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

Part 1 for public - redacted

Technology appraisal committee B 09 October 2024

Chair: Charles Crawley

External assessment group: Aberdeen Health Technology Assessment Group

Technical team: Madiha Adam, Anna Willis, Jo Richardson, Rich Diaz

Company: Pfizer

Timeline of ACM1 draft guidance decisions – optimised

Elranatamab recommendation: 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***

Teclistamab recommendation: Teclistamab is recommended 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. It is ***only recommended if: pomalidomide plus dexamethasone would otherwise be offered***

Figure 1: Timeline showing key dates in appraisals for elranatamab and teclistamab.

14 March Elranatamab ACM1

4 June Teclistamab ACM1

11 July Elranatamab FDG withdrawn

12 July Elranatamab DG published

16 July Teclistamab DG published

3 Sept Teclistamab ACM2

9 Oct Elranatamab ACM2

Abbreviations: ACM, appraisal committee meeting; DG, draft guidance; FDG, final draft guidance.

Elranatamab draft guidance – treatment pathway, comparators and positioning

RECAP

Draft guidance, paragraph 3.3:

- The company only compared with POM+DEX, which is used 4L – the CDF clinical lead suggested that because of this, elranatamab could only be considered at 4L or later
- The committee agreed that the comparison with POM+DEX alone, meant that the cost-effectiveness of elranatamab in the 3L setting was unknown
- Clinical experts were not concerned about elranatamab only being recommended as a 4L treatment, as people eligible earlier in the pathway would still be able to access elranatamab by using other treatments to bridge the gap between 3L and 4L
- The committee concluded that it would evaluate elranatamab after at least 3 lines of treatment in people whose condition was refractory to the last line of treatment. Previous treatments should have included a proteasome inhibitor, an immunomodulatory drug and an anti-CD38 monoclonal antibody. It added that elranatamab should be used only if POM+DEX would otherwise have been considered.

Abbreviations: 3L, third line; 4L fourth line; POM+DEX, pomalidomide plus dexamethasone.

Consultation comments

Received from:

- One patient organisation:
  - Myeloma UK

- Two other stakeholders:
  - Johnson & Johnson Innovative Medicine
  - Bristol Myers Squibb* (BMS)

- Company (Pfizer)

See Appendix: Patient organisation consultation response
See Appendix: J&J consultation response
See Appendix: Company consultation response

***Note**: BMS raised potential minor factual inaccuracies only – not summarised on the slides but will be addressed by the NICE technical team.

Company response overview

Draft guidance recommendation wording:

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.

Company response:

- Company argued that treatment line restriction should be removed:
  - wording should be after "3 or more treatments" rather than "after 3 or more lines of treatment"
- Company argued that POM+DEX restriction should be removed
- Company provided additional unanchored matching adjusted indirect comparisons (MAICs) against PANO+BORT+DEX and SEL+DEX to support removal of restrictions
- All additional comparisons show that elranatamab is cost-effective

NICE

Abbreviations: PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; POM+DEX, pomalidomide plus dexamethasone; SEL+DEX, selinexor plus dexamethasone.

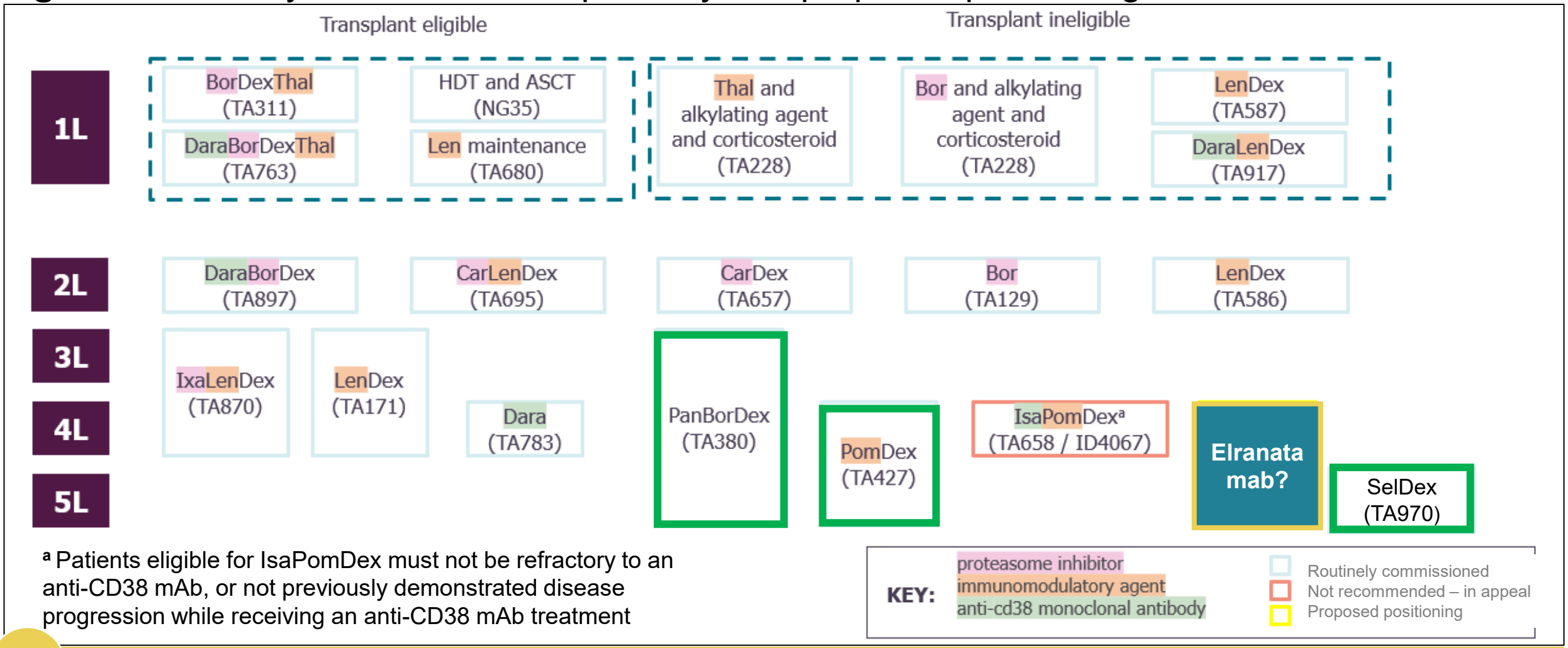
Key issues

Issue	Description	ICER impact
1) Positioning of elranatamab in the treatment pathway	a) Removal of treatment line restriction	Unknown
	b) Removal of POM+DEX restriction	
2) PANO + BORT + DEX – shared in committee papers 04/10	a) Unanchored matching adjusted indirect comparison (MAIC)	Unknown
	b) Subsequent treatments	Small/ moderate
	c) Survival modelling, elranatamab	Small/ moderate
3) SEL+DEX – shared in committee papers 08/10	a) Unanchored matching adjusted indirect comparison (MAIC)	Small
	b) Subsequent treatments and duration	Small/ moderate

Abbreviations: ICER, incremental cost-effectiveness ratio; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone; SEL+DEX, selinexor plus dexamethasone.

Key issue 1: Positioning of elranatamab in the treatment pathway

Figure 1: NHS myeloma treatment pathway and proposed positioning of elranatamab



[a] Patients eligible for IsaPomDex must not be refractory to an anti-CD38 mAb, or not previously demonstrated disease progression while receiving an anti-CD38 mAb treatment

Where are the company positioning elranatamab in the treatment pathway?

Abbreviations: ASCT, autologous stem cell transplantation; Bor, bortezomib; Car, carfilzomib; Dara, daratumumab; Dex, dexamethasone; Isa, isatuximab; Ixa, ixazomib; Len, lenalidomide; mAb, monoclonal antibody; Pan, panobinostat; Pom, pomalidomide; Sel, Selinexor; TA, technology appraisal; Thal, thalidomide.

Key issue 1a: Positioning of elranatamab in the treatment pathway- removal of treatment line restriction

Background:

- Wording in draft guidance recommendation for elranatamab - after 3 or more lines of treatment
- Wording in draft guidance recommendation for teclistamab – after 3 or more treatments

Company:

- Restricting treatment to later lines denies patients access to elranatamab earlier in the pathway, where triple class exposure occurs earlier.
- Restriction on elranatamab is inconsistent with the draft guidance for teclistamab, which does not impose the same restriction despite similar positioning and decision problem approaches.

EAG comments:

- Original submission did not provide a clinical or economic comparison for earlier-line treatments, though new analyses against PANO+BORT+DEX may be relevant.
- EAG suggests aligning the guidance for both drugs, supported by evidence that elranatamab may have more favourable outcomes than teclistamab.

Abbreviations: EAG, evidence assessment group; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone.

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Key issue 1b: Positioning of elranatamab in the treatment pathway and removal of POM+DEX restriction (1)

Company and other stakeholders

- Elranatamab shows efficacy in both pomalidomide-exposed and pomalidomide-naïve populations, making it inappropriate to restrict access based on POM+DEX eligibility
- POM+DEX is the most appropriate comparator for the triple class exposed population, aligning with NICE guidance, as most people eligible for elranatamab would receive it
- Restricting elranatamab to people who are eligible for POM+DEX contradicts prior decisions (TA783, ID2701) where POM+DEX was the sole comparator after three treatment lines
- Limiting access threatens ongoing research and trials involving elranatamab, creating uncertainty for trial centres and participants

Abbreviations: POM+DEX, pomalidomide plus dexamethasone; TA, technology appraisal.

Key issue 1b: Positioning of elranatamab in the treatment pathway and removal of POM+DEX restriction (2)

EAG comments

- Company's additional comparisons provide some insight for people who cannot have POM+DEX but a broader cost-effectiveness analysis for other comparators is still missing
- Acknowledges POM+DEX as the main comparator but notes that a small group of people who are POM-exposed may require alternative regimens, although this population is expected to decrease over time
- POM+DEX restriction limits the economic case for elranatamab and excludes some people who could benefit from the treatment, which could impact clinical decision-making and future research
- Further clinical advice is needed on whether decisions should be based on class exposure or treatment line, as this could affect recommendations for multiple myeloma treatments

Abbreviations: EAG, evidence assessment group; POM+DEX, pomalidomide plus dexamethasone

Key issue 2a: PANO+BORT+DEX, unanchored MAIC (1)

Company

- Did an unanchored matching-adjusted indirect comparison (MAIC) based on MagnetisMM-3 (elranatamab) and PANORAMA-2 (PANO+BORT+DEX)
- Used same methodological approach as in original submission for POM+DEX
- Hazard ratios (HRs) from MAIC were applied to chosen parametric reference curves for elranatamab
- HRs were adjusted so median overall survival aligned with UK real-world evidence for panobinostat
  - Company believed that applying HRs directly produced implausible overall survival extrapolations for PANO+BORT+DEX
- Results of the unanchored MAIC are presented on the next slides

Abbreviations: PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone.

Key issue 2a: PANO+BORT+DEX, unanchored MAIC (2)

Figure 1: Kaplan–Meier of PFS for the unanchored MAIC: MagnetisMM-3 vs. PANORAMA-2

Key issue 2a: PANO+BORT+DEX, unanchored MAIC (3)

Figure 1: Kaplan–Meier curves from the naïve comparison and the unanchored MAIC of OS for MagnetisMM-3 versus PANORAMA-2

Key issue 2a: PANO+BORT+DEX, unanchored MAIC (4)

Figure 1: Elranatamab Cohort A curve compared with PANO+BORT+DEX PANORAMA-2 OS curve – adjusted for excess mortality

Key issue 2a: PANO+BORT+DEX, unanchored MAIC (5)

EAG comments

- The small effective sample size after matching indicates the weights are highly variable and the estimates might be unstable
- There is evidence of benefit of elranatamab versus PANO+BORT+DEX but magnitude of effect, and how sustained this is, is uncertain
- Agree that modelled overall survival for PANO+BORT+DEX is implausibly high when the unadjusted HR is applied
- Identified several errors in application of HRs, transition probabilities, bortezomib vial size increments and drug acquisition costs – these have now been corrected
- Some remaining issues around which subsequent treatment distributions are most appropriate for PANO+BORT+DEX and elranatamab

Is the company's MAIC versus PANO+BORT+DEX with adjustment for excess mortality suitable for decision making?

Abbreviations: EAG, evidence assessment group; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PANO+BORT+DEX, panobinostat + bortezomib + dexamethasone.

Key issue 2b: PANO+BORT+DEX, subsequent treatments

Company

- In the POM+DEX exposed setting most people having PANO+BORT+DEX would have subsequent treatment with SEL+DEX

EAG comments

- People having elranatamab may also have subsequent treatment with SEL+DEX

Table 1: Company and EAG preferred subsequent treatment distributions in POM exposed

Subsequent treatment	Company preferred (3b*)		EAG preferred (3e*)	
	Elran.	PANO+BORT+DEX	Elran.	PANO+BORT+DEX
POM + DEX	90%	0%	0%	0%
PANO+BORT+DEX	8%	0%	8%	0%
CYCLO+DEX	2%	30%	28%	30%
SEL+DEX	0%	70%	64%	70%

***Note:** Numbering of scenarios corresponds to numbering in EAG critique document

Which subsequent treatment distributions are most appropriate for elranatamab and PANO+BORT+DEX?

Key issue 2c: PANO+BORT+DEX, survival modelling elranatmab (1)

Company

- Used parametric curves fitted to **unadjusted** MagnetisMM-3 cohort A data for elranatamab in the comparison with PANO+BORT+DEX
- Stated that the [MAIC] adjustment to the elranatamab curves is specific to the comparison with POM+DEX, based on data from MM-003
- Added that there is no specific 'adjusted' data for the PANO+BORT+DEX comparison
- Therefore, the comparison should be made using the unadjusted elranatamab data

EAG comments

- The MM-003 adjusted curves were presented for scrutiny at the first committee meeting and accepted as providing reasonable expectations for elranatamab in this indication
- Unadjusted cohort A extrapolations have not been scrutinised by committee in same way
- The company's OS extrapolation, in particular, is substantially more optimistic
- The plausibility of this should be considered in the context of the new comparison against PANO+BORT+DEX
- **Note:** The company and EAG OS approaches are shown on the next slide

Abbreviations: EAG, evidence assessment group; MAIC, matching-adjusted indirect comparison; OS, overall survival; PANO+BORT+DEX, panobinostat plus bortezomib plus dexamethasone.

Key issue 2c: PANO+BORT+DEX, survival modelling elranatamab (2)

Figure 1: Comparison of elranatamab MM-003 adjusted and unadjusted OS curves (provided by the EAG on request)

Should the unadjusted or MM-003 adjusted PFS and OS curves be used for elranatamab?

Abbreviations: EAG, evidence assessment group; OS, overall survival; PFS, progression-free survival.

Key issue 3a: SEL+DEX, unanchored MAIC (1)

Company

- Did an unanchored MAIC based on MagnetisMM-3 (elranatamab) and STORM (SEL+DEX)
- Used same methodological approach as in original submission for POM+DEX
- MagnetisMM-3 (Cohort A) data were weighted to match STORM
- This was then used to perform the unanchored MAIC, to estimate the adjusted HRs
- In the model, the company apply the hazard ratio (or parameter 'treatment effects') from the MAIC, to the MagnetisMM-3 unadjusted cohort A curves.

EAG comments

- Company's [modelling] approach is convoluted and somewhat inconsistent
- Would have been more intuitive to compare the treatments based on the curves fitted to the STORM-weighted MagnetisMM-3 Kaplan-Meier data, and the curves fitted to the digitised STORM data
- Furthermore, through utilising the POM+DEX arm of the original model, several other aspects of the comparison remain unchanged (such as time on treatment, AEs and subsequent treatment assumptions)

Abbreviations: AEs, adverse events; EAG, evidence assessment group; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; POM+DEX, pomalidomide+dexamethasone; SEL+DEX, selinexor plus dexamethasone.

Key issue 3a: SEL+DEX, unanchored MAIC (2)

Table 1: Company and EAG base case assumptions for comparison with SEL+DEX

Assumption	Company base case	EAG base case
Subs tx. proportions SEL+DEX	Same as POM+DEX	3*. Replace all subs tx. with cyclophosphamide, and reduce proportion to 20% (in line with TA970)
Subs tx. duration SEL+DEX	Not reported	4*. Reduce subsequent treatment duration to mean time-on-treatment for POM+DEX (4.8 months)
Survival modelling	MAIC HR or adjusted parameter treatment effect applied to unadjusted MagnetisMM-3 cohort A curves	6*. MAIC HR applied to SEL+DEX OS and PFS log-normal reference curves

***Note:** Numbers correspond to numbering in EAG critique document

Is the company's MAIC versus SEL+DEX suitable for decision making? Does the committee agree with the EAG's alternative approach to survival modelling in the comparison with SEL+DEX?

Abbreviations: HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; POM+DEX, pomalidomide+dexamethasone; SEL+DEX, selinexor plus dexamethasone; subs tx, subsequent treatment; TA, technology appraisal.

Key issue 3b: SEL+DEX, subsequent treatments

Table 1: Company and EAG base case assumptions for comparison with SEL+DEX

Assumption	Company base case	EAG base case
Subs tx. proportions SEL+DEX	Same as POM+DEX	3*. Replace all subs tx. with cyclophosphamide, and reduce proportion to 20% (in line with TA970)
Subs tx. duration SEL+DEX	Not reported	4*. Reduce subsequent treatment duration to mean time-on-treatment for POM+DEX (4.8 months)
Survival modelling	MAIC HR or adjusted parameter treatment effect applied to unadjusted MagnetisMM-3 cohort A curves	6*. MAIC HR applied to SEL+DEX OS and PFS log-normal reference curves

Does the committee agree with the EAG's alternative approach to modelling subsequent treatments for SEL+DEX?

See appendix for additional scenarios presented by the EAG

Abbreviations: HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; POM+DEX, pomalidomide+dexamethasone; SEL+DEX, selinexor plus dexamethasone; subs tx, subsequent treatment; TA, technology appraisal.

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

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Equality considerations

No new potential equality considerations raised in response to the draft guidance consultation