIC adjustment compared with PanVd based on the efficacy reported in the PANORAMA 2 trial.

The PFS and OS results from the indirect comparisons of elranatamab versus PanVd, with and without MAIC adjustment, are summarized in Table 1.1.1 and Figure 1.1.1.

Table 1.1.1 Summary of the naïve comparison and MAIC base case for elranatamab versus PanVd

Elranatamab versus	OS HR (95% CI)		PFS HR (95% CI)	
	Naïve comparison	MAIC base case	Naïve comparison	MAIC base case
PanVd	[redacted]	[redacted]	[redacted]	[redacted]

All numbers in bold were identified to be statistically significant at the specified threshold

Abbreviations: CI = confidence interval; HR = hazard ratio; MAIC = matching adjusted indirect comparison; OS = overall survival; PanVd = panobinostat, bortezomib, dexamethasone; PFS = progression-free survival

Figure 1.1.1: Forest plot summary of HRs (95% CIs) for the naïve and MAIC base case comparison of elranatamab versus PanVd

Note: Please refer to Table 1.1.1 for the specific HRs and 95% CIs values

Abbreviations: CI = confidence interval; HR = hazard ratios; MAIC = matching adjusted indirect comparison; OS = overall survival; PanVd = panobinostat, bortezomib, dexamethasone PFS = progression-free survival

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADC	antibody-drug conjugate
ASCT	autologous stem-cell transplant
BCMA	B-cell maturation antigen
BICR	Blinded Independent Central Review
CAR-T	chimeric antigen receptor
CI	confidence interval
CR	complete response
CRR	complete response rate
DOCR	duration of complete response
DOR	duration of response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EM	effective modifier
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
ESS	effective sample size
FDA	Food and Drug Administration
HR	hazard ratio
HTA	health technology assessment
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IPD	individual patient-level data
ISS	International Staging System
ITC	indirect treatment comparison
KM	Kaplan-Meier
mAb	monoclonal antibody
MAIC	matching-adjusted indirect treatment comparison
MM	multiple myeloma
MRD	minimal residual disease
NE	not evaluable
NMA	network meta-analysis
ORR	objective response rate
OS	overall survival
PAIC	population-adjusted indirect comparison
PD	progressed disease
PFS	progression-free survival
PH	proportional hazards
PI	proteasome inhibitor
PV	prognostic variable
R-ISS	Revised International Staging System
RR	relapsed/refractory
RRMM	relapsed/refractory multiple myeloma
RWE	real-world evidence
sCR	stringent complete response
SE	standard error
SLR	systematic literature review
SOC	standard of care

Abbreviation	Definition
STC	simulated treatment comparison
TCE	triple-class exposed
TCR	triple-class refractory
TTR	time to response
VGPR	very good partial response

1. INTRODUCTION

1.1. Background

Multiple myeloma (MM) is the second most common hematologic malignancy, characterized by the monoclonal proliferation of plasma cells in the bone marrow.[3] It is characterized by the monoclonal proliferation of plasma cells in the bone marrow.[3] The abnormal growth of plasma cells can lead to cytopenia, frail and brittle bones, renal failure, anaemia, and end-organ damage.[11] The worldwide incidence of MM is estimated at approximately 180,000 cases per year, with the highest proportion of cases occurring in North America, Western Europe, and Eastern Asia.[1] MM is more likely to be diagnosed in males and in those of older age (i.e., aged ≥60 years).[1] In the UK, MM accounts for 2% of all new cancer cases in the United Kingdom, making it the 19th most diagnosed cancer.[2] Approximately 5,951 new cases of MM are diagnosed each year in the UK. [2]

The prognosis of MM is poor in most cases. The 5-year survival rate is 52.3%, and it is estimated that less than a third (29%) of people diagnosed with MM survive for ten years or more.[2] Due to the nature of disease, patients eventually become resistant to therapies and, as a result, eventually relapse on treatment or become refractory to treatment. Refractory disease is defined as having disease progression while on therapy or within 60 days of last dose in any line, regardless of response, whereas relapsed disease is defined as progression within 60 days of last therapy in patients who have achieved a minimal response or better.[8] For patients with RRMM, survival decreases with increasing lines of therapy, with a median survival of only 1.5 years after two lines of therapy.[12,13] Survival further decreases to 9.2 months for patients who have received three to four prior lines, and to 5.6 months for patients who have received five prior lines.[14]

Novel therapies including proteasome inhibitors (PIs), immunomodulating drugs (IMiDs), and anti-CD38 monoclonal antibodies (mAbs) have been developed for the treatment of RRMM and have revolutionized the treatment landscape. PIs are increasingly used in treating MM, and especially in induction regimens prior to autologous stem cell transplantation (ASCT).[15,16] IMiDs, such as lenalidomide and pomalidomide, have also been found with good clinical outcomes for RRMM patients.[17] Daratumumab and isatuximab are two anti-CD38 mAbs, which can be used in patients who have relapsed after their first line of treatment.[16,18]

Patients who have been exposed to at least one PI, one IMiD, and one anti-CD38 mAb, or have become refractory to a PI, IMiD, and anti-CD38 mAb, are defined as having either triple-class exposed (TCE) MM or triple-class refractory (TCR) MM, respectively. This represents a heavily pre-treated patient population with a particularly poor prognosis.[19] The MAMMOTH (Monoclonal Antibodies in Multiple Myeloma: Outcomes after Therapy Failure) study conducted in the US investigated the outcomes of TCR patients after receiving subsequent treatment and reported a median PFS of 2.8 months and median OS of 8.6 months, with an ORR of only 30%.[20,21] In a European study investigating real-world outcomes in TCE patients, known as the LocoMMotion study, median PFS was 4.6 months, and median OS was 12.4 months.

Currently, there is no standard of care (SOC) therapy for patients with MM who are TCE/TCR. The European Society for Medical Oncology (ESMO) guidelines currently recommend selinexor plus dexamethasone or belantamab mafodotin monotherapy for the treatment of TCR MM. Other options can include conventional chemotherapy, salvage ASCT, or new novel approaches such as bispecific antibodies targeting B-cell maturation antigen (BCMA), such as teclistamab, talquetamab, and elranatamab, which have been recently approved by the FDA and the European Medicines Agency (EMA).[7,22-24] Chimeric antigen receptor (CAR) T-cell therapies have also been approved by FDA and EMA; however, CAR-T therapies are not widely available. As a result, there are limited options for TCE and TCR patients, resulting in a large unmet need.

Elranatamab is an FDA approved novel bispecific antibody that binds the B-cell maturation antigen (BCMA) on myeloma cells and the CD3 receptor on the surface of T-cells. BCMA is highly expressed on myeloma cells and therapies targeting this biomarker represent highly specific and innovative treatments for TCE/R MM.[7] The phase 2 study (MagnetisMM-3, NCT04649359) is an open-label, multicentre, non-randomized, registrational study to evaluate the efficacy and safety of elranatamab monotherapy in patients with MM who have been exposed and are refractory to at least one PI, one IMiD, and one anti-CD38 mAb. The primary endpoint is the ORR as assessed by BICR per IMWG criteria.[8,25]

2. RESEARCH QUESTION AND OBJECTIVES

Elranatamab is currently being appraised by National Institute for Health and Care Excellence (NICE) to determine the clinical and cost-effectiveness within the marketing authorization for treating patients with RR MM after 3 prior therapies. Therefore, the research question for the ITCs is as follows:

- What is the relative treatment effect of elranatamab compared with the relevant comparators for patients with RR MM after at least 3 prior therapies?

Based on the NICE indication for elranatamab, the selected relevant comparator for elranatamab is PanVd.[26] The endpoints included in this ITC analysis were OS and PFS.

3. RESEARCH METHODS

3.1. Study design – unanchored matching adjusted indirect comparison

Unanchored matching-adjusted indirect comparisons (MAICs), a type of population-adjusted indirect comparison (PAIC), were used to indirectly compare the treatment effect of elranatamab to that of relevant comparators. The selection of the MAIC method was based on the following:

1. Alternative approaches that require a network of evidence (e.g., network meta-analyses [NMA]) were not possible because of MagnetisMM-3's single-arm trial design.
2. Potential differences in the distributions of baseline characteristics were identified between the trials of elranatamab and PanVd (e.g., ISS disease stage, previous lines of treatment, etc.), leading to a potentially biased estimation of naïve comparison. There was a need for the PAIC approach (e.g., MAIC) which was able to adjust for the key population differences to derive unbiased estimations.
3. Compared with the simulated treatment comparison (STC), the MAIC approach allows for more flexibility (i.e., no need to make parametric assumptions for the outcome regression). In addition, it is preferred when there is a large overlap in the population characteristics between studies.[27]
4. A review of previous health technology assessments (HTA) submissions in RRMM found that MAICs were more commonly used to compare relative effects than other approaches.[5,28-30] For example, no STC methods were used in the identified HTA submissions in RRMM. The MAIC approach was selected to aid decision-makers in providing consistent methods that have been previously submitted.

For elranatamab, individual-level patient data (IPD) from the MagnetisMM-3 trial were used, with a median follow-up duration of 14.7 months. For PanVd, aggregated data was derived from the PANORAMA 2 trial.[10]

3.2. Data sources

3.2.1. Clinical trial selection

Elranatamab is currently being appraised by NICE to determine the clinical and cost-effectiveness within the marketing authorization for treating patients with RR MM after 3 prior therapies. Within the treatment guidelines in the UK, the relevant comparator to inform the comparative effectiveness was determined to be PanVd. PanVd is recommended by NICE for patients with MM at third or subsequent relapse.[31]

A compatibility assessment was carried out to compare the trial design, patient population, and outcome definitions between trials. Compatibility considerations focused on similarities and differences between the studies, and whether these could be adequately adjusted in the analyses.[27]

3.2.2. Index trial: MagnetisMM-3 trial (elranatamab)

For the MagnetisMM-3 trial [ClinicalTrials.gov number: NCT04649359], the statistical analysis plan and study protocol were used to inform the compatibility assessment.[8] For the comparative analysis, the IPD was provided by Pfizer.

The main indirect comparative analysis was conducted based on Cohort A of the MagnetisMM-3 trial and the respective comparator trial, as most other trials have excluded patients with prior BCMA treatments.

The data used to inform the efficacy of elranatamab were based on a median follow-up duration of 14.7 months.[9]

3.2.3. Comparator trials

Table 3.2.1 provides an overview of all the comparator trials used in MAIC analyses.

Table 3.2.1: Overview of the comparator trials

Treatment name	Trial name	Registration number	Source
PanVd	PANORAMA 2	NCT01083602	Richardson et al (2013)[31]

Abbreviations: NA = not applicable; NR = not reported; PanVd = panobinostat, bortezomib, dexamethasone

3.3. Statistical methods

3.3.1. Identifying prognostic variables and effect modifiers

Prognostic variables (PVs) are variables which are significantly associated with the outcome of interest; effect modifiers (EMs) are variables which modify the relationship between treatment and outcomes of interest.[27] Because MagnetisMM-3 is a single-arm trial, it was not possible to assess EMs based on its clinical data. Therefore, additional EMs (and PVs) were identified through literature reviews and were validated by clinicians.

To identify potential PVs to adjust for in the comparative analyses, several steps were taken. First, univariate Cox proportional hazard models were performed to identify any potential PVs for time-to-event outcomes based on the MagnetisMM-3 data. Any variables which exhibited a p-value of equal or less than 0.05 was included for further consideration as a key PV.

Additional PVs and EMs were identified through a systematic literature review (SLR) conducted in 2021 in RRMM, a review of the recent clinical trials in TCE/R MM, and a review of recently published indirect treatment comparisons in TCE/R MM. They were subsequently confirmed through clinical expert opinion. The details of the SLR are provided in APPENDIX A. The final list of PVs and EMs is presented in Table 3.3.1.

Table 3.3.1: Prognostic variables and effect modifiers identified based on the SLR and clinical opinion

	OS	PFS

Prognostic variables and effect modifiers	• Age • Sex • Time since initial diagnosis • Revised International Staging System (R-ISS) or ISS (where available) • High-risk cytogenetics • Extramedullary disease • Number of prior lines of therapy • Eastern Cooperative Oncology Group (ECOG) performance status • Creatinine clearance • Refractory/exposure status (penta-exposed; penta-refractory status) • Type of MM (IgG, IgA, IgD, light-chain)	• Age • Time since initial diagnosis • R-ISS or ISS (where available) • High-risk cytogenetics • Extramedullary disease • Number of prior lines of therapy • ECOG performance status • Creatinine clearance • Refractory/exposure status (penta-exposed; penta-refractory status) • Type of MM (IgG, IgA, IgD, light-chain)

Note: Revised ISS (R-ISS) was prioritized as a PV/EM if it was reported in the comparator's trial.

Abbreviations: OS = overall survival; PFS = progression-free survival

Table 3.3.2 summarizes the base case settings and scenario analyses. For the comparison with PanVd, the PVs and EMs identified in Table 3.3.1 were adjusted for where data were available in PANORAMA 2.

Table 3.3.2: Overview of base case settings and scenario analyses for MAIC

Scenario	Settings
Naïve comparison	Unadjusted comparison of elranatamab and PanVd.
Base case	Adjusting for PVs and EMs listed in Table 3.3.1
Sensitivity analysis (imputation)	Using imputed data for variables in MagnetisMM-3 data where there were missing data (imputed based on a random sample of the observed data)

Abbreviations: EM = effect modifier; PanVd = panobinostat, bortezomib, dexamethasone; PV = prognostic variable.

3.3.2. Main statistical methods

The first step in conducting the MAIC was to derive balancing weights such that the average baseline characteristics after re-weighting matched the published aggregate characteristics of the comparator population. For variables where the means (and the distributions) were reported in the aggregated data, weights were generated so that the weighted means and the standard deviations in the IPD matched those as reported in the aggregated data. For continuous variables where only the medians were reported (instead of means), binary variables were generated using the IPD based on the reported medians from the aggregated data and the weights were generated so that the weighted means of the binary variables were 0.5 (i.e., to match the median reported in the aggregated data).

A propensity score-type logistic regression equation was used to estimate the balancing weights; this equation predicted whether a given type of patient originated from the index trial or the comparator trial as a function of baseline characteristics. More specifically, weights were

estimated by the odds calculated as $w_i = exp(\alpha + x_i'\beta)$ where x_i' is the vector of baseline variables included for matching. The β coefficients were determined by the method of moments rather than the commonly used maximum likelihood because only aggregate data for the x's were available for the competitor populations.[32,33]

Once the coefficients were estimated, the equation was applied to the patients from the MagnetisMM-3 trial to calculate the individual patient weights. These weights were then used to calculate the effective sample size (ESS), achieved after weighting patients. The ESS was calculated by $(\sum w_i)^2/(\sum w_i^2)$. If the populations were perfectly balanced before adjustment, all patients would have $w_i = 1$, and the ESS would equal the original size of the MagnetisMM-3 population. Adjustments for population differences assigned patients uneven weights, which led to the inevitable loss of ESS. A low ESS indicated an irregular distribution of weights across patients, meaning that only a small fraction of patients shared common characteristics.[33]

To quantify the relative effect of treatments, an adjusted estimate of the effect of the index treatment was calculated to reflect the expected outcome in a population matching the characteristics of the comparator population. This was also compared with the naïve estimator. In the naïve comparison, the two treatments were compared without any adjustment.

The relative effect of the treatment used in the MagnetisMM-3 trial versus the treatment used in the comparator trials on any time-to-event endpoint was quantified as hazard ratios (HRs) with 95% confidence intervals (CIs). For this, the Kaplan-Meier (KM) curves from the comparator trial were digitized following the Guyot et al (2012) study.[34]

4. MAGNETISMM-3 (ELRANATAMAB)

4.1. Trial design

In the MagnetisMM-3 study, patients aged 18 and older with MM who are refractory to one IMiD, one PI, and one anti-CD38 mAb were enrolled in the trial. There were two cohorts in the trial: Cohort A and Cohort B. In Cohort A, patients had no prior BCMA-directed therapy. In Cohort B, patients received prior BCMA-directed ADC or BCMA-directed CAR T-cell therapy.

The primary endpoint of the trial was to determine the efficacy of elranatamab based on ORR, as assessed by BICR per IMWG criteria. Response to treatment was assessed based on the date of the first dose until the first documentation of progressed disease or death. Key secondary endpoints were duration of response (DOR), PFS, and OS, among other relevant endpoints.

4.2. Key inclusion and exclusion criteria

Patients were eligible to be enrolled in the MagnetisMM-3 trial if they were aged 18, had a prior diagnosis of MM, and were refractory to at least one IMiD, one PI, and one anti-CD398 mAb. Additionally, patients had to be relapsed or refractory to their last line of MM treatment. Refractory was defined as having disease progression while on therapy or within 60 days of the last dose in any line, regardless of response. Moreover, patients had to have an Eastern Cooperative Oncology Group (ECOG) performance score of 2 or lower.[8]

Patients with smouldering MM and those who received a stem cell transplant within 12 weeks prior to enrolment were excluded from Cohort A. Patients with prior BCMA-directed therapies were also excluded from Cohort A.

5. ELRANATAMAB VS. PANVD (PANORAMA 2)

5.1. Compatibility assessment

5.1.1. Trial design

The PANORAMA 2 trial ([NCT01083602]) is a single-arm, phase 2, open-label study in which patients with relapsed and bortezomib-refractory MM who have received at least two prior lines of therapy including an IMiD, received panobinostat in combination with bortezomib and dexamethasone.[10] Table 5.1.1 summarizes the characteristics and details of PANORAMA 2 and MagnetisMM-3.

The designs of the pivotal trials of elranatamab (MagnetisMM-3) and PanVd (PANORAMA 2) have some discrepancies, and therefore, any results based on this comparison should be interpreted with caution. The key difference between the two trials lies in patient populations, where MagnetisMM-3 included patients with TCE/R MM and PANORAMA 2 included patients with relapsed and bortezomib-refractory MM, who have received at least two lines of therapy including an IMiD.[10]

Table 5.1.1: Study design features: MagnetisMM-3 (elranatamab) vs. PANORAMA 2 (PanVd)

	MagnetisMM-3[8], elranatamab (Cohort A)	**PANORAMA 2[10], PanVd**
Trial number	NCT04649359	NCT01083602
Trial design	Single-arm, phase 2, open-label	Single-arm, phase 2, open-label
Enrolment	n = 123	n = 55
Treatment arm	Elranatamab monotherapy	Panobinostat, bortezomib, dexamethasone
Primary endpoint	ORR	ORR
Secondary endpoints	DOR, CRR, DOCR OS, PFS, TTR, MRD negativity rate	MR, DOR, PFS, OS
Patient population	Patients with TCR MM	Patients with relapsed & bortezomib-refractory MM who have received at least 2 prior lines of therapy and previously been exposed to an IMiD

Abbreviations: CRR = complete response rate; DOR = duration of response; MR= Minimal Response; MRD = minimal residual disease; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PanVd = panobinostat, bortezomib, dexamethasone; TCR MM = triple class refractory multiple myeloma; TTR = time to response

5.1.2. Key inclusion and exclusion criteria

Table 5.1.2 provides an overview of the key inclusion and exclusion criteria of MagnetisMM-3 and PANORAMA 2. As discussed in Section 5.1.1, a key difference between the two trials is that PANORAMA 2 enrolled patients who were relapsed and bortezomib-refractory MM, while the patient population in MagnetisMM-3 was TCR, defined as being refractory to a PI,

an IMiD, and an anti-CD38.[9,10] Both trials have included patients with an ECOG performance score of equal to 2 and above.

Table 5.1.2: Main trial inclusion and exclusion criteria: MagnetisMM-3 (elranatamab) vs PANORAMA 2 (PanVd)

	MagnetisMM-3[8], elranatamab (Cohort A)	PANORAMA 2[10], PanVd
Inclusion Criteria		
1	Age ≥18 years	Age ≥ 18 years
2	Prior diagnosis of MM as per IMWG criteria	Prior diagnosis of multiple myeloma, based on IMWG 2003 definitions
3	Measurable disease of MM as per IMWG criteria	Measurable disease of MM as per IMWG criteria
4	Refractory to at least one IMiD, at least one PI, and one anti-CD38 mAb	With relapsed and bortezomib-refractory MM
5	Relapsed or refractory to last anti-MM regimen	Refractory to at least 2 prior lines of therapy, which include an IMiD (thalidomide or lenalidomide)
6	ECOG performance score ≤2	ECOG performance score of ≤2
Exclusion Criteria		
1	Prior BCMA-directed therapy	With primary refractory disease
2	Stem cell transplant within 12 weeks prior to enrolment	Undergone allogeneic stem cell transplant with active graft-versus-host disease requiring immunosuppressive therapy
3		Prior MM therapy with a deacetylase inhibitor (including panobinostat)

Abbreviations: BCMA = B-cell maturation antigen; ECOG = Eastern Cooperative Oncology Group; IMiD = immunomodulatory drug; IMWG =International Myeloma Working Group; mAb = monoclonal antibody; MM = multiple myeloma; PI = proteasome inhibitor; PanVd = panobinostat, bortezomib, dexamethasone

5.1.3. Patient characteristics

Table 5.1.3 provides an overview of the baseline characteristics of patients enrolled in the MagnetisMM-3 and PANORAMA 2 clinical trials based on the list of identified PVs and EMs. Out of the identified PVs and EMs, extramedullary disease, creatine clearance, and refractory status were not adjusted for in the MAIC as they were not reported in the PANORAMA 2 data. Not adjusting for extramedullary disease and refractory status is a limitation of this MAIC, as these variables were identified as a key PVs/EMs (see Section 3.3.1).

Table 5.1.3: Baseline characteristics of patients: MagnetisMM-3 (elranatamab) vs. PANORAMA 2 (PanVd)

		MagnetisMM-3[8-10], elranatamab (Cohort A) (n = 123)	PANORAMA 2[10], PanVd (n = 55)
Age	≥65 years	80 (65%)	21 (38%)
Sex	Male	68 (55%)	29 (53%)
Time since initial diagnosis, median years		6.1	4.6[1]
ISS disease stage	Stage I	35 (28%)	18 (33%)
	Stage II	47 (38%)	23 (42%)
	Stage III	24 (20%)	13 (24%)
High-risk cytogenetics		31 (25%)	14 (26%)
Median prior lines of therapy		5	4
ECOG status	0	45 (37%)	26 (47%)
	1	71 (58%)	25 (46%)
	2	7 (6%)	4 (7%)
Type of MM	IgG	65 (53%)	35 (64%)
	Non-IgG	45 (37%)	13 (24%)

Notes: The table above shows only the patient characteristics that were identified as PVs and EMs and mutually reported in MagnetisMM-3 and PANORAMA 2.

The percentage was rounded to whole numbers, and as such, the sum of each subcategory may not exactly equal 100%

The variables ISS disease stage have missing data in MagnetisMM-3 patient-level data.

[1] In PANORAMA 2, the time since initial diagnosis is reported in months. It has been converted to years to facilitate comparison with MagnetisMM-3

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ISS = International Staging System; PanVd = panobinostat, bortezomib, dexamethasone

5.1.4. Outcome measures

Table 5.1.4 presents a comparison of the endpoint definition of OS and PFS used in MagnetisMM-3 and PANORAMA 2. As the definitions of OS and PFS were similar between the two trials, they were able to be compared as endpoints in the indirect comparative analysis.

In PANORAMA 2, the median OS for the PanVd arm was not reached, and the median PFS was 5.4 months.[10]

Table 5.1.4: Endpoint definitions - comparison between MagnetisMM-3 (elranatamab) and PANORAMA 2 (PanVd)

Endpoint	MagnetisMM-3[8]	PANORAMA 2[10,35] (PanVd)
OS	Time from the date of first dose until death due to any cause	Kaplan Meier estimates: median time to event
PFS	Time from the date of first dose until confirmed PD per IMWG criteria or death due to any cause	Time from the date of first study treatment to first occurrence of documented progressive disease /relapse or death

Abbreviations: IMWG = International Myeloma Working Group; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PanVd= panobinostat plus bortezomib and dexamethasone

5.2. Results

5.2.1. Overall survival

MagnetisMM-3 data were reweighted to the aggregated trial data from PANORAMA 2 based on the identified PVs and EMs (see Table 5.1.3). The adjusted PVs and EMs in this analysis were age (≥65 years), sex, median time since initial diagnosis, ISS disease stage, high-risk cytogenetics, median prior lines of therapy, ECOG status, and type of MM.

Weights were generated so that the distributions of these variables for elranatamab were the same as those reported for PanVd in the PANORAMA 2 study.

Table 5.2.1 provides the HRs for OS. In both naïve analysis and after MAIC adjustment, the OS of elranatamab was numerically longer than PanVd, though statistical significance was not reached. The HR of elranatamab compared with PanVd was [redacted] before weighting and [redacted] after weighting. The sensitivity analysis results were consistent with the base case.

Table 5.2.1: Hazard ratios of OS: elranatamab vs. PanVd (PANORAMA 2)

Scenario	ESS	HR (95% CI)	p-value
Naïve comparison	123	[redacted]	0.900
Base case	79	[redacted]	0.722
Sensitivity analysis (imputation)	83	[redacted]	0.717

Abbreviations: CI = confidence interval; ESS = effective sample size; HR = hazard ratio; OS = overall survival; PanVd = panobinostat, bortezomib, dexamethasone

Figure 5.2.1 shows the KM curves of OS for elranatamab (unweighted and weighted) and PanVd.

Figure 5.2.1: KM curve of OS - elranatamab vs. PanVd (PANORAMA 2)

Abbreviations: KM = Kaplan-Meier; OS = overall survival; PanVd = panobinostat, bortezomib, dexamethasone

5.2.2. Progression-free survival

MagnetisMM-3 data were reweighted to the aggregated trial data from PanVd, based on the identified PVs and EMs (see Table 5.1.3). The adjusted PVs and EMs in this analysis were age (≥65 years), median time since initial diagnosis, ISS disease stage, high-risk cytogenetics, median prior lines of therapy, ECOG status, and type of MM

Weights were generated so that the distributions of these variables for elranatamab were the same as those reported for PanVd in the PANORAMA 2 study.

Table 5.2.2 provides the HRs for PFS. The PFS of elranatamab was significantly longer than PanVd in both the naïve analysis and after MAIC adjustment. The PFS HR compared with PanVd was [redacted] before weighting and [redacted] after weighting. No essential changes were observed in the sensitivity analyses.

Table 5.2.2: Hazard ratios of PFS: elranatamab vs. PanVd (PANORAMA 2)

Scenario	ESS	HR (95% CI)	p-value
Naïve comparison	**123**	[redacted]	**≤0.001**
Base case	**80**	[redacted]	**≤0.001**
Sensitivity analysis (imputation)	**83**	[redacted]	**≤0.001**

Abbreviations: CI = confidence interval; ESS = effective sample size; HR = hazard ratio; PanVd = panobinostat, bortezomib, dexamethasone; PFS = progression-free survival

Figure 5.2.2 shows the KM curves of PFS for elranatamab (unweighted and weighted) and PanVd.

Figure 5.2.2: KM curve of PFS - elranatamab vs. PanVd (PANORAMA 2)

Abbreviations: KM = Kaplan-Meier; PanVd = panobinostat, bortezomib, dexamethasone; PFS = progression-free survival

6. DISCUSSION

6.1. Key results

To contextualize the clinical profile of elranatamab, unanchored MAICs were conducted based on the 15-month data cut of the MagnetisMM-3 trial and PanVd based on PANORAMA 2.[10] PFS and OS results from the indirect comparisons of elranatamab versus PanVd, with and without MAIC adjustment, are summarized in Table 6.1.1. Figure 6.1.1 shows the summary forest plots for the comparison of elranatamab versus PanVd for both endpoints.

Table 6.1.1 Summary of naïve comparison and MAIC base case for all comparators

Elranatamab versus	OS HR (95% CI)		PFS HR (95% CI)	
	Naïve comparison	MAIC base case	Naïve comparison	MAIC base case
PanVd	[redacted]	[redacted]	[redacted]	[redacted]

Note: All numbers in bold were identified to be statistically significant at the specified threshold.

Abbreviations: CI = confidence interval; HR = hazard ratio; MAIC = matching adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; PanVd = panobinostat, bortezomib, dexamethasone

Figure 6.1.1: Forest plot summary of HRs (95% CIs) for the naïve and MAIC base case comparison of elranatamab versus PanVd

Note: Please refer to Table 6.1.1 for the specific HRs and 95% CIs values

Abbreviations: CI = confidence interval; HR = hazard ratios; MAIC = matching adjusted indirect comparison; OS = overall survival; PanVd = panobinostat, bortezomib, dexamethasone PFS = progression-free survival

Compared with PanVd from PANORAMA 2, elranatamab had a numerically longer OS in the naïve analysis (i.e., before weighting) ([redacted]). After MAIC

adjustment, elranatamab had a numerically longer OS compared with PanVd ([redacted]). Regarding PFS, the PFS of elranatamab was significantly longer than PanVd, with MAIC adjustment. The HR was [redacted] before weighting and [redacted] after weighting.

6.2. Population comparability

The MAICs between elranatamab and PanVd from PANORAMA 2 had differences regarding the patient population. The efficacy data for PanVd was based on patients with relapsed and bortezomib-refractory MM and who had received at least two prior lines of therapy.[10] In comparison, the population in MagnetisMM-3 included patients with TCE/R MM. The patient populations are therefore not comparable between MagnetisMM-3 and PANORAMA 2. As a result of these differences, the results presented from this MAIC study should be interpreted with caution.

6.3. Proportional hazard assumption

The study measures relative treatment effects in terms of HRs for time-to-event outcomes, as it is the widely selected approach for survival analysis. However, the proportional hazards (PH) assumption was violated in some comparisons (see Table 6.3.1).

The detailed log cumulative hazard plots and the Schoenfeld residual plots are presented in APPENDIX B.

Table 6.3.1 Results of proportional hazards assumption test - summary

Comparator	Endpoint	PH assumption	p-value of Schoenfeld test
PanVd (PANORAMA 2)	OS	Holds	0.14
	PFS	Fails	≤0.01

Abbreviations: OS = overall survival; PanVd = panobinostat, bortezomib, dexamethasone; PFS = progression-free survival; PH = proportional hazards

6.4. Limitations

MAIC is designed to derive indirect comparisons while controlling for population differences across treatments studied in different trials when limitations prevent the use of more traditional approaches. Guidance published by NICE supports the use of population-adjusted indirect comparisons using the MAIC approach to indirectly compare different therapies.[27] Undoubtedly, MAIC analyses have limitations of their own, which are listed below, along with the extent to which they were addressed in our study:

- There is a potential for residual confounding due either to characteristics not available or not reported in a trial or to being measured differently.

To avoid the bias of missing key PVs or EMs, an SLR was performed to identify the key PVs and EMs for this population, alongside a review of the comparator's clinical trials to identify PVs from forest plots and a review of recently published ITCs. A list of PVs and EMs was

then generated, which was validated through clinical expert opinion. However, there were a few variables that were not included in the analyses as either the variables were not included in the studies. For example, creatinine clearance was not reported in PANORAMA 2. The limitations due to the exclusion of these variables were regarded as small. Two potential exceptions are "refractory status" and "extramedullary disease", which were identified as key PV/EM according to the clinical opinion and univariate Cox hazard models based on MagnestisMM-3 data.

- MAICs can only account for differences in patient-level characteristics that affect outcomes; other differences at the study level (e.g., study design) remain unaccounted for

Study designs were compared between the index and comparator trials. The key difference is that MagnetisMM-3 required patients to be TCR, while patients in PANORAMA 2 were required to have released and bortezomib-refractory MM and had previously received two prior lines of therapy. This discrepancy cannot be addressed with an MAIC, as accounting for this difference would lead to a small sample size of the MagnetisMM-3 trial. The MAIC analyses with elranatamab versus PanVd should be interpreted with caution.

- Small sample sizes may preclude adjustments for all available variables identified as EMs or PVs, thus resulting in a large reduction in the ESS. A large reduction in the ESS may lead to large uncertainty in estimated treatment effects.

Across the base case analyses for OS, the ESS declined by approximately 35% of the original sample size (36% in the comparison with PanVd for OS and 34% in the comparison with PanVd for PFS). When comparing the relative decline in ESS with other published MAICs in this indication, this decline can be considered small. For example, in a MAIC of teclistamab and belantamab mafodotin, the relative decrease in ESS was 78%.[36]

- Conducting a MAIC implies that the treatment effect is dependent upon the population and further assumes that the target population is closer to that represented in the competitor trial than in the index trial.[27]

Further assumptions are needed (i.e., the shared effect modifiers assumption) to transfer the results to other populations. The shared effect modifier assumption states that the effect modifiers and the modification effect of each are the same across the treatments being compared in the MAIC. In this instance, it is difficult to verify whether this assumption can be met as all the trials included are single-arm trials and, as such, cannot be tested for EMs.

Given the available data, an unanchored MAIC is the best available option to compare the efficacy of a comparator with elranatamab, as reported in MagnetisMM-3. The results of the MAICs need to be interpreted with caution. Despite these limitations, the evidence provided from this MAIC analysis is the best available evidence that demonstrates the comparative effectiveness of elranatamab compared with other therapies for this indication.

7. CONCLUSIONS

In order to contextualize the clinical profile of elranatamab, an unanchored MAIC was conducted against PanVd based on the pivotal PANORAMA 2 trial.

For the OS endpoint, the MAIC-adjusted results indicated that elranatamab was associated with numerically longer OS compared with PanVd, based on the PANORAMA 2 trial, though statistical significance was not reached.

Regarding the PFS endpoint, elranatamab was associated with significantly longer PFS after MAIC adjustment compared with PanVd based on the efficacy reported in the PANORAMA 2.

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9. APPENDIX A

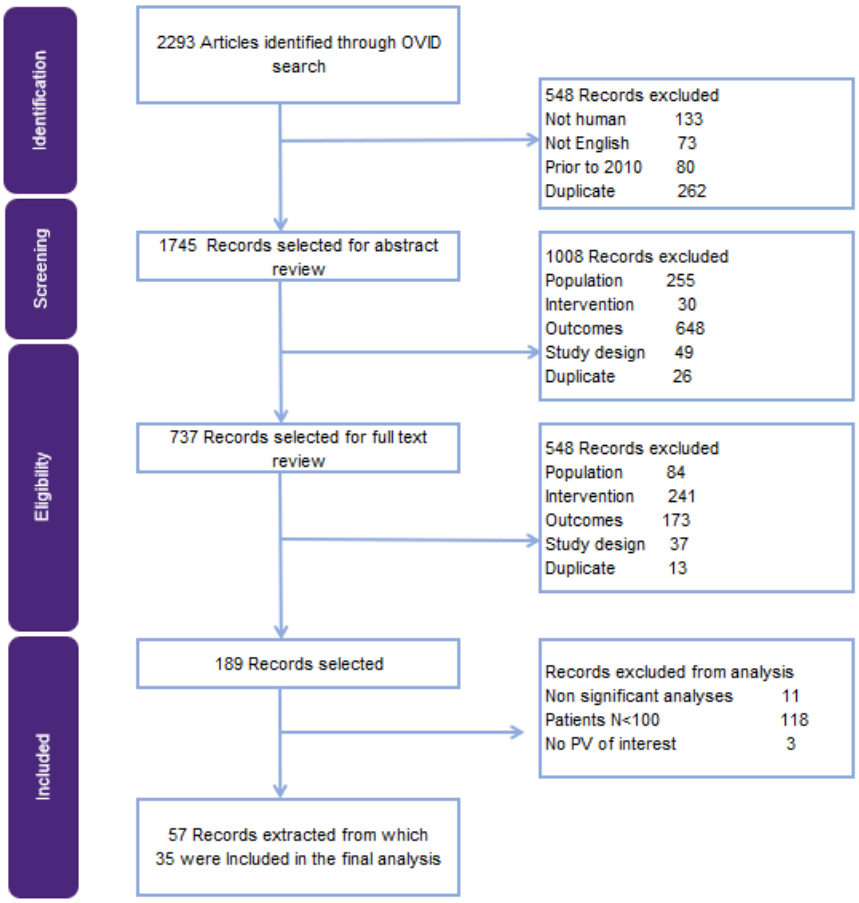
In June 2021, an SLR was conducted to identify the clinically important PVs and EMs in patients with RRMM from RWE studies. The PICOS is shown in Table 5.2.2.

Table 5.2.2: PICOS statement

Category	Inclusion criteria
Patient population	Patients diagnosed with relapsed or refractory multiple myeloma (RRMM) in any line
Intervention and comparators	Bortezomib, lenalidomide, carfilzomib, ixazomib, daratumumab, pomalidomide, panobinostat, elotuzumab, selinexor, melflufen, vorinostat, isatuximab, bendamustin, TJ202/MOR202 (felzartamab), encorafenib, binimetinib, pembrolizumab, nivolumab, erdafitinib, RAPA-201, belantamab mafodotin, idecabtagene vicleucel, ciltacabtagene autoleucel, CAR-T
Outcomes measures	• Overall survival (OS) • Progression-free survival (PFS) • Response rates (ORR/CR/sCR/VGPR) • Time to Progression (TTP), duration of response (DOR) • Minimal Residual Disease (MRD) • Other time-to-event measurements (event-free survival, time-to-next treatment, treatment-free survival, duration of response) • Patient reported outcomes (PRO) (EORTC-QLQ C30, MY20, FACT) • Utility values (EQ-5D, SF-36, VAS, etc.) • Safety (SAE, Grade 3/4 AE, special interest AE)
Study design	• Real world evidence (prospective, observational, longitudinal, retrospective) • Indirect treatment comparisons • Systematic reviews, meta-analyses and indirect comparisons • Pooled Analyses (for cross-checking only)

Figure shows the PRISMA diagram of the SLR. Thirty-five studies with multivariate analyses were extracted and analysed, which 22 studies with univariate analyses were extracted.

Figure 8.1.1.1: PRISMA diagram



The SLR identified two categories for PVs and EMs: 'likely' and 'potential' PVs and EMs. We only carried the 'likely' PVs and EMs into the MAIC for adjustment.

- 'Likely' PVs and EMs were defined if the variables were reported in 3 or more studies which support the association between the variable and outcome
- 'Potential' PVs and EMs were defined if the variable were reported in less than 3 studies with conflicting evidence to support an association between the variable and the outcomes

10. APPENDIX B

10.1. Log cumulative hazard plots and Schoenfeld residual plots for Cohort A

In this section, the log cumulative hazard plots and the Schoenfeld[37] residual plots are presented for the MAIC analyses of elranatamab (Cohort A) versus the respective comparators. Log cumulative hazard plots show the relationship of logarithm of time versus the determined log cumulative hazard. If the two curves presented are deemed to be parallel, it can be presumed that the proportional hazards assumption holds. Schoenfeld residual plots show the relationship between time and the residuals and are used to further test for proportional hazards. If the residuals show a non-random pattern in a Schoenfeld residual plot, the PH assumption has been violated. Both the Schoenfeld residual plots and the log-cumulative hazard plots were used to determine whether the PH assumption held.

Figure 10.1.1: Log cumulative hazard plot: elranatamab vs. PanVd (PANORAMA 2) (OS)

Figure 10.1.2: Schoenfeld residual plot: elranatamab vs. PanVd (PANORAMA 2) (OS)

Figure 10.1.3: Log cumulative hazard plot: elranatamab vs. PanVd (PANORAMA 2) (PFS)

Figure 10.1.4: Schoenfeld residual plot: elranatamab vs. PanVd (PANORAMA 2) (PFS)

NICE National Institute for Health and Care Excellence

Elranatamab for treating relapsed and refractory multiple myeloma after 3 or more treatments [ID4026]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 9 August 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Myeloma UK

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Disclosure
Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]
Please state:

- the name of the company
- the amount
- the purpose of funding including whether it related to a product mentioned in the stakeholder list
- whether it is ongoing or has ceased.

We have received funding from the manufacturer of the technology (Pfizer) in the last 12 months.

The table below shows the 2023 income from the relevant manufacturers. Funding is received for a range of purposes and activities namely core grants, project specific work, and gifts, honoraria, or sponsorship.

	Core grant	Research / Project	Donation	Consultancy/ Honoraria	Events	Total
AbbVie Ltd	-	10,000	-	870	-	10,870
Alexion Pharma UK Ltd	-	7,500	-	-	-	7,500
Amgen Ltd	-	20,000	-	-	-	20,000
The Binding Site Ltd	20,000	-	-	437	-	20,437
Bristol-Myers Squibb Pharmaceuticals Ltd	15,000	-	-	-	-	15,000
GlaxoSmithKline UK Limited	-	20,026	-	-	-	20,026
ITECHO Health Ltd	-	6,600	-	-	-	6,600
Janssen-Cilag Ltd	-	15,907	-	260	9,093	25,260
Menarini Stemline UK Limited	-	7,000	-	-	-	7,000
Pfizer Limited	-	-	-	73,448	-	73,448
Stemline Therapeutics Switzerland GmbH	-	-	-	1,451	-	1,451
Sanofi	-	-	-	-	27,990	27,990
Takeda UK	30,000	-	-	-	29,681	59,681
	65,000	**87,033**	**-**	**76,466**	**66,764**	295,263

Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.

None

Name of commentator person completing form:

[redacted]

Comment number	Comments
	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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NICE National Institute for Health and Care Excellence

Elranatamab for treating relapsed and refractory multiple myeloma after 3 or more treatments [ID4026]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 9 August 2024. Please submit via NICE Docs.

1	We welcome NICE's decision to approve elranatamab for relapsed and refractory myeloma patients. It is a highly effective treatment that will extend and improve myeloma patients' lives.
2	**We believe that NICE's decision to restrict the use of elranatamab is unfair and unreasonable.** The decision to recommend elranatamab only as an alternative to pomalidomide plus dexamethasone' is unclear, insufficiently explained and inconsistent with previous appraisals. In the last five years (August 2019-August 2024), NICE appraised and published guidance for ten myeloma-specific HTAs. Four of these appraisals were reappraisals following initial approvals through the Cancer Drugs Fund. Of the ten appraisals conducted, five resulted in an optimised recommendation. None of these optimised recommendations restricted the use of treatments under review as an alternative to a comparator. All of the restrictions applied to these treatments are related to the treatments that patients had already had (number of treatment lines or type of drug e.g. anti-CD38) rather than the type of treatments they have not had. For example, in TA974 (selinexor, bortezomib and dexamethasone), selinexor was compared to panobinostat in the third-line setting. The appraisal did not result in eligibility restrictions, which required the appraised technology to be used only when panobinostat was offered as an alternative. Therefore, we are concerned that this decision doesn't accurately reflect the evidence presented and believe the restriction is unfair and unreasonable.
3	**We believe that the restriction applied to elranatamab is unreasonable because pomalidomide is the only relevant comparator for the licenced indication.** Myeloma is a complex and highly individual cancer with a varied and rapidly evolving treatment pathway. As a result, the current patient population is very varied with the number and type, of previous treatments received dependent on when they were diagnosed and when they relapsed. It can also be influenced by the number and type of clinical trials and free of charge schemes that are available. Whilst other treatments are used at fifth, sixth and seventh line, it is highly challenging to gather sufficient data to appraise new treatments across multiple lines when there is no real standard of care, and the patient cohort is heterogenous and small. For the patient population (triple class exposed patients) in scope for this appraisal it gets even harder. The treatments available to patients at fifth, six or seventh line are often clinical trials or salvage/last chance drugs which are used whenever a patient runs out of more effective, more tolerable options. These treatments are old and therefore there is very limited data on their efficacy in triple class exposed patients. The heterogeneity of triple class exposed myeloma patients is highlighted in the data from the HMRN dataset attached which includes triple classed exposed myeloma patients diagnosed between 2004-2019 and who started fourth line treatment in 2017 (after pomalidomide was approved). In this data, most patient became triple class exposed at either fourth or fifth line.

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	The data also shows that pomalidomide is the preferred treatment for patients who become triple-class exposed and that pomalidomide is widely used across 4th, 5th, 6th and 7th lines. Therefore, pomalidomide is a relevant comparator at all lines. We believe comparing elranatamab to pomalidomide is sufficient to justify approval for the full licenced indication.
4	**We believe the restriction applied to elranatamab is unreasonable and unnecessary given the predominant use of elranatamab in the myeloma pathway.** The decision to only recommend elranatamab as an alternative to pomalidomide exclusively impacts triple-class exposed myeloma patients who are currently getting pomalidomide or have already had pomalidomide and who will be fit enough to get elranatamab as their next line of treatment. This a small and finite group of patients. Clinicians will choose to use elranatamab as early as they can in the pathway, therefore the number of pomalidomide exposed patients who could benefit from the treatment will significantly reduce over time. Furthermore, data suggests that only 15% of patients will get four lines of treatment and 1% five or more. (Yong. et.al. 2016). Therefore, the number of people who are triple-class exposed and would go on to get elranatamab after receiving pomalidomide at fourth or fifth line will be very small and insignificant when compared to the number of triple-class exposed, pom-naïve patients who will get elranatamab at fourth line now and in the future. As a result, we believe the restriction is unnecessary, resulting in a significant and unacceptable inequality for a cohort of current myeloma patients. Ref: Yong, K., et. al. (2016). Multiple myeloma: patient outcomes in real-world practice. British journal of haematology, 175(2), 252–264.
5	**We are concerned that the proposed recommendation excludes myeloma patients with the highest unmet need.** All patients who have already been exposed to pomalidomide will not be eligible for elranatamab due to the proposed restriction. Elranatamab could give these patients the chance of reaching complete response and significantly extending their life. It also gives them a kinder treatment option without high dose dexamethasone. The life expectancy for triple-class and pomalidomide exposed patients is typically less than < 6 months. On publication of the guidance Myeloma UK received several emails and calls from this group of patients worried about their future and their prospects beyond their current treatment. ***'Basically, this is close to a death sentence for me…… there aren't many people like me. I don't understand why it should be denied to the very people with no options left.'***

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	"Obviously Elarantamab was a huge beacon of hope for me and it's unavailability to me feels like a death-sentence." ***"I am currently on 4th line treatment of Isatuximab, Pomalidomide and Dexamethasone (IPD). My kappa light chains have just begun to rise, albeit currently still at a low level (27). I am anxious about the next line of treatment that may be necessary. I have read about the excellent results that bi-specific antibody have given to people in my situation in the USA. My haematological consultant, has said that they would be the obvious next treatment to have if available. I am writing therefore to ask if you can urgently reconsider the restrictions on use of bi-specific antibodies for people like me."***
6	**We believe NICE's decision to restrict the use of elranatamab will unfairly impact patients whose treatment was impacted by the pandemic.** During the COVID-19 pandemic (March 2020-September 2023) pomalidomide was approved as an interim treatment for second- and third-line myeloma patients to reduce the need for chemotherapy and reduce admissions and risk of neutropenia. With the current restriction patients in this cohort will not be eligible for elranatamab. We don't believe this was considered when the restriction was applied. We believe it is unfair for patient in this cohort to miss out on a potentially effective treatment.
7	**We are concerned that patient evidence submitted and presented was not considered when applying the restriction to the use of elranatamab.** In our submission and the committee meeting we highlighted that elranatamab was a highly effective treatment for multiply relapsed and refractory patients. We emphasised the need for treatments with new mechanisms of action to overcome treatment resistance, highlighting that this need gets more significant with every relapse. We discussed how treatments like elranatamab, which deliver high response rates at later lines gave patients hope that there would be an effective option when they relapse. This is particularly true for patients at 5th line and beyond because there aren't really any effective options. The treatment options at this stage are either palliative care or older drugs that have significant toxicity and low response rates with most patients only achieving partial responses. We also shared perspectives from patients who were lucky enough to get elranatamab through clinical trials or compassionate use, showing the benefit the treatment can deliver for refractory myeloma patients. We also highlighted that elranatamab had the potential to transform the myeloma pathway changing the belief that relapse leads to worse response rates and remission times. The need for better treatments and the benefit elranatamab delivers is relevant to all triple class exposed and triple class refractory patients whether they have had pomalidomide or not. We believe based on this evidence that there should have been flexibility when assessing a treatment indicated across multiple lines in a complex and dynamic treatment pathway.
8	**We are concerned that NICE did not consider the negative impact of their decision to restrict the use elranatamab would have on clinical trials access and uptake in England.** There are 11 myeloma clinical trials actively recruiting in England that include pomalidomide containing combinations in at least one of the trial arms. Nine of these trials are recruiting patients at earlier lines.

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	We believe the current restriction will discourage clinical recommendation and patients wishing to join these trials and future trials as they will be concerned that joining the trial will lead to them missing out on a highly effective myeloma treatment. The NICE statement on clinical trial participation and subsequent access to drugs approved by NICE is cited by clinicians and industry as being unclear unclear. Furthermore, most patients are not aware of this statement. As such, there will be considerable hesitation about joining trials with pomalidomide containing regimens because there will be concerns about jeopardising access to elranatamab. This could have significant impact on trial recruitment, UK life sciences and myeloma treatment innovation.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Started Fourth-line treatment from 2017 onwards

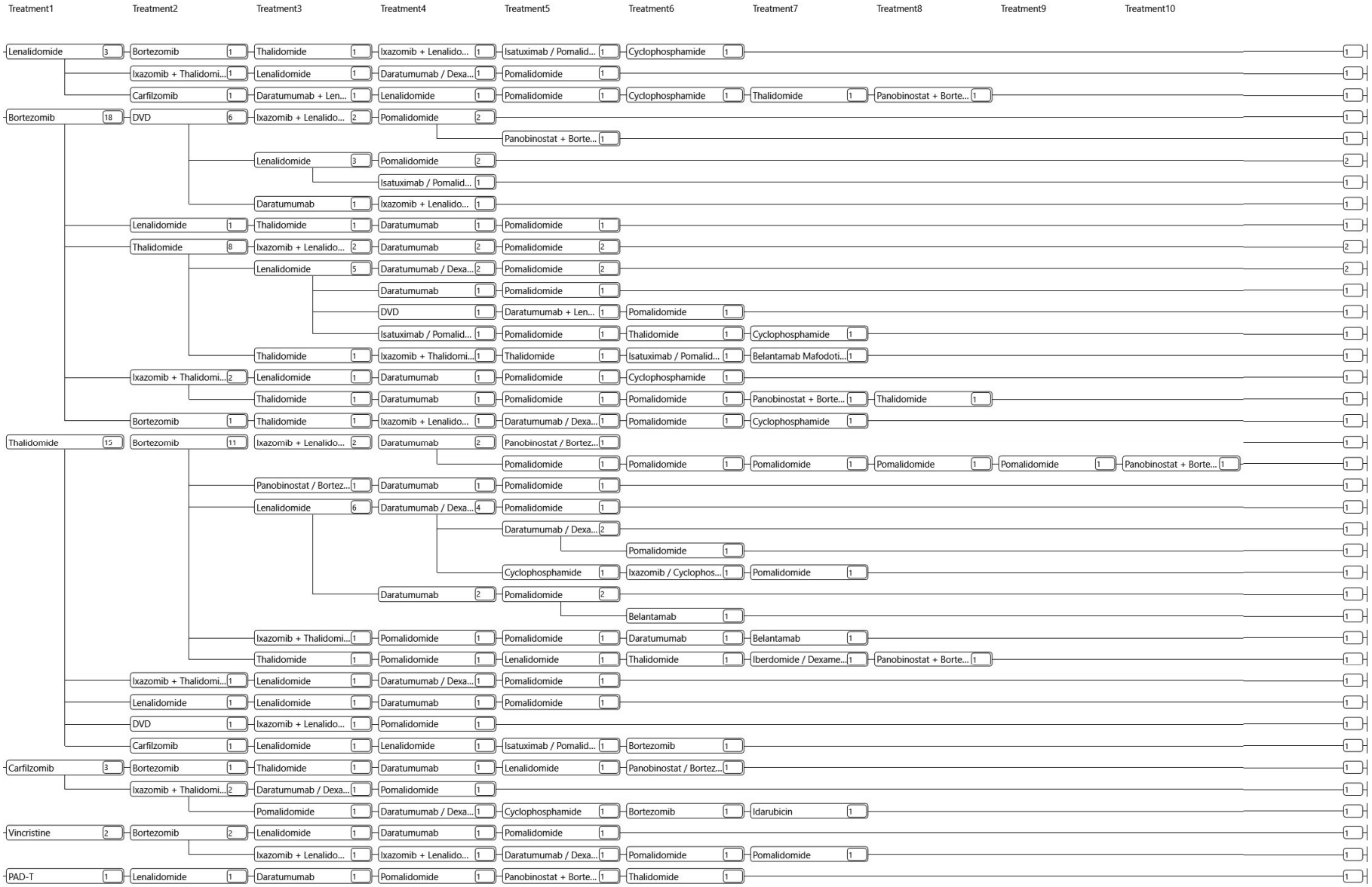
In total, 42 patients were identified who had received an immunomodulatory agent, a proteasome inhibitor, an anti-CD38 antibody (eligibility criteria) and they started Fourth-line treatment from 2017 onwards when pomalidomide was available (Table 3). Subjects are counted as many times at they received a treatment i.e. a patient who received 5th and 6th line after reaching the eligibility criteria their information will be included in the 5th and 6th line columns.

Table 1 Myeloma patients diagnosed 2004 to 2019 followed up to 2023 by treatment line: Haematological Malignancy Research Network

		Treatment line n (%)				
		4th Line	**5th Line**	**6th Line**	**7th Line**	**8th Line**
Total		**10**	**28**	**16**	**10**	**4**
No previous treatment with pomalidomide		10 (100)	24 (85.7)	6 (37.5)	1 (10.0)	0
Previous treatment with pomalidomide		0	4 (14.3)	10 (62.5)	9 (90.0)	4 (100)
Median age at start of treatment line years (IQR)	No previous treatment with pomalidomide	69.7 (64.3 - 76.0)	69.8 (65.7 - 73.3)	72.0 (48.4 - 76.2)	72.8 (72.8 - 72.8)	-
	Previous treatment with pomalidomide	-	68.0 (62.4 - 73.5)	70.4 (68.8 - 75.8)	69.1 (60.6 - 76.1)	69.7 (63.7 - 70.0)
Median time since diagnosis (years) (IQR)	No previous treatment with pomalidomide	4.9 (3.5 - 6.7)	4.9 (2.7 - 8.5)	5.2 (3.3 - 8.9)	6.2 (6.2 - 6.2)	-
	Previous treatment with pomalidomide	-	5.3 (4.8 - 7.8)	6.2 (5.2 - 9.4)	7.5 (6.0 - 8.3)	7.4 (5.6 - 8.4)
Median time since start of first-line chemotherapy (years) (IQR)	No previous treatment with pomalidomide	4.1 (3.5 - 5.5)	4.9 (2.7 - 8.5)	5.2 (3.3 - 8.8)	6.1 (6.1 - 6.1)	-
	Previous treatment with pomalidomide	-	5.3 (4.7 - 5.9)	5.9 (5.1 - 7.2)	6.5 (5.9 - 7.9)	7.3 (5.5 - 8.3)
Median year of previous treatment line (range)	No previous treatment with pomalidomide	2021 (2014 - 2022)	2019 (2017 - 2021)	2018.5 (2018 - 2020)	2019 (2019 - 2019)	-
	Previous treatment with pomalidomide		2020 (2018 - 2021)	2020 (2017 - 2021)	2020 (2017 - 2021)	2020 (2017 - 2021)
Treatment Regimen:						
Belantamab		-	-	1 (6.3)	2 (20.0)	-
Bortezomib / Dexamethasone		-	-	1 (6.3)	-	-
CTD		-	-	-	-	1 (25.0)
CTDa		-	-	-	1 (10.0)	-
Cyclophosphamide		-	-	1 (6.3)	-	-
Cyclophosphamide / Dexamethasone		-	2 (7.1)	2 (12.5)	1 (10.0)	-
Cyclophosphamide / Prednisolone		-	-	-	1 (10.0)	-
Daratumumab / Dexamethasone		-	2 (7.1)	-	-	-
Daratumumab / Lenalidomide / Dexamethasone		-	1 (3.6)	-	-	-
Iberdomide / Dexamethasone		-	-	-	-	-
Ixazomib / Cyclophosphamide / Dexamethasone		-	-	1 (6.3)	-	-
Isatuximab / Pomalidomide / Dexamethasone		1 (10.0)	-	-	-	-
Lenalidomide / Dexamethasone		1 (10.0)	1 (3.6)	-	-	-
Lenalidomide / Ixazomib / Dexamethasone		1 (10.0)	-	-	-	-
MPT		-	-	1 (6.3)	-	-
PAD		-	-	1 (6.3)	-	-
Panobinostat / Bortezomib		-	1 (3.6)	1 (6.3)	-	-
Panobinostat / Bortezomib / Dexamethasone		-	2 (7.1)	-	1 (10.0)	2 (50.0)
Pomalidomide			2 (7.1)			
Pomalidomide / Cyclophosphamide / Dexamethasone		1 (10.0)	1 (3.6)	2 (12.5)	-	1 (25.0)
Pomalidomide / Dexamethasone		6 (60.0)	16 (57.1)	4 (25.0)	3 (30.0)	-
TIDE		-	-	1 (6.3)	-	-

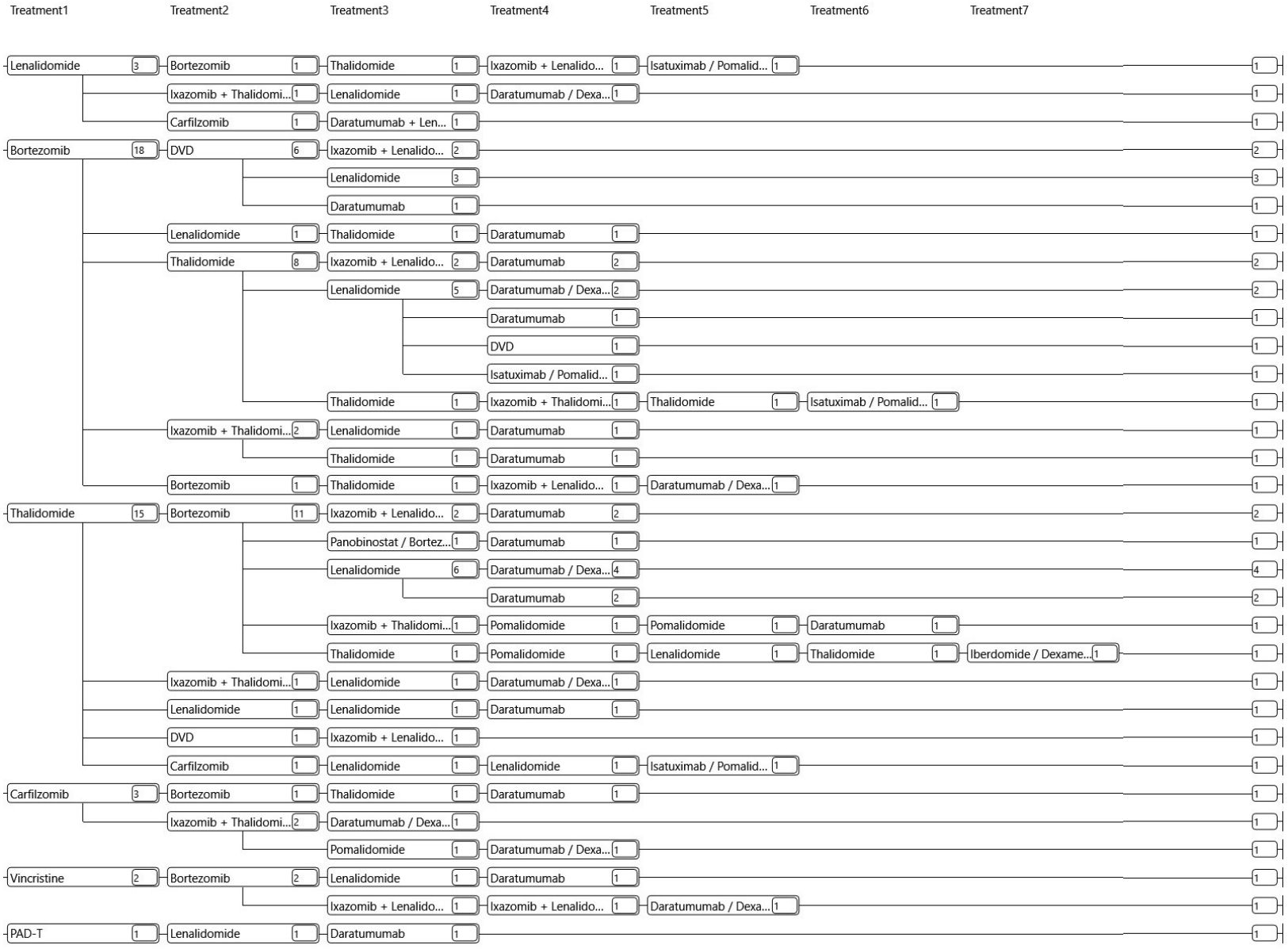
Z-DEX	-	-	-	1 (10.0)	-

Figure 1 Complete treatment[1] pathway for patients meeting criteria[2] and started Fourth-line treatment from 2017 onwards



[1] Grouped using main regimen agent(s). [2] Received an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody

Figure 2 Treatment[1] history for patients prior to criteria completion[2] where Fourth-line treatment started from 2017 onwards



[1] Grouped using main regimen agent(s). [2] Received an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibo

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Bristol-Myers Squibb Pharmaceuticals Ltd (BMS)

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Elranatamab for treating relapsed and refractory multiple myeloma after 3 or more treatments [ID4026]

Draft guidance comments form

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not applicable. We are the manufacturer of one of the comparator treatments.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Please see two comments below relating to errors in the description of the MM-003 pomalidomide/dexamethasone trial in Section 3.5. These are as follows; Section 3.5, 2nd sentence states, “This was a phase 3, randomised, open-label study in people with

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	relapsed, refractory multiple myeloma who had received at least 2 lines of lenalidomide and bortezomib alone or in combination." Please could this be corrected to, "This was a phase 3, randomised, open-label study in people with relapsed, refractory multiple myeloma who had received at least two prior anti-myeloma treatments including ≥ 2 consecutive cycles of lenalidomide and bortezomib (alone or in combination)."
2	Section 3.5, 5th sentence states, "Median OS was 11.9 months…". Please could this be corrected to, "Median OS 13.1 months…". NB: The 11.9 months relates to the interim OS and not the median OS which was 13.1 months.
3	
4	
5	
6	

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Johnson & Johnson Innovative Medicine

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	Johnson and Johnson Innovative Medicine (J&J IM) is concerned that the recommendation of elranatamab for treating relapsed and refractory multiple myeloma (RRMM) after three or more treatments is restricted to patients who would otherwise receive pomalidomide plus dexamethasone (PomDex).

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	J&J IM appreciates the opportunity to participate in the consultation for this guidance and would like to highlight the following comment detailed in the row below.
1	***Patients at this stage of the pathway are desperately in need of effective treatment options as they near the end of their terminal illness*** We note the ongoing NICE appraisal ID6333 (Teclistamab) and similarities in the patient group considered here. The current restriction prevents access in patients who currently face a severe unmet need for an effective treatment option, such as patients who have received and progressed on PomDex (or isatuximab plus PomDex [IsaPomDex]) in the fourth-line setting. Restriction of access to treatment evaluated in this setting, leaves pomalidomide-exposed patients with no effective treatment options following disease progression. J&J IM notes that pomalidomide exposure is expected to diminish over time based on the current MM treatment pathway due to (1) the positive draft recommendations which replaces PomDex with teclistamab or elranatamab i.e., these more effective therapies will replace PomDex over time, and (2) the negative recommendation issued for IsaPomDex (ID4067) in their appraisal assessing exit of IsaPomDex from the managed access scheme. Thus, J&J IM considers that removal of the restriction represents a low risk for decision making.
2	***There is very limited published evidence in triple-class exposed RRMM patients who have received pomalidomide-based regimens, however, based on the current treatment pathway and clinical advice, panobinostat plus bortezomib and dexamethasone (PanoBorDex) could be a treatment option to consider for the present decision making.*** The Committee papers for ID4026 indicate there is only a handful of published evidence reporting the effectiveness of treatments for triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM) patients. The most recent one, LocoMMotion, was the first international, observational study to assess effectiveness and safety of real-life treatments in this relapsed setting. Results showed a lack of well-established standard of care (SoC) for TCE RRMM with 91 unique treatment regimens reported at index line of therapy. With the lack of SoC treatments established when patients become TCE, the study did not report on the potential SoC treatments for pomalidomide-exposed patients. Therefore, to inform decision-making on the clinical and cost-effectiveness of elranatamab in the pom-exposed patients, UK real-world evidence and/or clinical advice would be advised to identify the appropriate comparator(s). The Company has indicated in their initial submission (CS, Table 1) that PanoBorDex would be considered as comparator "*after 4 previous lines of treatment, and as confirmed through Committee conclusions in TA658 and TA783*". This suggestion also concurs with the clinical advice received by J&J IM. Therefore, to remove the restriction on the positive CDF recommendation, supplementary evidence of elranatamab vs PanoBorDex could be considered for RRMM patients who are TCE and pom-exposed. Reference: • Mateos M-V, Weisel K, De Stefano V, Goldschmidt H, Delforge M, Mohty M, et al. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. Leukemia. 2022;36(5):1371-6

Checklist for submitting comments

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Company response to EAG Critique of the draft guidance – Factual inaccuracies and comments

On the 13th September we received a copy of the EAG critique of the company's response to consultation on the draft guidance. The EAG critique highlighted a number of key points supporting the removal of the optimization where pomalidomide plus dexamethasone (POM+DEX) would otherwise be considered and the alignment of recommendations between this appraisal and ID6333[1]. This response should be read in conjunction with the EAG critique and Company draft guidance response plus additional addendum.

The Company would like to highlight the following inaccuracies and misinterpretations as well as updated scenarios. Further detail is presented in **Factual inaccuracies** and Appendix A.:

A. In the draft guidance response, the company have provided an alternative comparison to POM+DEX using data presented in ID6333. The company approach used the lognormal (for OS) and gompertz (for PFS), based on the publicly available information published for ID6333. **(FAC 1)**

B. The Company acknowledge that the subsequent treatments in RRMM are complex and, for those in later lines, there is no standard of care. The Company would raise a number of inaccuracies related to subsequent treatments and have therefore suggested a number of scenarios that would be considered representative and applied these across Tables 1-4 in **Appendix A** and described further in **FAC 2.**

   - PANO+BORT+DEX is not currently used in 3L despite its reimbursement by NICE. As outlined in our DG response this medicine is often used in later lines after POM+DEX[2]
   - For consistency, the Company believes that, given the comments raised at the second appraisal committee meeting (ACM) for ID6333 which identified SEL+DEX as a potential comparator, and the subsequent submission of a cost effectiveness analysis of elranatamab versus SEL+DEX, it is relevant to consider this comparator within the subsequent treatment baskets across all analysis.

C. As detailed in **FAC 3** for the (MM-003) adjustment of OS and PFS in the PANO+BORT+DEX comparison, Scenario 1 in **Table 2** and **Table 3** is incorrect and should be removed.

   - The company would like to clarify for the EAG that the MM-003 adjustment is specific for the comparison with POM+DEX, based on data from MM-003. There is no specific 'adjusted' data for the PANO+BORT+DEX comparison and in this scenario an adjusted HR is applied. Therefore, for the correct interpretation of the relative outcomes the comparison should be made using the unadjusted elranatamab data.
   - Consequently, related combined scenarios should also be removed (EAG preferred 1,2, and 4 along with 1,3, and 4). **Table 2** and **Table 3** include the combined scenarios 2+4 and 3+4.

D. As detailed in **FAC 4**, Table 2 and Table 3 of the EAG critique of the company DG response, where scenarios 2 and 3 replaced subsequent PANO + BORT + DEX with POM+DEX in the PANO+BORT+DEX arm and resulted in a higher ICER, there was an error in the model that means the results of these scenarios are incorrect.

   - When replacing PANO+BORT+DEX with POM+DEX in the PANO+BORT+DEX arm results in the ICER decreasing from £35,602 to £18,457 (**Table 2**) and from £37,892 to £20,747 (**Table 3**).

E. We welcome the EAG correcting the original base case economic evaluation versus POM+DEX. However, we are concerned that this is being raised as this is not part of the draft guidance consultation and we would urge some caution on re-opening discussions given that additional updates should also be considered.

However, to provide reassurance for the committee, we have included updated POM-DEX subsequent treatment (**FAC 2**) and those related to ID6333 comparator source (**FAC 1)** scenario(s)/corrects, that results in further reduction of the ICER (Appendix, **Table 4** and **Table 5**).

F. In all scenarios the probabilistic ICERs are below the deterministic. The Company believes these should be considered for decision making. These illustrate the magnitude of direction to the deterministic ICERs.

Factual inaccuracies

<table>
<tr><th>EAG Critique Section Page Number</th><th>Factual Inaccuracy</th><th>Comment / Correction</th><th>EAG response</th></tr>
<tr><td>FAC 1
Section 1:
Page 5,6</td><td>However, the company have not described their approach here transparently, and appear not to have used the preferred Gompertz OS curve that was agreed upon for POM+DEX in ID16333. They have instead used a lognormal curve. And whilst they have chosen a Gompertz curve for PFS, the selected curve does not appear to match the Gompertz PFS curve that was accepted in ID16333.</td><td>We would like to explain the context to help the EAG understand as we believe the approach has been misinterpreted. Rather than a lack of transparency we would argue that there are many potential caveats that explain why the ID6333 POM+DEX curves and our version of the ID6333 POM+DEX curves don’t match exactly. We respectively ask that this is considered and the EAG report updated accordingly.

Firstly, the reason for the comparison is to show the lower decision risk in the elranatamab appraisal when compared with ID63331. In ID6333 a trial versus RWE was selected with minimal adjustment of critical confounding factors due to lack of</td><td>The EAG does not believe its critique of the survival curves utilised in the company’s scenario analysis of the POM+DEX survival curves from ID6333 to be a factual error. Whilst the company argue that this is down to digitising error, or that the EAG has access to information not in the public domain, the EAG would like to reassure the company that information used by the EAG was sourced from Figures 8 and 10 of the ID6333 public committee slides on the NICE website. These figures present the OS and PFS curves for POM+DEX attenuated using clinical opinion. To further reassure the Company and the committee that this criticism is not a factual inaccuracy the EAG presents estimates of survival based on these figures against the survival curves presented by the company in this scenario (table 1). These estimates were sourced by digitising also, therefore will have a small margin of error.

To illustrate the EAGs criticism detailed within its response; whilst the company(now) states that it has used the Lognormal for OS and Gompertz for PFS, the digitised figures are at least 5-10% higher at several time points. The inaccuracy of the methodology is more apparent in the PFS curve, where the company’s estimates are 10-15% higher than the EAGs digitisation. Without digitisation, the discrepancy is apparent through visual inspection. Therefore, the EAG is uncertain which survival curves the Company used to digitise the data.

Table 1. Estimates of PFS and OS for POM+DEX from ID16333 versus company extrapolations
<table>
<tr><th></th><th colspan="3">OS</th><th colspan="2">PFS</th></tr>
<tr><th>Year</th><th>Log normal*</th><th>Gompertz* (ID6333 agreed)</th><th>Company</th><th>Gompertz* (ID6333 agreed)</th><th>Company</th></tr>
<tr><td>1</td><td>44%</td><td>44%</td><td>55%</td><td>33%</td><td>49%</td></tr>
<tr><td>2</td><td>26%</td><td>21%</td><td>32%</td><td>11%</td><td>26%</td></tr>
<tr><td>3</td><td>18%</td><td>11%</td><td>21%</td><td>5%</td><td>15%</td></tr>
<tr><td>4</td><td>13%</td><td>6%</td><td>14%</td><td>2%</td><td>9%</td></tr>
</table>
</td></tr>
</table>

5	10%	3%	10%	1%	6%		
**Survival estimates are based on digitised data so will carry a small margin of error*							

The EAG believe that the company's choice of lognormal extrapolation for OS is perhaps down to misinterpretation of the wording in the draft guidance for ID16333: "The company selected log-normal and Gompertz distributions to model both long-term overall survival and progression-free survival in the economic model for the teclistamab arm and the pomalidomide plus dexamethasone arm, respectively." However, the EAG would like to point the company to slide 22 of the public committee slides for ID6333; where it states the extrapolations used for OS and PFS for POM+DEX was Gompertz. This clarifies that the EAG's interpretation is correct. Therefore, the EAG criticism of the choice of curves used by the Company is not a factual inaccuracy.

Finally, as only one extrapolation was included in the model, the EAG is not able to test the use of other extrapolations upon the ICER. However, the EAG do not deem this to be necessary given the focus of this consultation on the alternative PANO+BORT+DEX comparison.

In conclusion, we do not believe this to be a factual inaccuracy. The EAG stand by its view that this additional scenario is too unclear for interpretation.

available data. When this source of data is used in the appraisal of elranatamab, the ICER reduces significantly when compared with trial versus trial comparison (company base case). The argument is presented to support an alignment of recommendations as we believe the Company approach is more robust and therefore in this context is conservative. Given the EAG comments in the critique there is some alignment in believing this is a credible suggestion from the Company.

Secondly, to enable this comparison the Company needed to digitise the curves from the published committee slides and papers. The company is limited by information that is available in the public domain and this might explain any discrepancy.

In the EAG critique: page 11 draft guidance ID6333 "The company selected log-normal and Gompertz distributions to model both long-term overall survival and progression-free survival in the economic model for the teclistamab arm

		and the pomalidomide plus dexamethasone arm, respectively" Therefore, either the EAG potentially has information that isn't publicly available or this is an error as the committee papers clearly describe the preferred approach that are aligned with the company scenario as described below.[3] The company approach used the lognormal (for OS) and gompertz (for PFS), based on the publicly available information published for ID6333. The committee discussion mentions that the curves were adjusted to account for survival estimates derived from clinical judgments. As the exact mechanism of the adjustment was not published, we are unable to confirm if the adjustment included a change in curve. Note the curves are based on digitised data, so we would expect that they do not match exactly, to those presented in ID6333. Additionally, as we note above ,the ID6333 curves were adjusted to match survival estimates derived from clinical	

		experts.[3] The curves that were presented by the company in response to the consultation on the draft guidance are unadjusted for clinical experts' judgement, however, in the model (on the model engine sheets) they are adjusted by the application of a time varying SMR which may somewhat explain the inconsistencies between the two appraisals.	
FAC 2 **Section 2: Page 12**	Therefore, the EAG has assessed the impact of changing the distribution of subsequent therapy to remove PANO+BORT+DEX as a subsequent treatment option following PANO+BORT+DEX. Two alternative scenarios were considered: 1) Replacing PANO+BORT+DEX with POM+DEX (reflecting a subsequent treatment distribution that might be reasonable for those who receive PANO+BORT+DEX at third line, prior to being eligible for POM+DEX). 2) Replacing all subsequent treatment following PANO+BORT+DEX with cyclophosphamide (reflecting a subsequent treatment distribution for those who receive PANO+BORT+DEX as a comparator to elranatamab in later lines, having	The Company understands the approach taken by the EAG. However, the Company would raise a number of inaccuracies. Firstly, PANO+BORT+DEX is not currently used in 3L despite its reimbursement by NICE. As outlined in our DG response this medicine is often used in later lines after POM+DEX[2]. Clinical experts confirm this is the case. An analysis of SACT data suggests the use is ~3%. We therefore argue that considering PANO+BORT+DEX at 3L is not reasonable and is most often used subsequent to POM+DEX in 5L+ or in a minority of patients in 4L.	The EAG do not see the scenarios as factually inaccurate based on the information provided at the time this analysis was done, but simply possible scenarios aligned with NICE treatment line recommendations. The EAG do, however, acknowledge an inconsistency in the scenario using cyclophosphamide as the only relevant subsequent treatment following PANO+BORT+DEX in a POM+DEX ineligible population. By the same logic, if the population is ineligible for POM+DEX, then POM+DEX also ceases to be a relevant subsequent treatment following elranatamab, Therefore, the EAG has corrected this scenario so that cyclophosphamide also replaces POM+DEX as the subsequent treatment following elranatamab. The EAG also acknowledge the company's new point, that SEL+DEX may now become relevant as a subsequent treatment following both PANO+BORT+DEX and POM+DEX. The EAG have, therefore, incorporated the company's additional scenarios in Tables 2, 3 and 5 of its critique of the company's response to the draft guidance. However, following the same logic, SEL+DEX may also become a relevant subsequent treatment following progression on elranatamab, particularly in a cohort that is ineligible for POM+DEX due to prior exposure or inability to tolerate it. Therefore, the EAG has added further scenarios to Tables 2 and 3, in addition to the company's, which explore the effect of redistributing the proportion that don't receive PANO+BORT+DEX following elranatamab, between SEL+DEX and Cyclophosphamide +DEX. The EAG believe these scenarios may now be more relevant if SEL+DEX is accepted as a relevant subsequent treatment.

	already received POM+DEX).	In addition, following the elranatamab appraisal committee meeting and despite being out of scope, SEL+DEX is being suggested as a comparator in this appraisal based on discussions in ID6333. The company do not believe this is an appropriate comparator, but we have provided the comparison to support committee decision making. However, the Company argue that this context should now be considered as part of any subsequent treatment basket for all potential comparators. The Company believes it would be unfair to not do so for consistency. The Company acknowledge that the subsequent treatments in RRMM are complex and, for those in later lines, there is no standard of care. The Company have therefore suggested a number of scenarios that would be considered representative of those identified (reimbursed) comparators within ID6333 and applied these across Tables 1-4 below in **Appendix A**.	

		For the population of interest, ID6333 discussed POM+DEX (70%), PANO+BORT+DEX (20%) and SEL+DEX (10%). We would add that any subsequent lines for consideration would change the distribution of subsequent treatment baskets and we have represented this through the varying scenarios. Given the availability of these options we would argue that the use of CYCLO+DEX is minimal until it is used as a drug of last resort in later lines or as a bridging therapy for a short duration (as agreed by the CDF lead in ACM1).	
FAC 3 Section 2: Page 12, Table 2 and Table 3 (Scenario 1)	The EAG also questions the company's decision to revert to parametric curves fitted to unadjusted MagnetisMM-3 cohort A data for elranatamab in their additional scenario. The committee may remember that the company used curves fitted to the MM-003 adjusted cohort A data in their base case against POM+DEX. For consistency, the EAG would prefer to retain these curves in the additional scenario. The EAG noted previously that the curves fitted to unadjusted cohort A data result in a more optimistic extrapolation of OS for elranatamab.	The company understands the EAG's motives for requesting the MM-003 adjusted cohort A data. However, the company would like to clarify for the EAG that the MM-003 adjustment is specific for the comparison with POM+DEX based on data from MM-003. There is no specific 'adjusted' data for the PANO+BORT+DEX comparison and in this scenario an MAIC-derived HR is applied. We have provided a	The EAG acknowledges the apparent inconsistency, and for this reason provided scenarios that retained unadjusted cohort A extrapolations in combination scenarios. We also highlighted this as an area for further consideration by committee. However, the EAG's concern is that it was the MM-003 adjusted extrapolation curves that were presented for scrutiny at the first committee meeting and accepted as providing reasonable expectations for elranatamab in this indication. The cohort A extrapolations have not been scrutinized and agreed on by committee in the same way. The OS extrapolation in particular offers a substantially more optimistic long-term outlook. The plausibility of this should be considered in the context of these new scenarios against PANO+BORT+DEX, as pointed out in the EAGs critique.

		copy of the MAIC report, which provides an overview of the analysis for the EAG's review. Note that in the analysis we have assumed the PH assumption holds for both PFS and OS, for consistency across endpoints and for simplicity. Apologies for our oversight in not providing this data. Therefore, for the correct interpretation of the relative outcomes, the comparison should be made using the unadjusted elranatamab data.	
FAC 4 Section 2 Table 2 and 3, (Scenario 2)	2. Replace subsequent PANO+BORT+DEX treatment with POM+DEX in PANO+BORT+DEX arm	Please note that in Table 2 and Table 3 of the EAG critique of the company DG response, where scenarios 2 and 3 replaced subsequent PANO + BORT + DEX with POM+DEX in the PANO+BORT+DEX arm and resulted in a higher ICER, there was an error in the model that means the results of these scenarios are incorrect. When replacing PANO+BORT+DEX with POM+DEX in the PANO+BORT+DEX arm results in the ICER decreasing from £35,602 to £18,457 (**Table 2**) and	The EAG accept the company's acknowledgement of another error in the model and have updated this parameter and corrected the relevant scenarios in the critique document and confidential appendix.

		from £37,892 to £20,747 (**Table 3**). The POM+DEX percentage was hard coded as 0 incorrectly in the parameters sheet of the model, resulting in changes to the POM+DEX percentage not being considered correctly. Please accept our apologies for this oversight which in part resulted in the incorrect EAG analyses.	

References

1. NICE Teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments: draft guidance consultation 2024 [updated July 2024. Available from: https://www.nice.org.uk/guidance/GID-TA11418/documents/draft-guidance.
2. Pfizer. Draft guidance stakeholder form. ID4026. August 9 2024
3. NICE Teclistamab for treating relapsed and refractory multiple myeloma after 3 or more treatments (Review of TA869) [ID6333] Committee Papers 2024 [Available from: https://www.nice.org.uk/guidance/gid-ta11418/documents/committee-papers.

Elranatamab for treating relapsed or refractory multiple myeloma after 3 therapies [ID4026]

EAG critique of the company's response to consultation on the draft guidance

Produced by Aberdeen HTA Group

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Date completed **16 October 2024**

Version 4

Contains [redacted]

Following the first appraisal committee meeting, NICE published an appraisal consultation document detailing their draft final guidance for the use of elaranatamab for treating relapsed and refractory multiple myeloma after 3 or more treatments.

The company's original submission sought for elranatamab to be recommended for use within its marketing authorisation: "Adult patients with relapsed and refractory multiple myeloma, who have received at least 3 prior treatments, including a PI, an IMiD, and an anti-CD38 mAb, and have demonstrated disease progression on the last therapy".

The draft guidance restricted its use for "….treating relapsed and refractory multiple myeloma in adults ***after 3 or more lines of treatment*** (including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody) when the myeloma has progressed on the last treatment." It further restricts its use to include only those in whom "***pomalidomide plus dexamethasone would otherwise be offered"***.

The company response to the consultation has focussed on contesting these restrictions and argues for their removal as outlined in the eight related points of concern raised. This critique of the company response should be read in conjunction with the company response document. The EAGs comments are organised around the various arguments and evidence presented by the company to support 1) removal of the treatment line restriction; and 2) removal of the POM+DEX restriction.

The EAG understands that the restrictions applied by the committee are due to the company's comparative clinical and cost effectiveness case not fully covering the positioning of their marketing authorisation. The wording of the marketing authorisation would allow patients to become eligible for elrantanamab across different lines of therapy that have been established based on previous NICE guidance. The company argue for a recommendation by exposure/refractoriness rather than treatment line, as they believe this to be more consistent with UK clinical practice and the evidence presented. The EAGs clinical advisor agrees that recommendations by treatment line are becoming less useful in the context of a complex and evolving care pathway, where prior exposure and refractoriness are more important in clinical decision making. However, the draft guidance is understandable since the company only compared elranatamab against POM+DEX in their original submission, which is recommended by NICE "at third or subsequent relapse".

Section 1

Arguments for removal of the treatment line restriction

The company's first two points argue that the line of treatment restriction is 1) "inappropriate" (based on the evidence presented and clinical opinion); and 2) "inconsistent" with the recommendation made in the ongoing appraisal of teclistamab (ID6333) which took a very similar approach to the decision problem.(1)

Arguments for its inappropriateness are based around the changing treatment landscape resulting in triple class exposure/refractoriness occurring earlier in the treatment pathway (see company response). Thus, the restriction will 'inappropriately' deny access to patients who could benefit from elranatamab earlier in the treatment pathway, who will otherwise have limited efficacious treatments options available. However, the company's original submission made no clinical or economic case against comparators that are available before the fourth line for the triple class exposed population. In this respect, the further analysis presented by the company in their consultation response, against PANO+BORT+DEX, may be useful. Whilst it may not be representative of the full range of possible treatments that triple class exposed patients may receive at the third line, it may provide an option at this earlier stage according to NICE guidance (NICE TA380) (2).

The EAG have reviewed the company's new MAIC comparing elaranatamab with PANO+BORT+DEX, and the economic modelling based on the MAIC results, and provide a critique and commentary on these in section 2 below.

The company's second argument about inconsistency of the treatment line restriction, cites the draft guidance for teclistamab (ID6333) (1), a similar bispecific antibody with the same positioning as elaranatamab. Draft guidance for teclistamab did not receive the same ***treatment line*** restriction despite the submitting company taking a very similar approach to the decision problem. Instead, the draft guidance for telicistimab suggests eligibility after "…***3 or more treatments***…".

The EAG agrees with the company that there is an apparent inconsistency. However, the recommendations are not as inconsistent as they first seem because teclistamab does have the same restriction that it is only recommended only if pomalidomide plus dexamethasone would

otherwise be offered. Since according to NICE guidance POM+DEX is only available after three relapses (NICE TA427) (3), it seems that the two recommendations will not lead to any material difference in access. However, the latter may suggest that teclistamab could be offered at earlier treatment lines in the future if pomalidomide plus dexamethasone became routinely recommended earlier in the pathway. Given the similarity between the cases made, it does seem appropriate to the EAG that the wording of the guidance for each should be aligned. The company also present evidence from a published MAIC (Mol et al. 2024) (4), which suggests elranatamab has more favourable clinical effectiveness outcomes compared to teclistamab. This, along with the additional analysis assessing cost-effectiveness against PANO+BORT+DEX, may provide grounds for aligning the recommendations for elranatamab and teclistamab.

Arguments for removal of the POM+DEX restriction

The company offer arguments that the POM+DEX comparator restriction is inappropriate (company response points 3 and 4), inconsistent with prior appraisals (company response point 5), inequitable (response point 6), that it may undermine clinical decision making and patient choice (response point 7) and undermine future clinical research in the UK (response point 8).

POM+DEX comparator restriction is inappropriate

The first argument for its inappropriateness seems to focus on the fact that the accepted evidence supports the clinical efficacy of elranatamab in those who have already been exposed to pomalidomide containing regimens (81% of Cohort A in MagnetisMM-3) and those who are pomalidomide naïve; Therefore, the company argue it is inappropriate to restrict access for those who would not be eligible for POM+DEX in routine practice.

The EAG accept the fact that patients who are pomalidomide exposed and pomalidomide naïve do similarly well on elranatamab. The EAG also acknowledge the argument that the comparative case against POM+DEX is potentially conservative. To support this, the company say they have applied the real-world efficacy data for POM+DEX that was accepted in ID6333 within the cost effectiveness model (1). They find that this shows greater net health benefit for elaranatamab than in their own base case. However, the company have not described their approach here transparently, and appear not to have used the preferred Gompertz OS curve that was agreed upon for POM+DEX in ID16333. They have instead

used a lognormal curve. And whilst they have chosen a Gompertz curve for PFS, the selected curve does not appear to match the Gompertz PFS curve that was accepted in ID16333. The EAG, therefore, find this scenario unreliable and do not have the appropriate inputs and data to be able to check it properly.

It remains the case that no comparative clinical or cost-effectiveness case was made in the company's original submission for the sub-population of elranatamab eligible patients who would not otherwise receive POM+DEX in routine clinical practice. The efficacy of elranatamab for the overall population of cohort A has been considered generalisable to the POM+DEX naïve population for the purpose of comparing with POM+DEX. The comparative effectiveness estimates and ICER are, however, not applicable to those who would not otherwise receive POM+DEX. This may include people who are not yet at their third relapse (i.e. at a point in the pathway before POM+DEX is an option), or those who have had prior exposure to pomalidomide. However, the EAG acknowledges that there is no standard of care for this variable minority of patients. Nevertheless, the new comparison against PANO+BORT+DEX may be useful in this respect, as it is recommended by NICE as an option at third line (prior to POM+DEX) and subsequent treatment lines.

The second argument for inappropriateness of the POM-DEX restriction, is that it is the most relevant, plausible and feasible comparator for a TCE RRMM cohort. The company refer to their response to the EAG's clarification letter, where they suggest, based on clinical expert advice, that 80-85% of patients in the elranatamab eligible population would otherwise receive POM-DEX. The ongoing appraisal of teclistamab put this figure at ~90% (NICE ID16333). The company argue, therefore, that POM+DEX is the most relevant comparator and "*this is generalisable to the entire eligible patient population*". They refer to the NICE manual which suggests comparators for an appraisal will *"normally be guided by established practice in the NHS"*(NICE, 2022) (5).

However, based on the company's reconning, 10-20% of patients who would be eligible for elranatamab according to the wording of its marketing authorisation, would not otherwise receive POM+DEX in routine practice. This could be because they have not yet reached the point in the care pathway where NICE recommend it (≥ fourth line), they have already been exposed to pomalidomide, or they are intolerant to it or the IMiD class (or steroid use). This suggests, POM+DEX would not be established practice for 10-20% of the cohort.

It is in response to this issue that that the company have now provided a new scenario comparing against PANO+BORT+DEX, which as discussed above may be considered by the committee as evidence to support removal of the treatment line and POM-DEX comparator restrictions. The additional analysis does not cover the range of possible treatments that patients who are ineligible for POM+DEX might receive, but it may provide some guidance in the context of a complex and variable treatment pathway. The company have also referenced further published evidence to support the comparative clinical effectiveness of elranatamab against a comparator of physician's choice of treatment based on real-world US data (Costa et al. 2024) (6), which the EAG agree shows a comparable magnitude of PFS and OS benefit as demonstrated against POM+DEX in the company's MAIC. The PFS and OS also seem consistent with other data sources reporting PFS and OS for TCE/TCR MM treated with physician's choice of treatment (Mol et al. 2024) (7). A cost-effectiveness case has not, however, been made against a similar basket of comparator treatments.

POM+DEX comparator restriction is inconsistent

The company make the argument that restricting access to those who would otherwise receive POM+DEX is inconsistent with previous appraisals in TCE RRMM, in which the committee concluded that POM+DEX was the only relevant comparator in TA783 and ID2701 (8, 9). However, it should be noted that these previous recommendations are specific to the positioning "after 3 previous lines of treatment". The consultation response received from Myeloma UK, also notes that no prior NICE recommendations in multiple myeloma have restricted access based on the counterfactual treatment. They further argue that POM+DEX is the broadly representative treatment option for TCE patients at fourth line and beyond, and present evidence to support its use in the 4th, 5th, 6th and 7th lines.

These precedents could be used to argue for omitting the POM+DEX comparator restriction for elaranatamab, as they imply POM+DEX is the only relevant comparator from the fourth line onwards. It could not, however, be used to support removal of the restriction of after three lines of treatment, since POM+DEX is not routinely available before 3rd relapse. Further, the company also allude to the fact that there are patients at fourth line and beyond, who could benefit from elranatamab who have already received a pomalidomide containing regimen and will therefore receive other comparators (such as PANO+BORT+DEX). The EAG accept that POM+DEX is the main comparator for the TCE cohort at fourth line and

beyond, but there are other comparators that are relevant for a minority of patients who are already pomalidomide exposed. It is, however, appropriate to note that this population is small and will diminish further over time if elranatamb displaces the use of POM+DEX at fourth line. It is also fair to acknowledge that there is no standard care for these patients, who may receive various different treatments based on their fitness and prior treatment history.

POM+DEX comparator restriction is inequitable

In comment 6, the company have highlighted several groups of TCE RRMM patients that would not be eligible for elranatamab per the POM+DEX restriction. This includes current patients who have already received POM+DEX, those who would not be offered POM+DEX due to steroid toxicity and participants who are/have been enrolled in randomised trials that include pomalidomide containing treatment regimens.

The EAG acknowledges that under the draft guidance, there are patients who could benefit from treatment with elranatamab (per the indication and clinical effectiveness evidence) who would not be eligible to receive it. However, the positioning and arguments for inclusion of POM+DEX as the only comparator for TCE RRMM patients, inherently omits the groups described by the company from the economic case. The PANO+BORT+DEX treatment regimen would be a relevant option for some who have received POM+DEX, and so this may be informative. It should also be acknowledged in this comparison that 81% of MagnetisMM-03 (elranatamab) participants had previously received POM+DEX. This could provide reassurance to the committee that elranatamab is similarly efficacious in a POM+DEX exposed TCE/TCR cohort.

The EAG also acknowledge the points made by Myeloma UK, which argue that it is unnecessary to restrict access to those who would otherwise receive POM+DEX, as the pomalidomide exposed cohort is a minority that will be diminishing over time. They make strong arguments that it would be unfair to exclude those who have been exposed to pomalidomide already in the context of the historical care pathways. This, they argue, is a much smaller group that will be diminishing over time due to the new elranatamab recommendation, and in which there is no established standard of care.

POM+DEX comparator restriction undermining clinical decision making and future clinical research in the UK

The company have indicated that the restriction to those who would be offered POM+DEX would undermine clinical care and patient choice (Comment 7). The company have provided evidence within the submission and sought clinical advice that treatment decisions for MM in the UK are based upon class exposure/refractoriness and not treatment line. Therefore, recommending by treatment line, and with the POM+DEX restriction, may cause clinicians to make decisions based on eligibility for future treatment rather than treatment which would benefit the patient most in their current treatment line. The company also highlight other pomalidomide containing regimens that are being considered for earlier treatment lines in the future – hence elranatamab would not be available at fourth line to patients who receive those regimens in the future.

The EAG acknowledges the company's concern - the arguments for the undermining of clinical decision-making are plausible. However, this is linked to the lack of comparative clinical and cost-effectiveness case being made for those patients who would not otherwise receive POM+DEX; i.e. those who are TCE at third line or who have previously received pomalidomide. It would be beneficial for the committee to seek further clinical advice on the implications of the restriction for future clinical decision making. In particular, whether clinical decisions are based predominantly on class exposure/refractoriness rather than treatment line. Should the committee agree, this would have a broader impact upon previous and future recommendations of other treatments within MM.

The company also argue that the restriction will negatively impact upon ongoing research of elranatamab in the UK – pointing to the withdrawal of a research site and indication to withdraw based on uncertainty surrounding the draft guidance for elranatamab. The company is concerned that the implications of this restriction on research have not been detailed in the draft guidance nor have NHS England publicly shared assurances for centres or participants taking part in randomised trials that utilise POM+DEX or pomalidomide containing regimens as a comparator.

The EAG acknowledges the uncertainty that has been created out of the restriction in reference to ongoing and future research. However, treatment guidance for participants within clinical trials are outside the remit of NICE. The company also state that NHS

England has assured them that the participation in these trials would not affect eligibility for elranatamab. If this is the case, it could be made clear in the guidance.

Section 2

EAG comment of the company's MAIC against PANO+BORT+DEX

The company has included an additional comparison between MagnetisMM-3 and PANORAMA-2. There are some population differences between the MagnetisMM-3 elranatamab cohort and the PANO+BORT+DEX cohort in PANAROMA-2. These notably include differences in age category (≥65 years old) and that PANAROMA-2 were not TCE RRMM. This may be more in favour for PANO+BORT+DEX having younger and less severe patients.

The company used the same unanchored MAIC approach as the original submission to compare elranatamab with PANO+BORT+DEX. The EAG agree that this is the best approach given that there is no control group in the MagnetisMM-3 cohort and that only PANAROMA-2 aggregated data were available. Although the unanchored MAIC is the best possible method to be used, the small effective sample size relative to the original sample size indicates the weights are highly variable and the estimates might be unstable. There is evidence of benefit of elranatamab over the PANO+BORT+DEX combination for this patient population for PFS and OS. However, the magnitude of effect, and how sustained this is, is uncertain.

EAG critique of the company cost-effectiveness scenario against PANO+BORT+DEX

The company describe their implementation of a cost-effectiveness scenario comparing elranatamab with PANO+BORT+DEX using the hazard ratios derived from the new unanchored MAIC described above. They apply the derived hazard ratios for PFS and OS to the chosen parametric reference curves for elranatamab. Time to treatment discontinuation has been reasonably approximated by applying a ratio of median ToT:PFS from a published UK cohort, to the derived PFS curve for PANO+BORT+DEX.

The EAG note that the company's approach to modelling overall survival for PANO+BORT+DEX does not apply the hazard ratio from the MAIC directly. The company argue that this produced implausible OS extrapolations for PANO+BORT+DEX, which exceed clinical expectation. Therefore, the company further adjust the HR so that its application yields median OS for PANO+BORT+DEX which aligns with that observed in real-work studies of UK cohorts (Maouche et al. 2022; Bird et al. 2020) (10, 11).

The EAG agree that the modelled OS for PANO+BORT+DEX is implausibly high for the TCE cohort when the unadjusted hazard ratio is applied, and that it is more consistent with real-world evidence with the adjusted hazard ratio. However, the EAG has identified two errors in the way the derived hazard ratios for PFS and OS have been applied in the company's new scenario:

1) The hazard ratios have been applied multiplicatively to the estimated cycle specific transition probabilities for OS and PFS, rather than the underlying hazard rate.
2) The estimated transition probabilities for modelling PFS and OS for PANO+BORT+DEX have been applied out of sync with the cycle number.

The EAG has, therefore, corrected these errors and recalculated the company's ICER (Table 1).

In checking through the company's application of costs for PANO+BORT+DEX, a further inconsistency was identified between administration costs, which stopped at 48 weeks, and drug acquisitions costs which were assumed to continue to progression. Since the SmPC states a total duration of treatment up to 16 cycles (48 weeks), the EAG assume that this was an error, and that treatment acquisition costs for PANO+BORT+DEX should stop at 48 weeks.

The checking of PANO+BORT+DEX costs also highlighted a minor error in the costing of PANO+BORT+DEX as a subsequent treatment in the company's model, in which the number of 3.5mg bortezomib vials was estimated based on body surface area thresholds that can be treated with increments of 2.5mg vials, rather than the 3.5mg vial assumed for the up front treatment costs. The EAG has corrected this but it has minimal impact. Furthermore, in checking through the subsequent treatment calculation for the PANO+BORT+DEX comparator, the EAG identified another bug in the company's model, resulting in the subsequent treatment distribution for the elranatamab arm also being applied in the POM+DEX arm of the model. Therefore, the EAG has corrected this bug, and provided corrected company PANO+BORT+DEX scenario (Table 1) and POM+DEX base case (Table 4).

A further issue related to the PANO+BORT+DEX comparison commandeering the POM+DEX arm of the model, is that the subsequent treatment distribution was not updated from the POM+DEX comparison, and so suggested that 70% of patients who receive further treatment following progression on PANO+BORT+DEX, go on to receive PANO+BORT+DEX again. This clearly lacks clinical validity. Therefore, the EAG assessed the impact of changing the distribution of subsequent therapy to remove PANO+BORT+DEX as a subsequent treatment option following PANO+BORT+DEX. Two alternative scenarios were considered Tables 2 and 3):

1) Replacing PANO+BORT+DEX with POM+DEX (reflecting a subsequent treatment distribution that might be reasonable for those who receive PANO+BORT+DEX at third line, prior to being eligible for POM+DEX).
2) Replacing all subsequent treatment following PANO+BORT+DEX with cyclophosphamide (reflecting a subsequent treatment distribution for those who receive PANO+BORT+DEX as a comparator to elranatamab in later lines, having already received POM+DEX). In this scenario the same logic is followed for the elranatamab arm, with those who are not receiving PANO+BORT+DEX as a subsequent treatment all assumed to receive cyclophosphamide (noting this represents an POM+DEX ineligible population).

In their factual accuracy response to an earlier version of this document, the company pointed out that the recent approval of Selinexor plus dexamethasone (TA970), may now also make it relevant as a subsequent treatment following both PANO+BORT+DEX and POM+DEX. The EAG have, therefore, incorporated the further additional scenarios proposed by the company in Tables 2, 3 and 5 of its further analysis below. However, following the same logic, SEL+DEX may also become a relevant subsequent treatment following progression on elranatamab, particularly in a cohort that is ineligible for POM+DEX due to prior exposure or inability to tolerate it. Therefore, the EAG has added further scenarios to Tables 2 and 3, in addition to the company's, which explore the effect of redistributing the proportion that don't receive PANO+BORT+DEX following elranatamab, between SEL+DEX and Cyclophosphamide+DEX. The EAG believe these scenarios may now be more relevant if SEL+DEX is accepted as a relevant subsequent treatment.

In implementing these further scenarios, it was also noted that the assumed duration of subsequent treatment (POM+DEX and PANO+BORT+DEX) was optimistic compared to the modelled time on these treatments in the first line of the company model. Therefore, the EAG has assessed further scenarios that equate the duration of subsequent treatment with the mean duration of treatment on POM+DEX in the first line of the company's model (4.8 months, under committee preferred modelling assumptions)

The EAG also questions the company's decision to revert to parametric curves fitted to unadjusted MagnetisMM-3 cohort A data for elranatamab in their additional scenario. The committee may remember that the company used curves fitted to the MM-003 adjusted cohort A data in their base case against POM+DEX. For consistency, the EAG would prefer to retain these curves in the additional scenario. The EAG noted previously that the curves fitted to unadjusted cohort A data result in a more optimistic extrapolation of OS for elranatamab.

Results of the EAG's corrections to the company's PANO+BORT+DEX scenario are provided in Table 1 below. Further scenarios applied to the EAG's company corrected base case are provided in Table 2 (assuming [redacted] IVIG usage in the elranatamab arm) and Table 3 (assuming 43.1% IVIG usage in the elranatamab arm). Analyses inclusive of confidential prices for comparator and subsequent treatments are provided in a separate confidential appendix to this document. It should be noted that all analyses include 1.2 weighting of QALY gains as per the original submission, which the EAG agrees are met based on the proportional QALY shortfall for both the PANO+BORT+DEX and POM+DEX comparators.

It may also be noted that the company's PANO+BORT+DEX comparison is not ideal, because it has not been fully developed and clinically validated in the same way the POM+DEX comparator has. The modelling suggests that PANO+BORT+DEX has better OS and PFS than POM+DEX, and that it generates a greater number of QALYs. This seems inconsistent with the argument that it is rarely used in clinical practice for the TCE cohort due to poor efficacy and toxicity. Further, certain parameters have not been informed and so rely on POM+DEX specific parameters, including the adverse event profile and RDI. For the above reasons, the results of the PANO+BORT+DEX comparison should be interpreted with caution.

Table 1 EAG corrected company base case against PANO+BORT+DEX

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (£/QALY)	% change from base case
Elranatamab (43.1% IVIG)	[redacted]	[redacted]				
PANO+ BORT+DEX	[redacted]	[redacted]	[redacted]	[redacted]	£5,359	NA
EAG Corrections (applied independently)						
Company base			[redacted]	[redacted]	£5,359	NA
1. Correction of PANO+BORT+DEX PFS and OS curves			[redacted]	[redacted]	£8,543	59%
2. Removal of RDI switch to 100% at 25 weeks to never+			[redacted]	[redacted]	Dominant	-118%
3. Subsequent treatment distribution for PANO+BORT+DEX switched from Elranatamab to PANO+BORT+DEX			[redacted]	[redacted]	£16,104	200%
4. Drug acquisition cost of PANO+BORT+DEX equals 0 from 48 weeks (no change to drug administration costs which are £0 from 48 weeks).			[redacted]	[redacted]	£16,403	206%
5. Assume only 1 3.5mg Bortezomib vials are used for subsequent treatment			[redacted]	[redacted]	£5,360	0%
6. POM+DEX subsequent treatment distribution in comparator arm not carrying through to model calculations++			[redacted]	[redacted]	£5,359	0%
EAG company corrected base case– [redacted] IVIG			[redacted]	[redacted]	£21,039	584%+++
EAG company corrected base case – 43.1% IVIG			[redacted]	[redacted]	£23,329	335%

+ the company corrected this themselves in an updated document following their initial response. ++company corrected in response to FAC; +++ % change calculated from original company base case ICER assuming [redacted] IVIG in the Elranatamab arm (£3,077)

Table 2 EAG cost-effectiveness scenarios of EAG corrected company base case against PANO+BORT+DEX – [redacted] IVIG

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (£/QALY)	% change in ICER
Elranatamab	[redacted]	[redacted]				
PANO+ BORT+DEX	[redacted]	[redacted]	[redacted]	[redacted]	£21,039	NA
Retention of MM-003 adjusted Elranatamab PFS and OS curves			[redacted]	[redacted]	£26,093	24%
2. Subsequent treatment distribution Elranatamab • POM+DEX = 90% • PANO+BORT+DEX = 8% • CYCLO+DEX = 2% • SEL+DEX = 0% PANO+BORT+DEX • POM+DEX = 70% • PANO+BORT+DEX = 0% • CYCLO+DEX = 30% • SEL+DEX = 0%			[redacted]	[redacted]	£18,457	-12%
2.a Subsequent treatment distribution Elranatamab • POM+DEX = 90% • PANO+BORT+DEX = 8% • CYCLO+DEX = 2% • SEL+DEX = 0% PANO+BORT+DEX • POM+DEX = 70% • PANO+BORT+DEX = 0% • CYCLO+DEX = 0% • SEL+DEX = 30%			[redacted]	[redacted]	£6,346	-70%
2.b Subsequent treatment distribution Elranatamab • POM+DEX = 90% • PANO+BORT+DEX = 8% • CYCLO+DEX = 2% • SEL+DEX = 0% PANO+BORT+DEX • POM+DEX = 70% • PANO+BORT+DEX = 0% • CYCLO+DEX = 10% • SEL+DEX = 20%			[redacted]	[redacted]	£10,383	-51%
2.c Subsequent treatment distribution Elranatamab • POM+DEX = 64.4% • PANO+BORT+DEX = 8.0% • CYCLO+DEX = 0% • SEL+DEX = 27.6% PANO+BORT+DEX • POM+DEX = 70% • PANO+BORT+DEX = 0% • CYCLO+DEX = 0% • SEL+DEX = 30%			[redacted]	[redacted]	£11,001	-48%

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (£/QALY)	% change in ICER
2. d Subsequent treatment distribution Elranatamab • POM+DEX = 64.4% • PANO+BORT+DEX = 8.0% • CYCLO+DEX = 9.2% • SEL+DEX = 18.4% PANO+BORT+DEX • POM+DEX = 70% • PANO+BORT+DEX = 0% • CYCLO+DEX = 10% • SEL+DEX = 20%			[redacted]	[redacted]	£11,517	-45%
3. Subsequent treatment distribution Elranatamab • POM+DEX = 0% • PANO+BORT+DEX = 8% • CYCLO+DEX = 92% • SEL+DEX = 0% PANO+BORT+DEX • POM+DEX = 0% • PANO+BORT+DEX = 0% • CYCLO+DEX = 100% • SEL+DEX = 0%			[redacted]	[redacted]	£14,726	-30%
3.a Subsequent treatment distribution Elranatamab • POM+DEX = 90% • PANO+BORT+DEX = 8% • CYCLO+DEX = 2% • SEL+DEX = 0% PANO+BORT+DEX • POM+DEX = 0% • PANO+BORT+DEX = 0% • CYCLO+DEX = 0% • SEL+DEX = 100%			[redacted]	[redacted]	Dominant	-123%
3.b Subsequent treatment distribution Elranatamab • POM+DEX = 90% • PANO+BORT+DEX = 8% • CYCLO+DEX = 2% • SEL+DEX = 0% PANO+BORT+DEX • POM+DEX = 0% • PANO+BORT+DEX = 0% • CYCLO+DEX = 30% • SEL+DEX = 70%			[redacted]	[redacted]	£7,239	-66%
3.c Subsequent PANO+BORT+DEX Elranatamab • POM+DEX = 90% • PANO+BORT+DEX = 8% • CYCLO+DEX = 2% • SEL+DEX = 0% PANO+BORT+DEX • POM+DEX = 0%			[redacted]	[redacted]	£15,313	-27%

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (£/QALY)	% change in ICER
• PANO+BORT+DEX = 0% • CYCLO+DEX = 50% • SEL+DEX = 50%						
3.d Subsequent treatment distribution Elranatamab • POM+DEX = 0% • PANO+BORT+DEX = 8% • CYCLO+DEX = 0% • SEL+DEX = 92% PANO+BORT+DEX • POM+DEX = 0% • PANO+BORT+DEX = 0% • CYCLO+DEX = 0% • SEL+DEX = 100%			[redacted]	[redacted]	£9,568	-55%
3.e Subsequent treatment distribution Elranatamab • POM+DEX = 0.0% • PANO+BORT+DEX = 8.0% • CYCLO+DEX = 27.6% • SEL+DEX = 64.4% PANO+BORT+DEX • POM+DEX = 0% • PANO+BORT+DEX = 0% • CYCLO+DEX = 30% • SEL+DEX = 70%			[redacted]	[redacted]	£11,116	-47%
3.f Subsequent treatment distribution Elranatamab • POM+DEX = 0% • PANO+BORT+DEX = 8% • CYCLO+DEX = 46% • SEL+DEX = 46% PANO+BORT+DEX • POM+DEX = 0% • PANO+BORT+DEX = 0% • CYCLO+DEX = 50% • SEL+DEX = 50%			[redacted]	[redacted]	£12,147	-42%
4. Reduce subsequent treatment duration to mean Time-on-Treatment for POM+DEX (4.8 months)			[redacted]	[redacted]	£17,914	-15%
2+4			[redacted]	[redacted]	£16,344	-22%
3+4			[redacted]	[redacted]	£14,101	-33%
2b+4 (Company preferred)			[redacted]	[redacted]	£11,491	-45%
3b+4 (Company preferred)			[redacted]	[redacted]	£9,604	-54%
2d + 4			[redacted]	[redacted]	£12,172	-42%
3e + 4			[redacted]	[redacted]	£11,931	-43%
1 + 2d + 4 (EAG preferred)			[redacted]	[redacted]	£15,524	-26%
1 + 3e + 4 (EAG preferred)			[redacted]	[redacted]	£15,234	-28%

Table 3 EAG cost-effectiveness scenarios of EAG corrected company base case against PANO+BORT+DEX – 43.1% IVIG

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (£/QALY)	% change in ICER
Elranatamab	[redacted]	[redacted]				
PANO+ BORT+DEX	[redacted]	[redacted]	[redacted]	[redacted]	£23,329	NA
Retention of MM-003 adjusted Elranatamab PFS and OS curves			[redacted]	[redacted]	£28,824	24%
2. Subsequent treatment distribution Elranatamab • POM+DEX = 90% • PANO+BORT+DEX = 8% • CYCLO+DEX = 2% • SEL+DEX = 0% PANO+BORT+DEX • POM+DEX = 70% • PANO+BORT+DEX = 0% • CYCLO+DEX = 30% • SEL+DEX = 0%			[redacted]	[redacted]	£20,747	-11%
2.a Subsequent treatment distribution Elranatamab • POM+DEX = 90% • PANO+BORT+DEX = 8% • CYCLO+DEX = 2% • SEL+DEX = 0% PANO+BORT+DEX • POM+DEX = 70% • PANO+BORT+DEX = 0% • CYCLO+DEX = 0% • SEL+DEX = 30%			[redacted]	[redacted]	£8,636	-63%
2.b Subsequent treatment distribution Elranatamab • POM+DEX = 90% • PANO+BORT+DEX = 8% • CYCLO+DEX = 2% • SEL+DEX = 0% PANO+BORT+DEX • POM+DEX = 70% • PANO+BORT+DEX = 0% • CYCLO+DEX = 10% • SEL+DEX = 20%			[redacted]	[redacted]	£12,673	-46%
2.c Subsequent treatment distribution Elranatamab • POM+DEX = 64.4% • PANO+BORT+DEX = 8.0% • CYCLO+DEX = 0% • SEL+DEX = 27.6% PANO+BORT+DEX • POM+DEX = 70% • PANO+BORT+DEX = 0% • CYCLO+DEX = 0% • SEL+DEX = 30%			[redacted]	[redacted]	£13,291	-43%

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (£/QALY)	% change in ICER
2. d Subsequent treatment distribution Elranatamab • POM+DEX = 64.4% • PANO+BORT+DEX = 8.0% • CYCLO+DEX = 9.2% • SEL+DEX = 18.4% PANO+BORT+DEX • POM+DEX = 70% • PANO+BORT+DEX = 0% • CYCLO+DEX = 10% • SEL+DEX = 20%			[redacted]	[redacted]	£13,807	-41%
3. Subsequent treatment distribution Elranatamab • POM+DEX = 0% • PANO+BORT+DEX = 8% • CYCLO+DEX = 92% • SEL+DEX = 0% PANO+BORT+DEX • POM+DEX = 0% • PANO+BORT+DEX = 0% • CYCLO+DEX = 100% • SEL+DEX = 0%			[redacted]	[redacted]	£17,016	-27%
3.a Subsequent treatment distribution Elranatamab • POM+DEX = 90% • PANO+BORT+DEX = 8% • CYCLO+DEX = 2% • SEL+DEX = 0% PANO+BORT+DEX • POM+DEX = 0% • PANO+BORT+DEX = 0% • CYCLO+DEX = 0% • SEL+DEX = 100%			[redacted]	[redacted]	Dominant	-111%
3.b Subsequent treatment distribution Elranatamab • POM+DEX = 90% • PANO+BORT+DEX = 8% • CYCLO+DEX = 2% • SEL+DEX = 0% PANO+BORT+DEX • POM+DEX = 0% • PANO+BORT+DEX = 0% • CYCLO+DEX = 30% • SEL+DEX = 70%			[redacted]	[redacted]	£9,529	-59%
3.c Subsequent PANO+BORT+DEX Elranatamab • POM+DEX = 90% • PANO+BORT+DEX = 8% • CYCLO+DEX = 2% • SEL+DEX = 0% PANO+BORT+DEX • POM+DEX = 0%			[redacted]	[redacted]	£17,603	-25%

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (£/QALY)	% change in ICER
• PANO+BORT+DEX = 0% • CYCLO+DEX = 50% • SEL+DEX = 50%						
3.d Subsequent treatment distribution Elranatamab • POM+DEX = 0% • PANO+BORT+DEX = 8% • CYCLO+DEX = 0% • SEL+DEX = 92% PANO+BORT+DEX • POM+DEX = 0% • PANO+BORT+DEX = 0% • CYCLO+DEX = 0% • SEL+DEX = 100%			[redacted]	[redacted]	£11,858	-49%
3.e Subsequent treatment distribution Elranatamab • POM+DEX = 0% • PANO+BORT+DEX = 8.0% • CYCLO+DEX = 27.6% • SEL+DEX = 64.4% PANO+BORT+DEX • POM+DEX = 0% • PANO+BORT+DEX = 0% • CYCLO+DEX = 30% • SEL+DEX = 70%			[redacted]	[redacted]	£13,405	-43%
3.f Subsequent treatment distribution Elranatamab • POM+DEX = 0% • PANO+BORT+DEX = 8% • CYCLO+DEX = 46% • SEL+DEX = 46% PANO+BORT+DEX • POM+DEX = 0% • PANO+BORT+DEX = 0% • CYCLO+DEX = 50% • SEL+DEX = 50%			[redacted]	[redacted]	£14,437	-38%
4. Reduce subsequent treatment duration to mean Time-on-Treatment for POM+DEX (4.8 months)			[redacted]	[redacted]	£20,204	-13%
2+4			[redacted]	[redacted]	£18,634	-20%
3+4			[redacted]	[redacted]	£16,391	-30%
2b+4 (Company preferred)			[redacted]	[redacted]	£13,781	-41%
3b+4 (Company preferred)			[redacted]	[redacted]	£11,894	-49%
2d + 4			[redacted]	[redacted]	£14,462	-38%
3e + 4			[redacted]	[redacted]	£14,221	-39%
1 + 2d + 4 (EAG preferred)			[redacted]	[redacted]	£18,255	-22%
1 + 3e + 4 (EAG preferred)			[redacted]	[redacted]	£17,965	-23%

Further analysis for the POM+DEX comparison

Since checking of the model for the new PANO+BORT+DEX scenario identified an error in the subsequent treatment distribution applied in the POM+DEX arm of the model, Table 4 (below) shows the impact of correcting this and the cost calculation for bortezomib as subsequent treatment in the comparison against POM+DEX.

In addition, Table 5 shows the impact of reducing mean time on subsequent treatment (for those who progress) to align better with the assumed durations of treatment for those who receive POM+DEX or PANO+BORT+DEX in the first line of the company model (4.8 months). Again, all these analyses have been repeated with confidential prices for comparator and subsequent treatments applied, and the results presented for the committee in the separate confidential appendix to this document.

Table 4 Committee preferred assumptions against POM+DEX with model errors corrected which were identified during EAG critique of the company response to FAD

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (£/QALY)	% change from base case
Elranatamab ([redacted]_IVIG)	[redacted]	[redacted]				
POM+DEX	[redacted]	[redacted]	[redacted]	[redacted]	£6,116	NA
Elranatamab (43.1% IVIG)	[redacted]	[redacted]				
POM+DEX	[redacted]	[redacted]	[redacted]	[redacted]	£8,472	NA
EAG corrections						
[redacted] IVIG						
Subsequent treatment distribution for POM+DEX switched from Elranatamab to POM+DEX			[redacted]	[redacted]	£17,320	183.18%
Assume only 3.5mg Bortezomib vials are used for subsequent treatment			[redacted]	[redacted]	£6,117	0.02%
EAG corrected committee preferred base case – [redacted]% IVIG			[redacted]	[redacted]	£17,474	185.70%
43.1% IVIG						
Subsequent treatment distribution for POM+DEX switched from Elranatamab to POM+DEX			[redacted]	[redacted]	£19,676	132.24%
Assume only 3.5mg Bortezomib vials are used for subsequent treatment			[redacted]	[redacted]	£8,474	0.01%
EAG corrected committee preferred base case – 43.1% IVIG			[redacted]	[redacted]	£19,830	134.06%

ICER, Incremental cost effectiveness ratio; MAIC, matching adjusted indirect comparison; PANO, panobinostat; QALY, quality adjusted life year.

Table 5 EAG scenarios for Elranatamab versus POM+DEX with corrected committee preferred base case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (£/QALY)	% change from base case
Elranatamab ([redacted]% IVIG)	[redacted]	[redacted]				
POM+DEX	[redacted]	[redacted]	[redacted]	[redacted]	£17,474	NA
Elranatamab (43.1% IVIG)	[redacted]	[redacted]				
POM+DEX	[redacted]	[redacted]	[redacted]	[redacted]	£19,830	NA
EAG Scenarios						
EAG corrected committee preferred base case – [redacted] IVIG						
1. Reduce subsequent treatment duration to mean Time-on-Treatment for POM+DEX (4.8 months)			[redacted]	[redacted]	£14,312	-18%
2. a. Subsequent treatment distribution Elranatamab • POM+DEX = 90% • PANO+BORT+DEX = 8% • CYCLO+DEX = 2% • SEL+DEX = 0% PANO+BORT+DEX • POM+DEX = 0% • PANO+BORT+DEX = 70% • CYCLO+DEX = 0% • SEL+DEX = 30%			[redacted]	[redacted]	£4,914	-72%

2. b. Subsequent treatment distribution Elranatamab • POM+DEX = 90% • PANO+BORT+DEX = 8% • CYCLO+DEX = 2% • SEL+DEX = 0% PANO+BORT+DEX • POM+DEX = 0% • PANO+BORT+DEX = 70% • CYCLO+DEX = 10% • SEL+DEX = 20%	[redacted]	[redacted]	£9,101	-48%
1 + 2b	[redacted]	[redacted]	£9,279	-47%
EAG corrected committee preferred base case – 43.1% IVIG				
3. Reduce subsequent treatment duration to mean Time-on-Treatment for POM+DEX (4.8 months)	[redacted]	[redacted]	£16,668	-16%
4. b. Subsequent treatment distribution Elranatamab • POM+DEX = 90% • PANO+BORT+DEX = 8% • CYCLO+DEX = 2% • SEL+DEX = 0% PANO+BORT+DEX • POM+DEX = 0% • PANO+BORT+DEX = 70% • CYCLO+DEX = 0% • SEL+DEX = 30%	[redacted]	[redacted]	£7,271	-63%
4. b. Subsequent treatment distribution Elranatamab • POM+DEX = 90% • PANO+BORT+DEX = 8% • CYCLO+DEX = 2% • SEL+DEX = 0% PANO+BORT+DEX • POM+DEX = 0% • PANO+BORT+DEX = 70% • CYCLO+DEX = 10% • SEL+DEX = 20%	[redacted]	[redacted]	£11,457	-42%
3 + 4b	[redacted]	[redacted]	£11,635	-41%

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Elranatamab for treating relapsed or refractory multiple myeloma after 3 therapies [ID4026]

EAG critique of the company's additional comparison versus Selinexor plus dexamethasone

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Version 1

Contains [redacted]

Ahead of the second appraisal committee meeting for this appraisal, the company submitted new evidence to support the committee's decision making, in the form of new matched adjusted indirect comparison (MAIC) and economic case against the comparator Selinexor plus dexamethasone. This brief commentary and critique focusses on this new comparison.

Comment on the matched adjusted indirect comparison against SEL+DEX

The company has included an addition comparison between MagnetisMM-3 (elranatamab) and STORM, a phase 2b, multicenter, open-label single arm study of 122 patients receiving selinexor (80 mg) plus dexamethasone (20 mg) twice weekly in United States and Europe. Eligible patients had previously been exposed to bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, and an alkylating agent and had disease refractory to at least one proteasome inhibitor, one immunomodulatory agent, and daratumumab (triple-class refractory). As noted by the company, STORM data did not report extramedullary disease which was identified as a prognostic value in the SLR and based on clinical opinion. There are some population differences between the MagnetisMM-3 elranatamab cohort and the selinexor and dexamethasone cohort in STORM. In MagnetisMM-3, 42% of patients were penta-drug refractory and in STORM, 68% were penta-drug refractory. There were more patients with high-risk cytogenetics in STORM compared to MagnetisMM-3. This may favour for elranatamab in Naïve comparison, having less severe patients.

The company used the same unanchored MAIC approach as the original submission to compare elranatamab with selinexor and dexamethasone. The EAG agree that this is the best approach given that there is no control group in the MagnetisMM-3 cohort and that only STORM aggregated data were available. The company did not provide the characteristics after matching and therefore, the EAG could not assess the characteristics of the cohort after weighting. Although the unanchored MAIC is the best possible method to be used, the small effective sample size relative to the original sample size indicates the weights are highly variable due to only small fraction of patients shared common characteristics and the estimates might be unstable. There is evidence of benefit of elranatamab over the selinexor and dexamethasone combination for this patient population for PFS and OS. However, the magnitude of effect, and how sustained this is, is uncertain.

Comment on the cost-effectiveness modelling comparison against Selinexor plus dexamethasone

Limited information was provided by the company regarding their economic modelling approach for the comparison of Elranatamab versus Selinexor plus Dexamethasone (SEL+DEX). From the company response and interrogation of the model, the EAG understands that the following has been done.

- The OS and PFS data from cohort A in MagnetisMM-3 has been weighed to match the covariate distribution of the STORM trial, and a MAIC performed (as above and described in the company's ITC report).
- The company then use the MAIC OS hazard ratio for SEL+DEX versus elranatamab (=1/([redacted]), and apply this to the reference generalised gamma curve fitted to unadjusted elranatamab overall survival data for cohort A of MagnetisMM-3.
- Since they have rejected the proportional hazards assumption between SEL+DEX and elranatamab for PFS, the EAG understand that the company has done the following:
    1. Fitted parametric curves to digitised PFS data from STORM
    2. Fitted parametric curves to the STORM weighted PFS data from MagnetisMM-3
    3. Taken the difference between the parameter estimates of the parametric distributions between 1 and 2.
    4. Applied these differences (from 3), to the parameter estimates of the parametric distributions fitted to the unadjusted cohort A data, to derive parameter estimates for modelling PFS for SEL+DEX
    5. For 4 (above), they appear to have used the derived generalised gamma curve for SEL+DEX PFS, for reasons that are not discussed.

This approach gives a comparison against SEL+DEX in a cohort matching the characteristics of Cohort A from MagnetisMM-3. To achieve this, the company have substituted the survival curves for POM+DEX in the model with those for SEL+DEX.

The EAG find the company's approach to be rather convoluted and somewhat inconsistent. The approach to estimating survival distribution parameter treatment effects is not a recognized method that the EAG is aware of and may lack validity. Rather than apply the

MAIC hazard ratio or adjusted parameter treatment effects to the unadjusted cohort A curves, it would have seemed more intuitive to make a comparison based on curves fitted to the STORM weighted MagnetisMM-3 KM data, and the curves fitted to the digitised STORM data. This would have provided a comparison for a cohort matching the characteristics of the STORM trial population; which has been considered appropriate for informing the decision to recommend the use of SEL+DEX for treating relapsed or refractory multiple myeloma after 4 or more treatments (albeit based on a subgroup of penta-refractory patients).

Furthermore, through utilising the POM+DEX arm of the original model, several aspects of the comparison have not been considered. Assumptions relating to time on treatment, the adverse event profile and downstream subsequent treatment proportion and distribution remain unchanged from the comparison with POM+DEX, which may be less appropriate for a comparison beyond the fourth line.

Through inspection of the model the EAG identified further inaccuracies in the application of the hazard ratio to the survival curves, which were subsequently corrected by the company. As alternative approaches to the company's, the EAG have presented cost-effectiveness results for:

a) *a naïve comparison with SEL+DEX utilising the lognormal parametric distribution for OS and PFS. This is based on best visual fit and AIC/BIC statistics for each distribution. Figure 1 below illustrates the alternative overall survival curves fitted to the digitised STORM trial data.*
b) *A comparison that applies the MAIC hazard ratios to model OS and PFS for elranatamab relative to the selected SEL+DEX reference curves fitted to the STORM trial data.*

The EAG has a preference towards the b), because despite the caveat of assuming proportional hazards, it is the only approach that adjusts the elranatamab curves towards the harder to treat Penta-refractory population that is eligible for SEL+DEX after the fourth line of treatment. The resultant curves are provided in Figure 2.

Figure 1. Parametric survival extrapolations of Overall Survival for SEL+DEX (reproduced from Company Model)

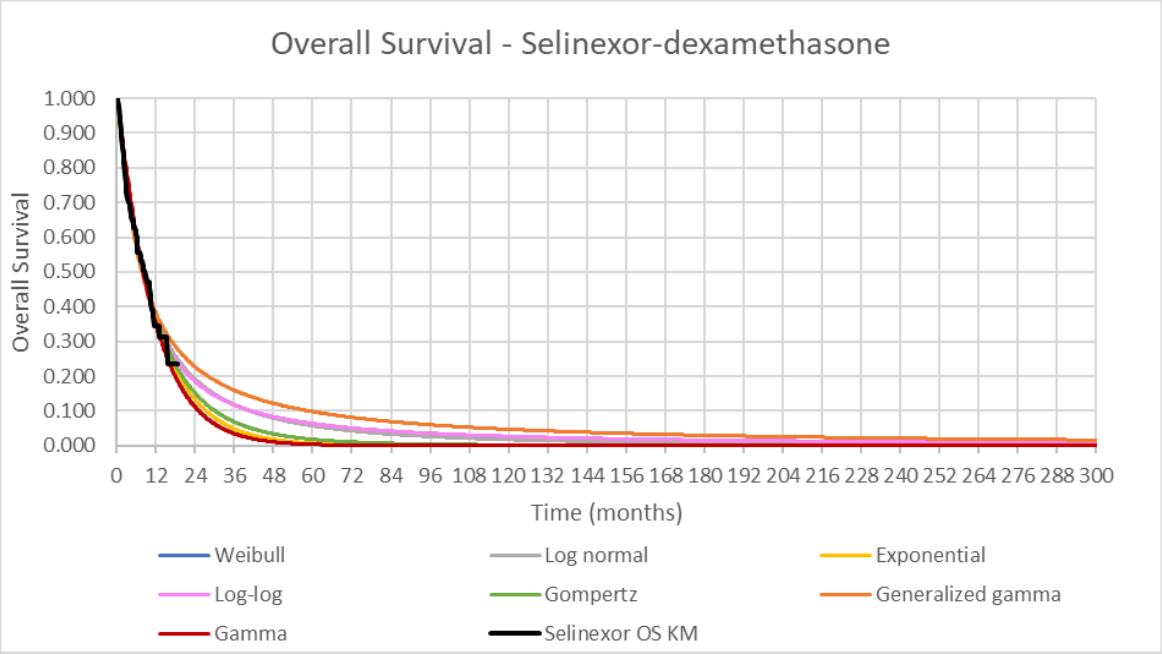

Figure 2 Extrapolated curves when elranatamab OS and PFS are modelled by applying hazard ratios from the MAIC to lognormal reference curves for SEL+DEX

[redacted]

Similar to the comparison with POM+DEX, the company have estimated Time-to-Treatment Discontinuation (TTD) using a median PFS:median TTD ratio. The ratio has not been updated with comparable estimates for Selinexor. Within the submitted base case, this estimates a median TTD of 2.76 months, which is a good bit higher than that reported in the STORM trial and TA970 (2.07 months). The EAG have provided a scenario which estimates TTD independently from the PFS curve by assuming an exponential distribution based on the median TTD observed within STORM (EAG report page 80, TA970).

In terms of cost, the company have also included the treatment acquisition and administration costs for SEL+DEX based upon the assumption of 160mg of Selinexor and 40mg of dexamethasone per week. Given this is an oral therapy, an initial unit cost of oral chemotherapy has been applied to the first treatment cycle and assumed zero thereafter. A Relative Dose Intensity (RDI) of 90% has also been applied, based upon the average across three studies: MAMMOTH(94.44%), LocoMMotion(93.35%) and COTA (83.67%). Other costs within the model such as adverse events, monitoring and subsequent treatment remain equivalent to the comparison of Elranatamab with POM+DEX.

The RDI used within the model for SEL+DEX is higher than that used in TA970, where it was assumed that, on average, patients would receive 120mg per week (or 114.4mg rounded to the nearest 20mg tablet). The EAG have conducted a scenario to explore the impact of this.

With respect to subsequent treatment, the EAG believe it may be more suitable to reduce the proportion who move onto any subsequent treatment, and change the distribution so that only cyclophosphamide is considered relevant. This matches the assumption used in TA970 (Selinexor with dexamethasone for treating relapsed or refractory multiple myeloma after 4 or more treatments).

Table 1 below presents the impact of corrections to the company's submitted SEL+DEX cost-effectiveness comparison, included correction of minor bugs described in the EAG critique of the company's PANO+BORT+DEX comparison.

Table 2 presents the results of the further scenarios conducted by the EAG to address the uncertainties identified in the above critique.

Table 1 EAG corrected company base case against SEL+DEX

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (£/QALY)	% change from base case
Elranatamab	[redacted]	[redacted]				
SEL+DEX	[redacted]	[redacted]	[redacted]	[redacted]	Dominant*	NA
EAG Corrections (applied independently)						
Company base			[redacted]	[redacted]	Dominant	0.00%
1. Correction of SEL+DEX OS curves			[redacted]	[redacted]	Dominant	1.25%
2. Subsequent treatment distribution for SEL+DEX switched from Elranatamab to SEL+DEX			[redacted]	[redacted]	£5,945	272.02%
3. Assume only 1 3.5mg Bortezomib vials are used for subsequent treatment			[redacted]	[redacted]	Dominant	0.03%
EAG company corrected base case– [redacted] IVIG			[redacted]	[redacted]	£4,112	218.98%
EAG company corrected base case – 43.1% IVIG			[redacted]	[redacted]	£6,098	276.43%
**Company base case assumes 43.1% IVIG use*						

Table 3 EAG cost-effectiveness scenarios of EAG corrected company base case against SEL+DEX – 43.01% IVIG

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER incremental (£/QALY)	% change from base case
Elranatamab	[redacted]	[redacted]				
SEL+DEX	[redacted]	[redacted]	[redacted]	[redacted]	£6,098	NA
1. Retention of MM-003 adjusted Elranatamab PFS and OS curves			[redacted]	[redacted]	£13,919	128.28%
2. Assume 120mg Selinexor per week rather than 160mg per week with 90% RDI			[redacted]	[redacted]	£12,638	107.25%
3. Replace all subsequent treatment with cyclophosphamide, and reduce proportion to 20%			[redacted]	[redacted]	Dominant	-109.90%
4. Reduce subsequent treatment duration to mean Time-on-Treatment for POM+DEX (4.8 months)			[redacted]	[redacted]	£3,441	-43.58%
5. Naïve comparison of SEL+DEX utilising log-normal for OS and PFS			[redacted]	[redacted]	£6,098	0.01%
6. Elranatamab OS and PFS via MAIC hazard ratio applied to SEL+DEX OS and PFS log-normal reference curves			[redacted]	[redacted]	£1,666	-73%
7. Time-on-Treatment for SEL+DEX based on exponential distribution on median time on treatment within (2.07 months) rather than PFS:TTD ratio within MM-003 for POM+DEX.			[redacted]	[redacted]	£16,666	173.33%
1+3+4+7			[redacted]	[redacted]	£11,624	91%
1+3+4+5+7			[redacted]	[redacted]	£11,462	88%
EAG preferred 3+4+6			[redacted]	[redacted]	Dominant	-233%
EAG scenario 3+4+6+7			[redacted]	[redacted]	£463	-92%

ICER, Incremental cost effectiveness ratio; MAIC, matching adjusted indirect comparison; PANO, panobinostat; QALY, quality adjusted life year.