Elranatamab for treating relapsed or refractory multiple myeloma after 3 therapies

Part 1 for public - redacted

Technology appraisal committee B [14 March 2024]

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Company: Pfizer

Elranatamab for treating relapsed or refractory multiple myeloma after 3 therapies

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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See appendix: Background on multiple myeloma
See appendix: Clinical perspectives

Patient and carer perspectives

Submission from Myeloma UK:

- Complications of myeloma can be significant, debilitating and painful, and have a substantial impact on quality of life
- The relapsing-remitting nature of myeloma has a huge psychological impact, as people are aware that treatment options and life expectancy reduce with each relapse
- Caring for someone with myeloma is extremely physically and emotionally challenging – many carers mention changes in their social life, relationships, income, and wider family dynamics
- There is an unmet need for innovative treatments which deliver deep, durable responses for people with multiply relapsed/refractory myeloma
- Elranatamab has a new mechanism of action and therefore has the potential to overcome treatment resistance and fulfil this unmet need
- Weekly, bi-weekly and eventually monthly subcutaneous injection without combination with steroids is a distinct advantage of this treatment

"Myeloma has had a major impact on my quality of life. No day is the same as you can wake up and find you are in chronic pain and unable to do anything for yourself and have to rely on your carers which has a really negative effect on your mental health."

"There is a constant pressure of wondering what's going to happen… every month there's the possibility of relapse and it's hard to ignore that. It's a massive relief when I'm told that my paraproteins haven't risen."

"The further you get along people write you off. They think the drugs are unlikely to work or they are not going to work as well… I want a chance to carry on living this life."

Elranatamab (Elrexfio, Pfizer)

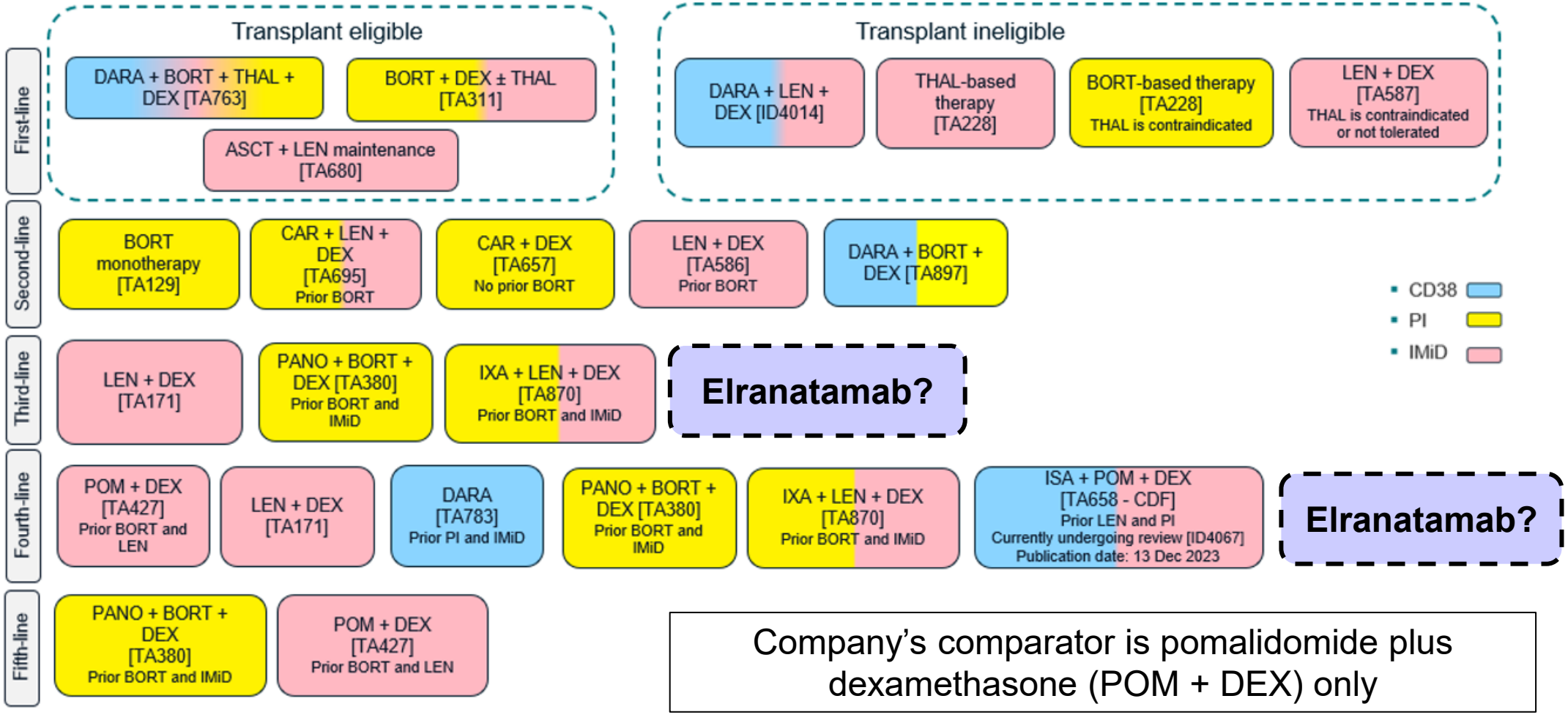
Marketing authorisation	• Elranatamab received a UK marketing authorisation from the MHRA on 04 January 24: • *"As monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy."*
Mechanism of action	• Bispecific monoclonal antibody that binds to B-cell maturation antigen (BCMA) on plasma cells, plasmablasts, and multiple myeloma cells and to the CD3 receptor on T-cells, leading to cytolysis of the BCMA-expressing cells.
Administration	• Subcutaneous injection • 12 mg on day 1, 32 mg on day 4, then 76 mg weekly from week 2 to week 24 • People who have received at least 24 weeks of treatment and have a response should transition to an every-2-week schedule • Patients should be monitored for 48 hours after administration of each of the 2 step-up doses and instructed to remain within proximity of a healthcare facility
Price	• The list price for elranatamab is £4,243 (76mg vial) and £2,456 (44mg vial) • Company has a confidential PAS discount in place.

Abbreviations: MHRA, Medicines and Healthcare Products Regulatory Agency; PAS, patient access scheme; SmPC, summary of product characteristics.

See appendix: Decision problem

Treatment pathway

Figure 1: NICE-approved treatments for multiple myeloma (company submission, Figure 2), with the potential positioning of elranatamab added



Abbreviations: ASCT, autologous stem cell transplant; BORT, bortezomib; CAR, Carfilzomib; CDF, Cancer Drugs Fund; DARA, daratumumab; DEX, dexamethasone; IMiD, immunomodulatory drug; ISA, isatuximab; IXA, ixazomib; LEN, lenalidomide; PANO, panobinostat; PI, proteasome inhibitor; POM, pomalidomide; THAL, thalidomide.

Key issues

#	Issue	Resolved?	ICER impact
Clinical-effectiveness			
1	Heterogeneity in the proposed population	No	Unknown
2	Immaturity of survival data	No	Unknown
Cost-effectiveness			
3	Extrapolation of progression-free survival (PFS) and overall survival (OS) for elranatamab	No	Large
4	Time-to-treatment-discontinuation (TTD) for POM+DEX	No	Large
5	Relative dose intensity (RDI) for elranatamab	No	Large
6	Stopping rule for elranatamab	No	Large

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Abbreviations: ICER, incremental cost-effectiveness ratio; POM + DEX, pomalidomide plus dexamethasone.

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Clinical trial results

MagnetisMM-3 (elranatamab) and MM-003 (POM + DEX)

	MagnetisMM-3 cohort A (n = 123)	MM-003 (n = 455)
Objective response rate (ORR)	Based on interim analysis (n = [redacted]): 61.0% (95% CI: 51.8, 69.6)	31.0%
Median overall survival (OS)	At 15 months: Not reached (95% CI: 13.9, NE) OS at 12 months: ~62%	11.9 months (95% CI: 10.4, 15.5)
Median progression-free survival (PFS)	At 15 months: Not reached (95% CI: 9.9, NE) PFS at 12 months: ~57%	4.0 months (95% CI: 3.6, 4.7)

Real-world evidence:

- **Company** – also present data from an external control arm study (n=[redacted]) that was conducted by the company using real-world data collected from the Arcturis UK dataset which includes over 5,500 people with multiple myeloma from 4 NHS centres
- **Lead team** – has identified a further, recently published, real-world study by Costa et al. which compared elranatamab efficacy in MagnetisMM-3 with real-world control arms in the US

Abbreviations: CI, confidence interval; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; POM + DEX, pomalidomide plus dexamethasone.

See appendix: Key clinical trials - overview

Clinical trial / MAIC results – PFS

Unanchored matching-adjusted indirect comparisons (MAICs) were used to indirectly compare the treatment effect of elranatamab from MagnetisMM-3 to POM+DEX from MM-003

Figure 1: Kaplan–Meier of PFS MagnetisMM-3 versus MM-003

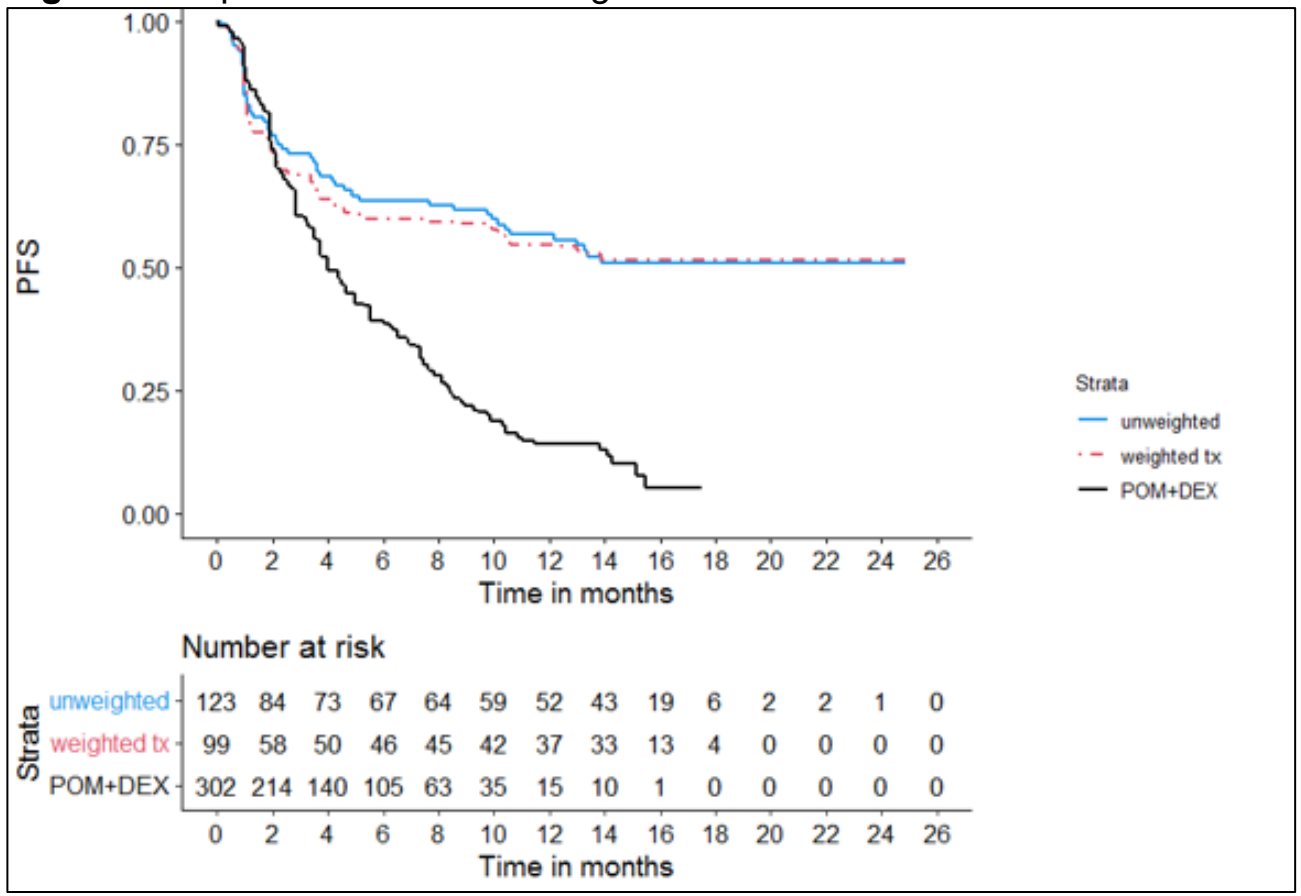


Table 1: Naïve and unanchored MAIC hazard ratios for PFS

Outcome and analysis	Hazard ratio (95% CI)
PFS – naïve comparison	0.359 (0.263, 0.490)
PFS – unanchored MAIC	0.386 (0.253, 0.589)

Blue line = elranatamab naïve comparison

Red dashed line = elranatamab unanchored MAIC

Notes: Median follow-up in MagnetisMM-3, 15 months (data cut-off: 14 March 2023); median follow-up in MM-003, 10 months.
Abbreviations: CI, confidence interval; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; POM + DEX, pomalidomide plus dexamethasone.

Clinical trial / MAIC results – OS

Figure 1: Kaplan–Meier of OS MagnetisMM-3 versus MM-003

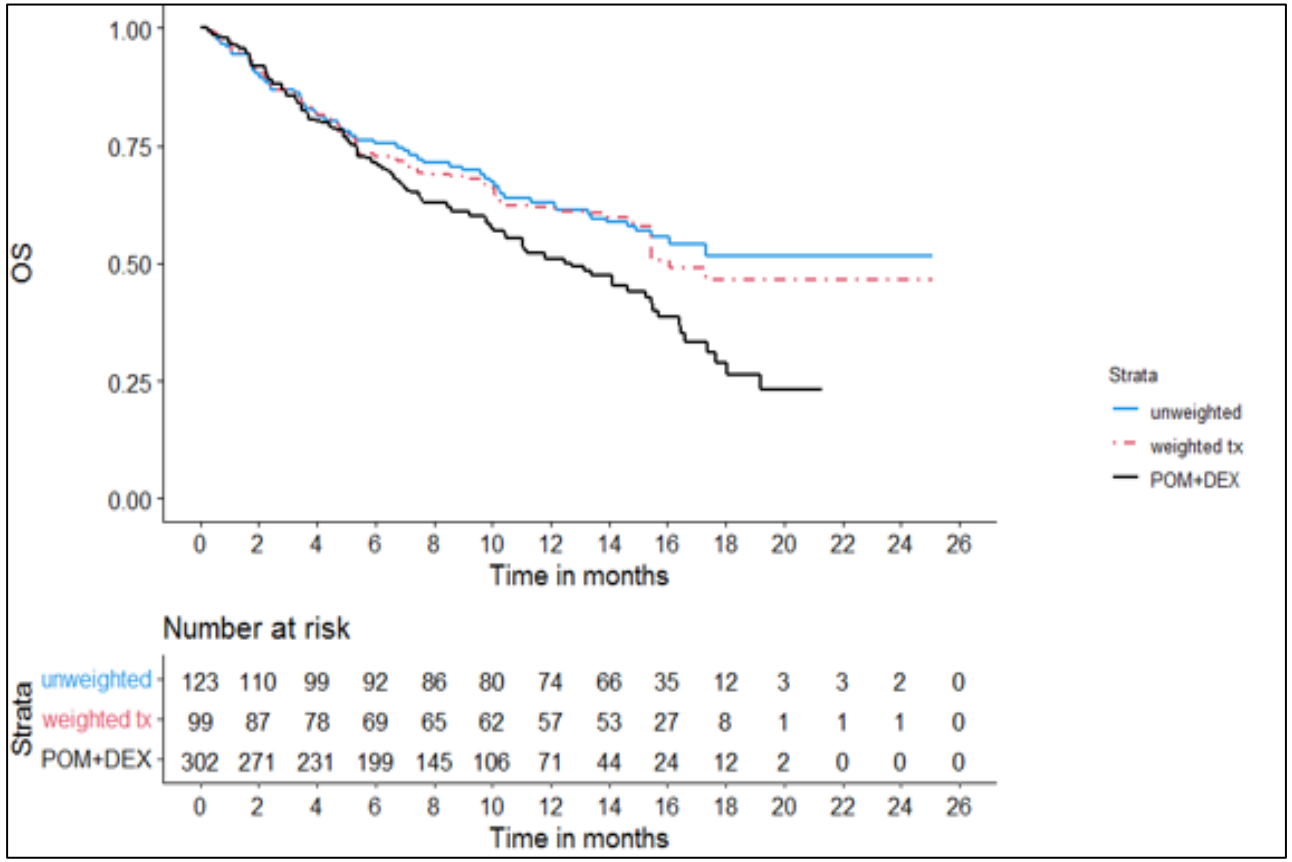


Table 1: Naïve and unanchored MAIC hazard ratios for OS

Outcome and analysis	Hazard ratio (95% CI)
OS – naïve comparison	0.655 (0.477, 0.900)
OS – unanchored MAIC	0.705 (0.494, 1.007)

Blue line = elranatamab naïve comparison

Red dashed line = elranatamab unanchored MAIC

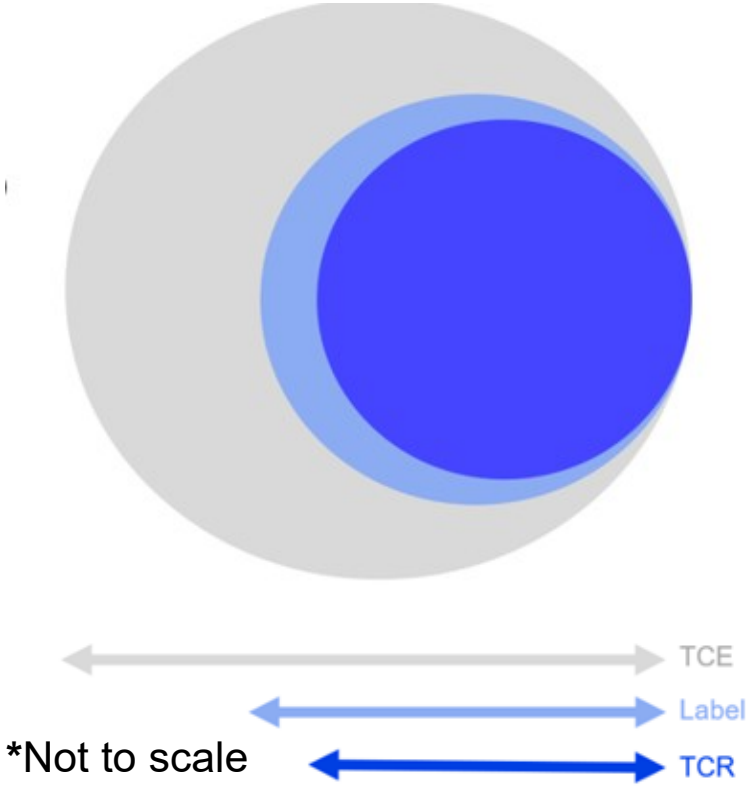
Notes: Median follow-up in MagnetisMM-3, 15 months (data cut-off: 14 March 2023); median follow-up in MM-003, 10 months.
Abbreviations: CI, confidence interval; MAIC, matching-adjusted indirect comparison; OS, overall survival; POM + DEX, pomalidomide plus dexamethasone.

Key issue 1: Heterogeneity in the proposed population (1/3)

Company

- Positioning of elranatamab is in line with the marketing authorisation (label):
  - *"Adults 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**"*
- Acknowledges that the population of the MagnetisMM-3 trial was narrower than the marketing authorisation as the trial only included people who were refractory to all 3 treatments (that is, triple class refractory [TCR])
- Proposed positioning will include some patients who are triple class exposed (TCE) but not TCR
- Clinical expert feedback suggests all people will be TCE by their 4L, with up to 85% of these being TCR, but difficult to determine exact proportion

Figure 1: Relative sizes of TCE, label and TCR cohorts in the UK*



Notes:

- TCE = received at least 3 prior therapies (drug classes) including an IMiD, a PI and an anti-CD38
- Label = TCE with 3 prior therapies and have progressed on last therapy (i.e. they could be refractory to 1, 2 or all 3 classes)
- TCR = TCE and refractory to all 3 classes

Abbreviations: IMiD, immunomodulatory drug; mAb, monoclonal antibody; PI, proteasome inhibitor; TCE, triple class exposed; TCR, triple class refractory.

See appendix: Potential routes to eligibility

Key issue 1: Heterogeneity in the proposed population (2/3)

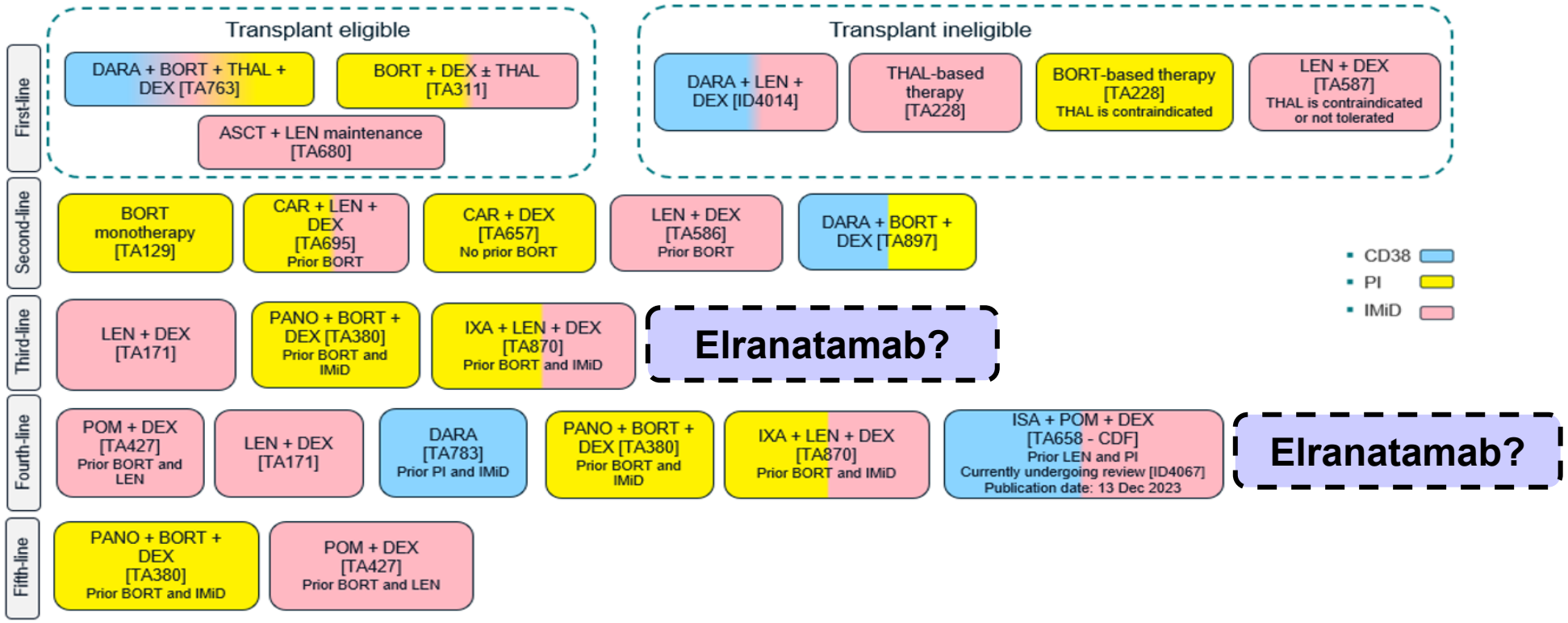
EAG comments

- Concerned that the company's proposed positioning may result in a heterogenous group of patients at different lines of treatment being considered eligible for elranatamab
- A small group of people eligible for treatment according to the marketing authorisation are likely to be refractory to 1 or 2, rather than 3, classes of treatment and become eligible in earlier lines than 4L
- It is unclear exactly what proportion of people this might apply to or what their alternative treatment options might be
- However, the EAG's clinical advisor suggested that people who are TCE would have similarly limited treatment options available to them as those who are TCR
- This is because there would be reluctance to rechallenge with treatments that may have been stopped due to toxicity

Abbreviations: EAG, External Assessment Group; TCE, triple class exposed; TCR, triple class refractory.

Key issue 1: Heterogeneity in the proposed population (3/3)

Figure 1: NICE-approved treatments for multiple myeloma (company submission, Figure 2), with the potential positioning of elranatamab added



If recommended, where would elranatamab fit into the treatment pathway?
Which of the classes of drugs would be reused if a patient is exposed but not refractory?
What is/are the most appropriate comparator(s)?
Is the trial data generalisable to patients in NHS expected to receive elranatamab?

Key: ASCT, autologous stem cell transplant; BORT, bortezomib; CAR, Carfilzomib; CDF, Cancer Drugs Fund; DARA, daratumumab; DEX, dexamethasone; IMiD, immunomodulatory drug; ISA, isatuximab; IXA, ixazomib; LEN, lenalidomide; PANO, panobinostat; PI, proteasome inhibitor; POM, pomalidomide; THAL, thalidomide.

Key issue 2: Immaturity of survival data

EAG comments

- As of the 14 March 2023 data cut of MagnetisMM-3, median PFS and OS had not been reached
- There is heavy censoring in the Kaplan-Meier curves at around 15 months, making the shape of the distributions and longer-term extrapolations highly uncertain
- This issue cannot be resolved without extended follow-up of people treated with elranatamab
- The company refer to a new data cut being available in November 2023, but longer-term follow-up is likely to be required to substantially reduce the current uncertainties.

Company

- Acknowledges the uncertainty around the OS, PFS and time-to-treatment-discontinuation (TTD) projections
  - The estimated completion date for MagnetisMM-3 is December 2025
  - Evidence from MM-15 (extension of MM-3), MM-16 (real-world-study) and the systemic anticancer therapy (SACT) dataset will be available within the next 5 years

Abbreviations: EAG, External Assessment Group; OS, overall survival; PFS, progression-free survival; TTD, time-to-treatment-discontinuation.

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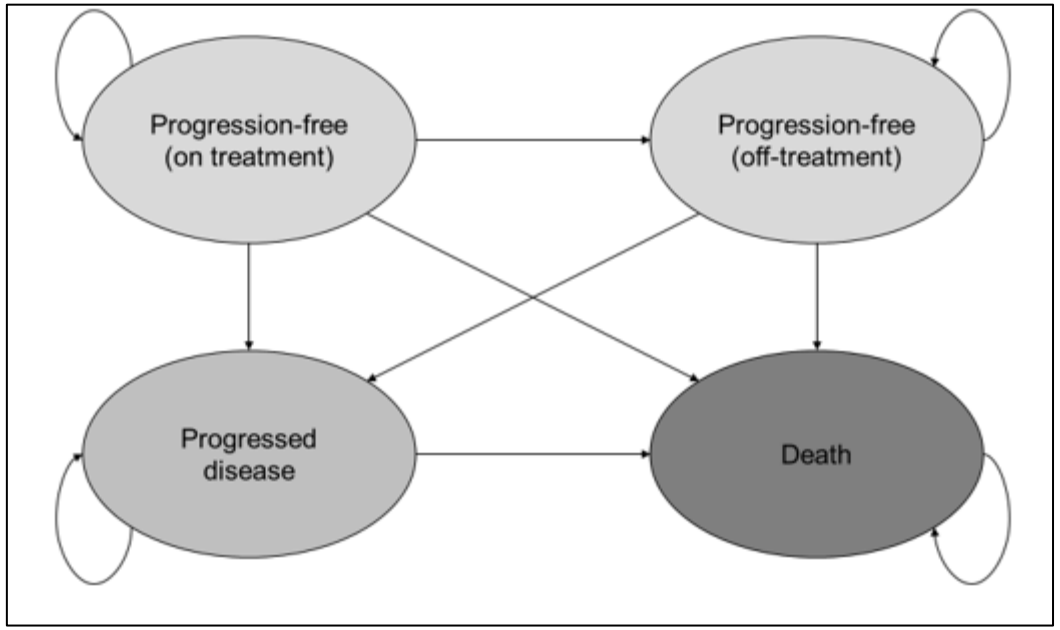
Company's model – overview

- Partitioned survival model with four health states:
  - Progression free on treatment
  - Progression free off treatment
  - Progressed disease
  - Death
- State occupancy informed by trial OS, PFS and TTD

Figure 1: Company's model structure



Elranatamab affects QALYs by:

- Increasing survival
- Prolonging time spent progression-free
- Having a different adverse event profile

Elranatamab affects costs by:

- Having different acquisition and administration costs
- Increasing health care resource use by increasing survival
- Reducing subsequent treatment costs
- Increasing adverse event costs

Table 1: Company's model features

Model features:
Time horizon: 25 years (lifetime)
Cycle length: 1 week

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Abbreviations: OS, overall survival; PFS, progression-free; QALY, quality-adjusted life year; survival; TTD, time-to-treatment-discontinuation.

See appendix: Model inputs and evidence sources

Key issue 3: Extrapolation of PFS and OS elranatamab

Company's parametric fits of PFS and OS

Company

- Base case uses MAIC weighted KM data from MagnetisMM-3 for elranatamab and digitised KM data from MM-003 for POM + DEX (not shown here)
- Individual parametric curves were fit as proportional hazards assumption rejected

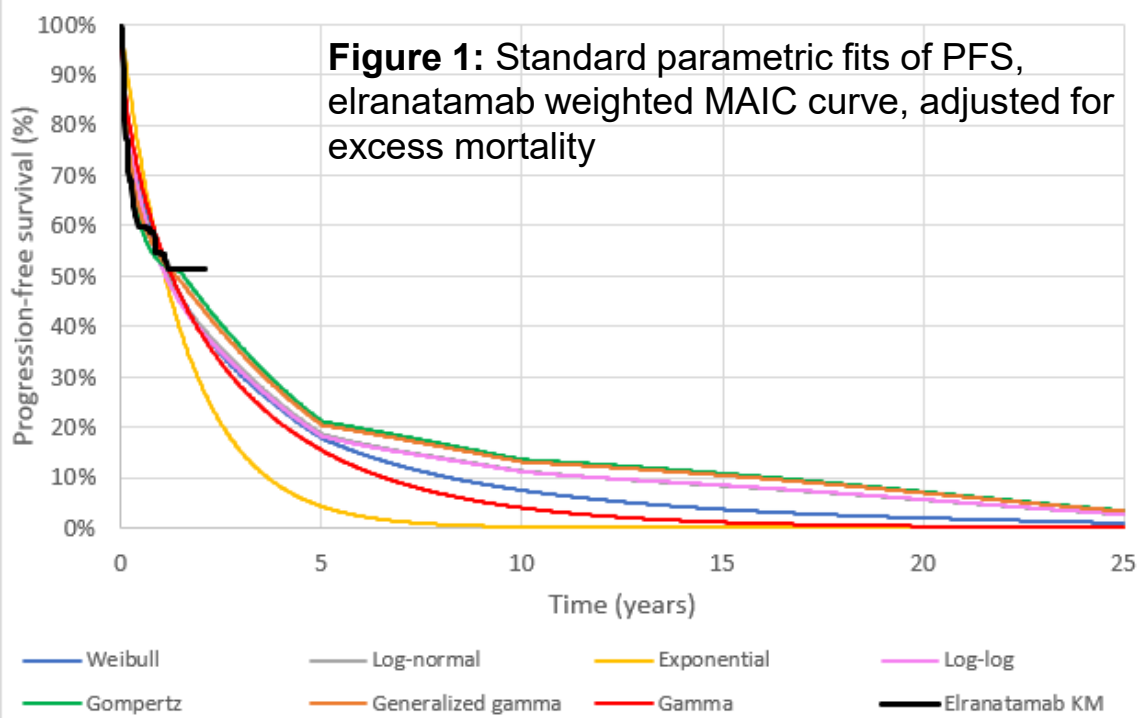


Figure 1: Standard parametric fits of PFS, elranatamab weighted MAIC curve, adjusted for excess mortality

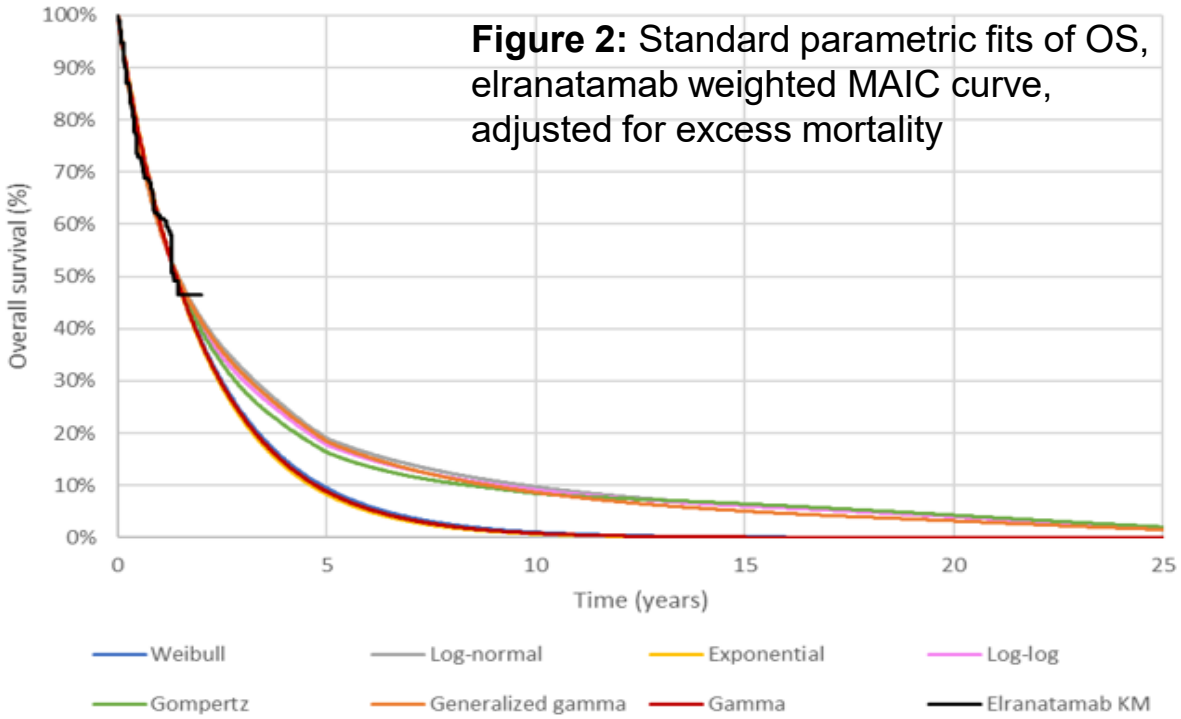


Figure 2: Standard parametric fits of OS, elranatamab weighted MAIC curve, adjusted for excess mortality

Notes: Curves based on MAIC weighted KM data presented here, however company selected curves based on unweighted data. OS curve drops below 50% due to MAIC weighting

Abbreviations: KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival.

See appendix: Goodness-of-fit statistics and landmark survival estimates

Key issue 3: Extrapolation of PFS and OS elranatamab

Company's preferred extrapolations and rationale

Company

PFS base case → generalised gamma:
Best statistical and visual fit to **unweighted** MagnetisMM-3 KM data. After adjustment for all-cause mortality, provides 5- and 10-year projections in line with clinical expert suggestions

OS base case → generalised gamma
Best visual fit to observed KM data and hazards for **unweighted** MagnetisMM-3 KM data. Exponential, Weibull and gamma provide implausibly low projections of OS at 10 years.

Abbreviations: OS, overall survival; PFS, progression-free survival.

Key issue 3: Extrapolation of PFS and OS elranatamab

EAG's preferred extrapolations and rationale

EAG comments

- Unclear why company selected curves based on unweighted KM data when base case relies on curves fitted to MAIC weighted KM data
- Parametric curves from weighted data are broadly similar but provide slightly more pessimistic projections

PFS base case → gamma

- Plateau in tail of KM curve may be a chance occurrence due to heavy censoring and small numbers at risk
- Long-term follow up is required to confirm shape of PFS curve
- More pessimistic gamma or Weibull curves should be considered
- These provide extrapolations consistent with ranges suggested by clinical experts without requiring a post hoc adjustment for excess mortality
- EAG base case uses gamma distribution for PFS

OS base case → generalised gamma

- Exponential or lognormal curves provide a better statistical fit than generalised gamma
- To address issue of crossing OS and PFS curves, company give priority to PFS curve, which is not plausible (discussed in later slide)
- EAG's clinical advisors suggested the generalised gamma was too optimistic for OS, but alternatives were potentially too pessimistic
- Therefore, EAG base case is in line with company and uses generalised gamma, but EAG presents alternative scenario using exponential distribution

Abbreviations: EAG, External Assessment Group; KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival.

Key issue 3: Extrapolation of PFS and OS elranatamab

Consideration of the proportional hazards assumption

Company

- Fit independent parametric curves to MAIC weighted MagnetisMM-3 KM data and MM-003 KM data
- Prefer independently-fitted curves, rather than applying MAIC hazard ratio to the POM + DEX reference curves, as proportional hazards assumption was rejected

EAG comments

- EAG base case also uses independently fitted curves
- However, data are immature – benefit may be overestimated
- Provides more conservative scenarios using the MAIC hazard ratios (shown later in slides)

Which parametric curves are most appropriate to model OS and PFS?
Should independent curves be used or should the MAIC hazard ratio be applied?

Abbreviations: EAG, External Assessment Group; KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; POM + DEX, pomalidomide plus dexamethasone.

Key issue 3: Extrapolation of PFS and OS

Standardised mortality ratio (SMR) adjustment

Company

- Adjusted PFS and OS curves for excess mortality
- This was done by applying time-varying standardised mortality ratios (SMRs) to general population mortality data and ensuring extrapolated hazards do not fall below this
- SMRs were derived from Giri et al. 2021 for people who had survived to two years following autologous peripheral blood stem cell transplantation (see appendix: Giri et al. for further details)
  - Overall SMR: 5.27
  - Time-varying SMR: 15.3 in the first 5 years, 3.5 in years 6-10 and 1.0 after 10 years (equal to general population) suggesting a fraction of the elranatamab cohort would be cured

EAG comments

- The population eligible for elranatamab in clinical practice does not align with the cohort studied in Giri et al. so the SMRs may not be applicable
- Most people eligible for elranatamab will be triple class refractory
- People eligible will have progressed multiple times and may or may not have had an initial transplant
- EAG presents a scenario adjusting OS only using an SMR of 1.2 beyond 10 years, as it is questionable that a fraction of the cohort would be cured

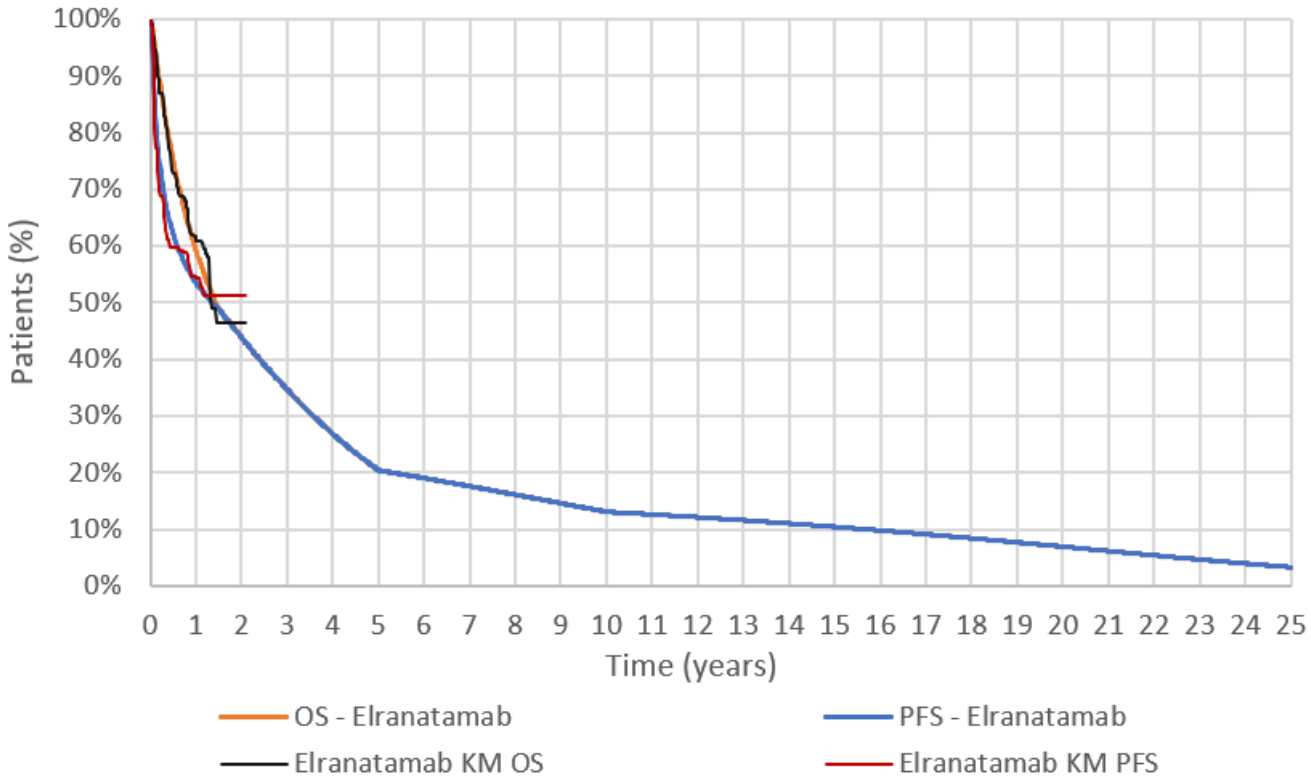
What is the committee's preferred approach to SMR adjustment?
Would a proportion of patients be cured with elranatamab?

Key issue 3: Extrapolation of PFS and OS

Company's final PFS and OS extrapolations

Company

Figure 1: Final company OS (generalised gamma) and PFS (generalised gamma) extrapolations applied in the model, adjusted for excess mortality



- Company's preferred OS and PFS curves (and MAIC weighted KM curves) cross early in the extrapolation period
- To overcome this, priority is given to excess-mortality adjusted PFS curve – allowing OS to converge with PFS which is more mature

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Abbreviations: KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival.

Key issue 3: Extrapolation of PFS and OS

EAG comments on company's final extrapolations

EAG comments

- Company's preferred approach results in one single curve being used to partition the cohort between progression-free and dead states
- Not plausible that hazards of OS and PFS should be the same and set equal to SMR-adjusted all-cause mortality from so early in the model time horizon
- This infers no progression risk and pre-progression mortality only
- This also underestimates time spent with progressive disease, subsequent treatment costs and overestimates QALY gain
- Company's extrapolated OS generalised gamma curve adjusted for excess mortality already provides an optimistic extrapolation of OS

Is the company's approach of allowing PFS to override OS appropriate?

Abbreviations: EAG, External Assessment Group; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; SMR, standardised mortality ratio.

Key issue 3: Extrapolation of PFS and OS

EAG base case and scenario analysis

Figure 1: EAG base case – elranatamab MAIC weighted PFS (gamma) and OS (generalised gamma)

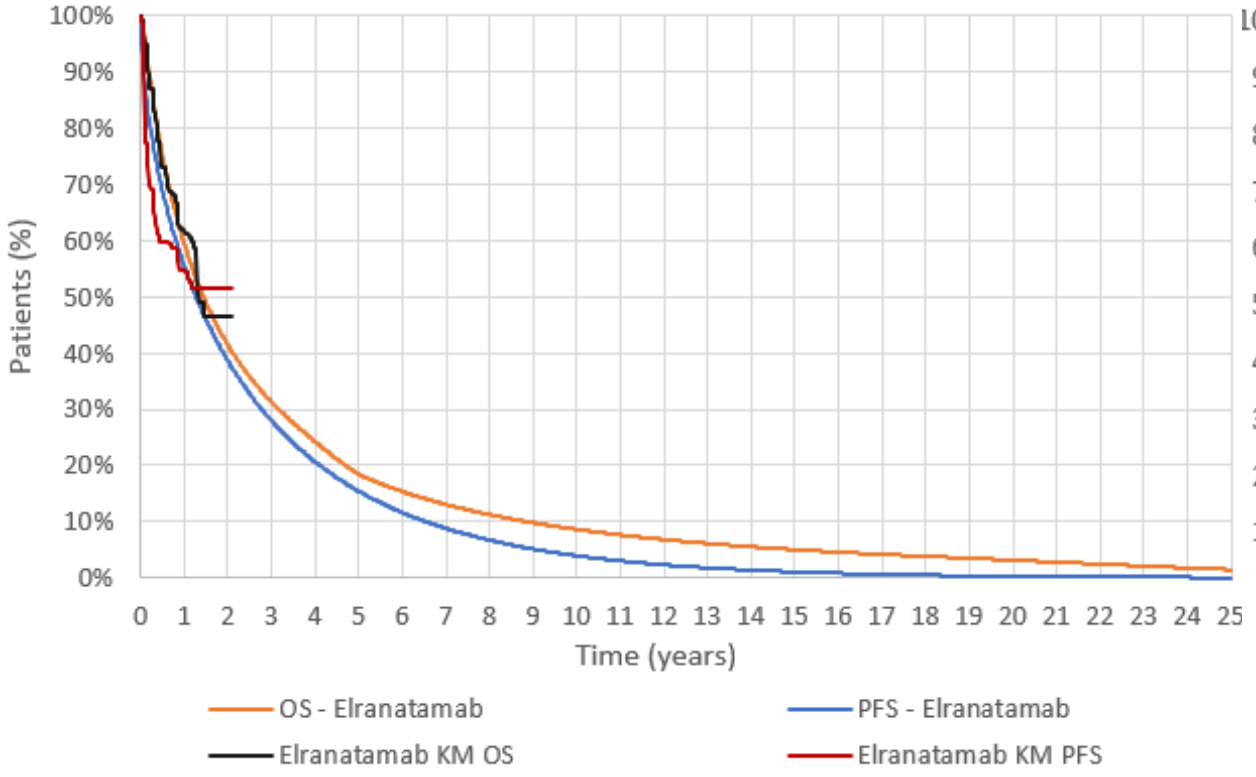
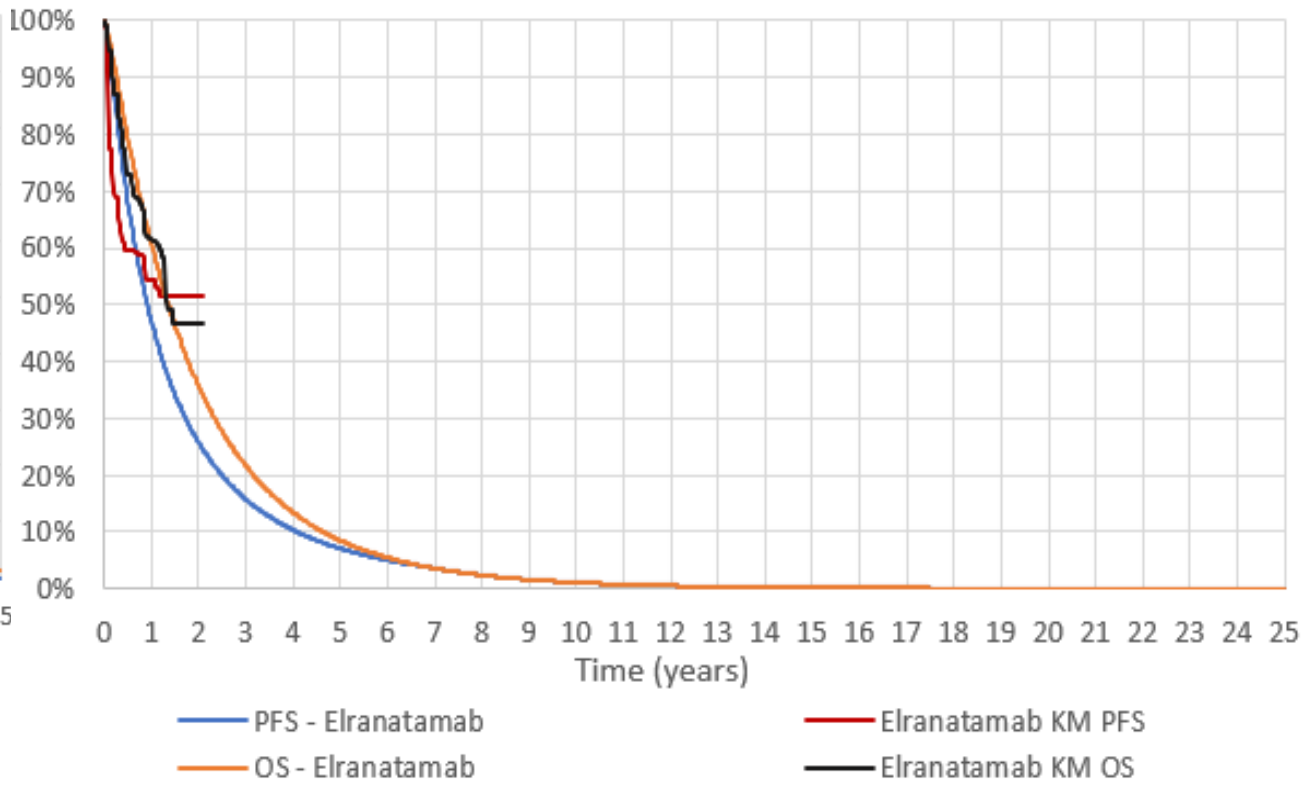


Figure 2: EAG scenario – elranatamab PFS and OS, MAIC HRs applied to POM + DEX reference curve (OS takes priority over PFS)



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Abbreviations: EAG, External Assessment Group; HR, hazard ratio; KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival.

Key issue 4: Time-to-treatment-discontinuation (TTD) for POM+DEX

Company

- Suitable KM data for time-to-treatment-discontinuation (TTD) were lacking from the MM-003 trial
- Therefore, TTD was modelled using the ratio between median TTD (4.7 months) and median PFS (4.0 months), as reported in San Miguel et al. (the MM-003 publication)
- This resulted in a multiplier of 1.18 which was applied as a hazard ratio to the POM + DEX PFS curve
- Alternative scenarios are presented including a scenario assuming TTD is equal to PFS

EAG comments

- The company's approach results in a TTD curve that lies above PFS – which is implausible
- Data underpinning company's calculation have been misinterpreted – San Miguel et al. does not report a median TTD of 4.7 months, rather, it reports a median time-to-progression (TTP) of 4.7 months
- In the appraisal for POM + DEX (TA427), TTD was estimated based on time-to-treatment-failure (TTF)
- The EAG has recalculated the hazard ratio based on the ratio of median TTF (2.9 months) to median PFS (4.0 months), resulting in a hazard ratio of 0.725 which is applied in the EAG base case
- This remains an area of uncertainty which requires further discussion

What is the most appropriate approach to modelling TTD for POM + DEX?

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Abbreviations: EAG, External Assessment Group; KM, Kaplan–Meier; PFS, progression-free survival; POM + DEX, pomalidomide plus dexamethasone; TA, technology appraisal; TTD, time-to-treatment-discontinuation; TTF, time-to-treatment-failure; TTP, time-to-progression.

Key issue 5: Relative dose intensity (RDI) for elranatamab

Company

- Apply an RDI of [redacted]% to drug and administration costs for elranatamab, based on data from MagnetisMM-3
- This is applied throughout the time horizon of the model

EAG comments

- Uncertain whether RDI observed over the follow-up period in MagnetisMM-3 would apply over the remaining time horizon
- It is unclear to what extent dose reductions captured in the RDI would translate into cost savings as vial sizes are fixed and there is no vial sharing
- Similarly, it is uncertain whether RDI should be applied to administration costs, which are a discrete unit of resource, not expected to decrease when the dose is reduced
- However, the company confirmed in response to Factual Accuracy Check that RDI is driven more by dose interruptions ([redacted]%) than dose reductions ([redacted]%) which alleviates these concerns somewhat
- EAG explores scenarios using higher RDIs of 100% from month 15 onwards, and 90% and 85% over the entire time horizon to reflect potentially limited resource savings associated with dose reductions

What RDI is expected to apply a) during the trial follow-up period b) over the remaining model time horizon?

Abbreviations: EAG, External Assessment Group; RDI, relative dose intensity.

Key issue 6: Stopping rule for elranatamab

Company

- Model TTD using the log normal distribution (**Fig. 1** in **grey**), adjusted to ensure hazard of discontinuing treatment is never below the SMR-adjusted all-cause mortality hazard
- Apply a stopping rule for elranatamab at 36 months (3 years)
- At this time point, the log normal predicts that [redacted]% would be on treatment
- Separation between PFS and TTD curves shows that people on elranatamab can achieve deep and durable responses which are maintained after stopping treatment
- Applying stopping rule balances long-term risks of remaining on treatment with ongoing efficacy

Figure 1: Standard parametric fits of TTD elranatamab compared to PFS*

Abbreviations: KM, Kaplan–Meier; PFS, progression-free survival; SMR, standardised mortality ratio; TTD, time-to-treatment-discontinuation.

Key issue 6: Stopping rule for elranatamab

EAG comments

- Concerned about validity of stopping rule given lack of long-term data
- Uncertain what impact stopping treatment might have on disease progression (or survival)
- Unclear whether stopping rule would be implemented in NHS practice
- Issue cannot be resolved without substantially longer follow-up
- Provided scenario where stopping rule is removed

Summary of product characteristics – elranatamab

- *"Treatment should be continued until disease progression or unacceptable toxicity"*

Is it reasonable to expect treatment to be stopped at 3 years?
Would efficacy continue after stopping treatment? If so, for how long?

Assumptions relating to key issues

See appendix: Other assumptions

Issue #	Assumption	Company base case	EAG base case
3	PFS extrapolation elranatamab	Generalised gamma	Gamma Scenario analysis: MAIC HR
3	OS extrapolation elranatamab	Generalised gamma	As per company Scenario analyses: exponential, MAIC HR
3	SMR	Time varied (by 10 years, SMR = 1)	As per company Scenario analysis: SMR 1.2 beyond 10 years
3	Adjustment for crossing PFS and OS	PFS takes priority	OS takes priority
4	TTD assumption POM + DEX	Ratio between TTD:PFS = 1.18	Corrected ratio between TTD:PFS = 0.725
5	RDI elranatamab	[redacted]% throughout model time horizon	As per company Scenario analyses: 90%, 85%, after 15 months –100%
6	Stopping rule	Included at 36 months	As per company Scenario analysis: excluded

Abbreviations: EAG, External Assessment Group; HR, hazard ratio; KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; POM + DEX, pomalidomide plus dexamethasone; RDI, relative dose intensity; SMR, standardised mortality ratio; TTD, time-to-treatment-discontinuation.

Cost-effectiveness results

- All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts
- When comparator PAS discounts are included, the company base case is within the £20,000-£30,000 threshold range
- The EAG base case is over £30,000.
- Scenarios presented in Part 2 will include alternative OS and PFS modelling approaches and RDI estimates

Elranatamab for treating relapsed or refractory multiple myeloma after 3 therapies

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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Other considerations

- Equality considerations
  - No issues raised at scoping stage, or by patient or professional groups
  - Company claim that reimbursing by line of treatment will create inequalities in treatment access for people who become triple class refractory at third-line or earlier

- Severity weighting
  - Company and EAG agree 1.2 weighting is appropriate

- Potential for managed access?
  - Managed access proposal submitted by company

Are there any equalities issues?
Is a severity weighting of 1.2 appropriate?

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Abbreviations: EAG, External Assessment Group; QALY, quality-adjusted life year.

See appendix: QALY weightings for severity
See appendix: Managed access

Elranatamab for treating relapsed or refractory multiple myeloma after 3 therapies

- ❑ Background and key issues
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- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Key issues and questions for committee – clinical

#	Issue
1	Heterogeneity in the proposed population • If recommended, where would elranatamab fit into the treatment pathway? • Which of the classes of drugs would be reused if a patient is exposed but not refractory? • What is/are the most appropriate comparator(s)? • Is the trial data generalisable to patients in NHS expected to receive elranatamab?
3	Extrapolation of progression-free survival (PFS) and overall survival (OS) • Which parametric curves are most appropriate to model OS and PFS? • Should independent curves be used or should the MAIC hazard ratio be applied? • What is the committee's preferred approach to SMR adjustment? • Would a proportion of patients be cured with elranatamab? • Is the company's approach of allowing PFS to override OS appropriate?

Abbreviations: MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; SMR, standardised mortality ratio.

Key issues and questions for committee – cost

#	Issue
4	Time-to-treatment-discontinuation (TTD) for POM+DEX • What is the most appropriate approach to modelling TTD for POM + DEX?
5	Relative dose intensity (RDI) for elranatamab • What RDI is expected to apply over the model time horizon?
6	Stopping rule for elranatamab • Is it reasonable to expect treatment to be stopped at 3 years? • Would efficacy continue after stopping treatment? If so, for how long?
Other	Other considerations • Are there any equalities issues? • Is a severity weighting of 1.2 appropriate?

Abbreviations: POM + DEX, pomalidomide plus dexamethasone; RDI, relative dose intensity; TTD, time-to-treatment-discontinuation.

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Supplementary appendix

Background on multiple myeloma

Causes

- Multiple myeloma (MM) is a malignancy of plasma cells in the bone marrow

Epidemiology

- Accounts for 2% of all new cancer cases and is more common in men than women
- Median age at diagnosis is around 74 years
- Approximately 6,000 new cases of MM per year in UK (incidence rate: 9.7/100,000)

Symptoms and prognosis

- Symptoms and complications include bone pain and fractures; tiredness, weakness and shortness of breath caused by anaemia; high levels of calcium in the blood (hypercalcaemia); kidney problems and repeated infections
- 5-year survival rate for people who are newly diagnosed is around 55%
- MM is considered incurable; all people will eventually progress or relapse

Clinical perspectives

Joint submission from UK Myeloma Society, Royal College of Physicians and Royal College of Pathologists

- Myeloma is incurable – the aim of treatment is to prolong survival, delay progression, and maintain or improve quality of life
- Current NHS treatments after 3 prior therapies include pomalidomide / bortezomib / panobinostat with dexamethasone
- Elranatamab will provide a new treatment modality for patients with difficult to treat disease
- Currently available drugs induce a response in only a third of patients. Elranatamab, although not in a randomised study, shows up to 61% response
- Requires inpatient treatment for the first 2 doses – monitoring for cytokine release syndrome and severe infections is required

"Elranatamab is a new technology in myeloma targeting [the novel target] BCMA using a bispecific antibody. Results from a single arm Phase 2 study are very encouraging"

"[Inpatient monitoring] may be challenging in smaller hospitals with no dedicated bed resource. Patients may need tocilizumab if they develop grade 2 cytokine release syndrome."

Abbreviations: BCMA, B-cell maturation antigen.

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Decision problem (1/2)

Population and intervention from the scope

	Final scope	Company	EAG comments
Population	People with relapsed or refractory multiple myeloma after at least 3 prior therapies	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	Aligned with marketing authorisation, but not with MagnetisMM-3 trial which included triple class refractory (TCR) patients only
Intervention	Elranatamab	As per scope	N/A

Key: EAG, External Assessment Group; IMiD, immunomodulatory drug; mAb, monoclonal antibody; N/A, not applicable; PI, proteasome inhibitor; TCR, triple class refractory.

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Decision problem (2/2)

Comparators and outcomes from the scope

	Final scope	Company	EAG comments
Comparators	• Pomalidomide plus low-dose dexamethasone • Lenalidomide plus dexamethasone • Panobinostat plus bortezomib and dexamethasone • Daratumumab monotherapy • Ixazomib plus lenalidomide and dexamethasone • Belantamab mafodotin • Cyclophosphamide plus dexamethasone	• Pomalidomide plus low-dose dexamethasone	• EAG's clinical expert generally agrees with company's rationale for excluding comparators • There is less certainty around the justification for excluding ixazomib plus lenalidomide and dexamethasone
Outcomes	Overall survival, progression-free survival, response rate, adverse events, health-related quality of life	As per scope	N/A

Key: EAG, External Assessment Group; N/A, not applicable.

Key clinical trials – overview

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Clinical trial designs and outcomes

	MagnetisMM-3 cohort A* (n = 123)	MM-003 (n = 455)
Design	Phase II non-randomised, open-label study (single arm)	Phase III randomised, open-label study
Population	People with RRMM refractory to at least one PI, one IMiD, and one anti-CD38 mAb – who were relapsed or refractory to their most recent regimen (known as triple class refractory [TCR])	People with RRMM who have received at least 2 lines of lenalidomide and bortezomib, alone or in combination
Intervention	Elranatamab monotherapy	Pomalidomide plus dexamethasone (POM+DEX)
Comparator(s)	N/A	Dexamethasone monotherapy
Duration	Median follow-up ~15 months	Median follow-up 10 months
Dates	Feb 2021-Jun 2022 (primary completion)	Mar 2011-Mar 2013 (primary completion)
Primary outcome	Objective response rate (ORR)	Progression-free survival (PFS)
Locations	76 sites across 10 countries, including one UK site	Multicentre with sites in Australia, Canada, Europe, Russia, and the USA

Notes: *Cohort A has not received prior BCMA-directed therapies for example antibody–drug conjugates or chimeric antigen receptor (CAR) T-cells.
Abbreviations: IMiD, immunomodulatory drug; mAb, monoclonal antibody; PI, proteasome inhibitor; RRMM, relapsed refractory multiple myeloma.

Baseline characteristics, MagnetisMM-3 and MM-003

	MagnetisMM-3 Cohort A	MM-003
Age (median)	68 years	64 years
Male	55%	60%
Time since diagnosis (median)	6.1 years	5.3 years
ECOG 0	36.6%	36%
ECOG 1	57.7%	46%
ECOG 2	5.7%	17%
ECOG missing	0%	1%
Median (range) number of prior lines	5 (4, 6)	5 (2-14)
Type of prior therapy - contains PI (%)	43.9%	100%
Type of prior therapy - contains IMiD (%)	30.9%	100%
Type of prior therapy – contains anti-CD38, n (%)	38.2%	NR

Note: A comprehensive comparison of baseline characteristics presented in EAR Table 7

Company

As people in MM-003 were not TCR, the efficacy outcomes from this trial will provide upper bound estimates of efficacy outcomes (for the comparator), given that people with TCR myeloma will have worse outcomes.

Adverse event rates

Adverse event category	MagnetisMM-3 Cohort A (n=123)	MM-003 (n=300)
Any serious adverse event, n (%)	[redacted]	183 (61)
Any death, n (%)	55 (44.7)	144 (48)
Deaths related to study treatment, n (%)	[redacted]	11 (4)
Any treatment-related adverse event, all grades, n (%)	[redacted]	NR
Any treatment-related adverse event, grade 3 / 4, n (%)	[redacted]	NR
Cytokine release syndrome (CRS), all grades, n (%)	[redacted]	NR
Cytokine release syndrome (CRS), grade 3 / 4, n (%)	[redacted]	NR
Immune-effector cell-associated neurotoxicity syndrome (ICANS), all grades, n (%)	[redacted]	NR

Abbreviations: NR, not reported.

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Potential routes to eligibility – company

Figure 1: Transplant eligible setting

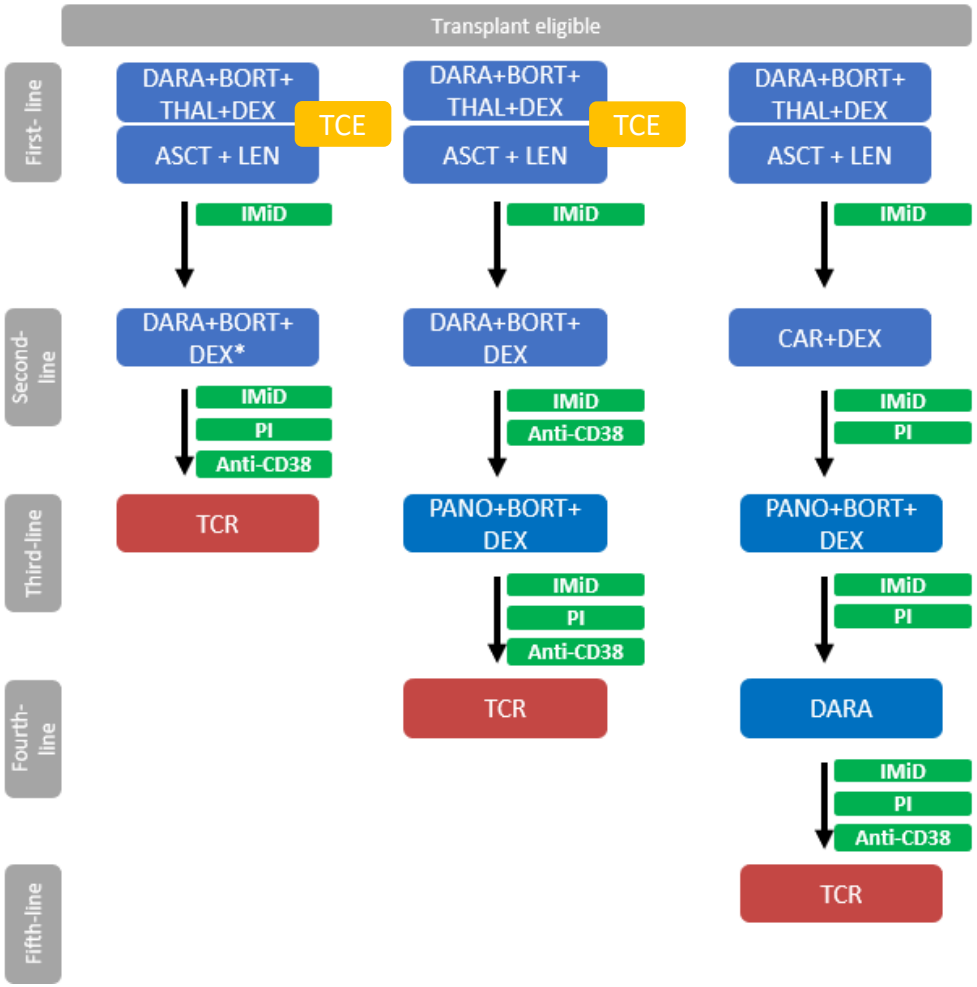
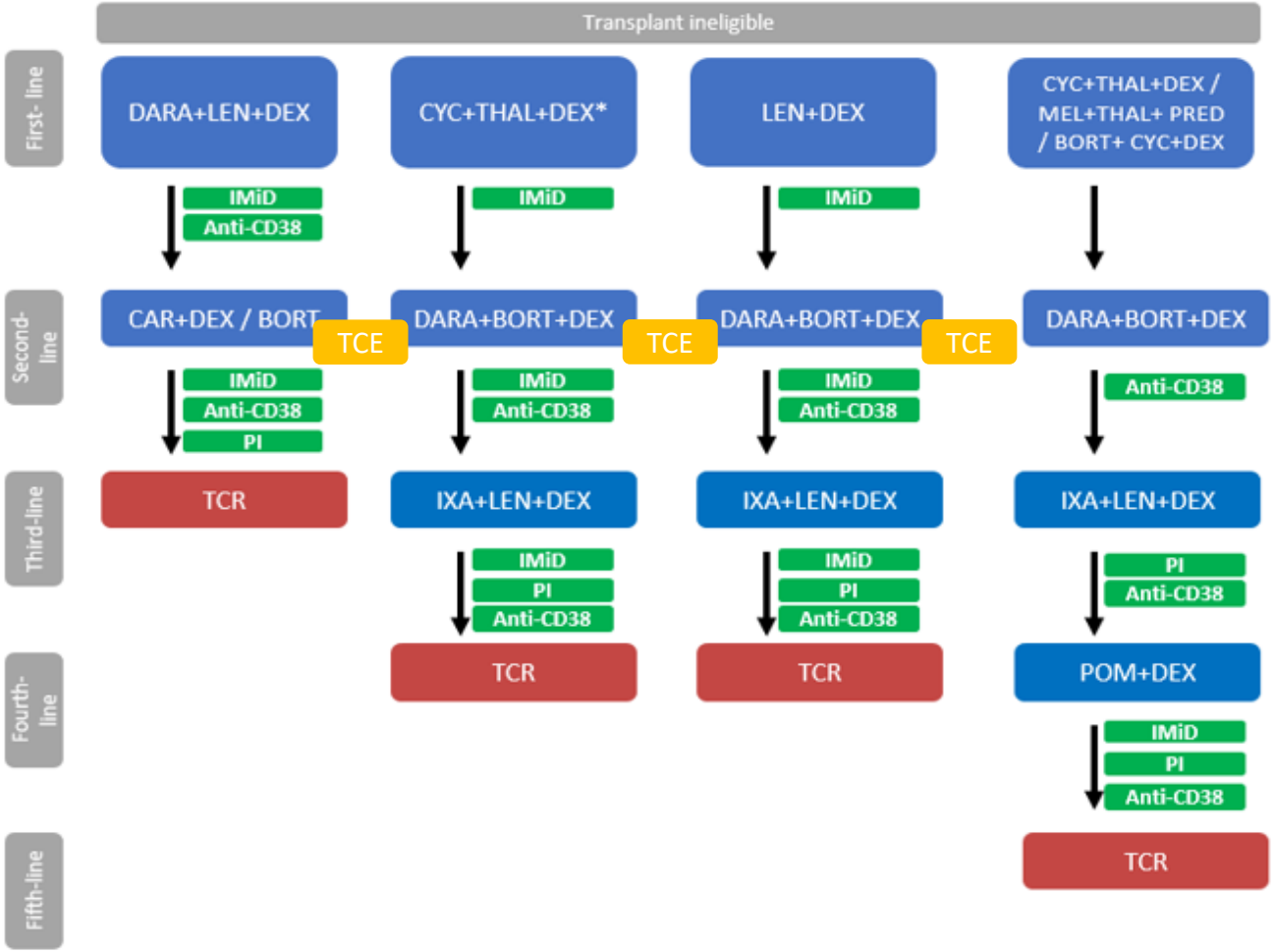


Figure 2: Transplant ineligible setting



Indicates the drug-class to which a patient will be refractory at that point in the pathway

Abbreviations: TCR, triple class refractory; TCE, triple class exposed.

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Model inputs and evidence sources

Input	Assumption and evidence source
Baseline characteristics	Mean age 67 years; 55% males – MagnetisMM-3
Model structure	• Partitioned survival model with four health states (progression free on treatment, progression free off treatment, progressed disease and death) • Informed by trial OS, PFS and TTD
Intervention and comparator efficacy	Independent parametric curves fit to: • KM data from MM-003 (POM + DEX) • MAIC weighted KM data from MagnetisMM-3 (elranatamab)
Utilities	MagnetisMM-3 EQ-5L data mapped to EQ-3L: • Progression free utility – 0.71 • Post-progression utility – 0.63
Costs	• Drug acquisition – elranatamab, informed by company; POM + DEX, MIMS 2023*, costs calculated based on recommended doses • Drug administration – based on NHS reference costs 2021-2022 • Subsequent treatment – proportions for each arm based on clinical expert advice, duration based on median subs tx. duration in MagnetisMM-3 • Health state – resource use frequencies based on TA658, costs based on NHS reference costs 2021-2022 *__Note:__ results including the PAS discount for POM presented in Part 2

Key issue 3: Extrapolation of PFS and OS elranatamab

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Goodness-of-fit statistics and landmark survival estimates

Table 1: AIC and BIC statistics, elranatamab (weighted MAIC curves for PFS and OS)

	PFS				OS			
Parametric model	**AIC**	**BIC**	**Average**	**Rank**	**AIC**	**BIC**	**Average**	**Rank**
Weibull	304	310	307	5	394	400	397	5
Log-normal	295	300	298	3	393	398	396	2
Exponential	318	320	319	7	392	395	394	1
Log-logistic	299	305	302	4	394	399	396	3
Gompertz	290	295	292	2	394	400	397	4
GG	286	294	290	1	395	403	399	7
Gamma	307	312	310	6	394	400	397	6

Table 2: Survival landmarks for PFS and OS adjusted for excess mortality

Distribution	**Proportion of people progression-free at:**						**Proportion of people alive at:**					
	6 mo	**1 yr**	**2 yr**	**5 yr**	**10 yr**	**25 yr**	**6 mo**	**1 yr**	**2 yr**	**5 yr**	**10 yr**	**25 yr**
Weibull	67%	55%	40%	18%	7%	1%	77%	61%	38%	10%	1%	0%
Log-normal	65%	53%	40%	19%	11%	3%	75%	59%	42%	19%	10%	2%
Exponential	73%	53%	28%	4%	0%	0%	78%	61%	37%	8%	1%	0%
Log-logistic	65%	52%	39%	18%	11%	3%	76%	60%	41%	18%	9%	2%
Gompertz	60%	53%	45%	21%	14%	3%	77%	60%	40%	16%	8%	2%
GG	62%	54%	44%	20%	13%	3%	75%	59%	41%	18%	9%	2%
Gamma	69%	56%	39%	15%	4%	0%	78%	61%	37%	9%	1%	0%

Key issue 3: Extrapolation of PFS and OS

Standardised mortality ratio (SMR) adjustment – Giri et al. 2021

	Giri et al. (n = 1906)
Design	Prospective cohort study
Population / intervention	People with multiple myeloma who have had an autologous peripheral blood stem cell transplantation (aPBSCT) between 1989 and 2014 who had survived for 2 years after transplant, irrespective of disease status
Subgroups	• 1989-1999 (pre-thalidomide era) • 2000-2005 (thalidomide era) • 2006-2014 (lenalidomide era)
Duration	Median follow up 9.2 years
Outcome	All-cause mortality
Location	US
Reference population	Age/sex matched US general population
SMR	• Overall SMR: 5.27 (95% CI 4.9-5.65) • Time-varying SMR: 15.3 in the first 5 years, 3.5 in years 6–10 and 1.0 after 10 years (equal to general population)

Source: Giri et al. (2021)

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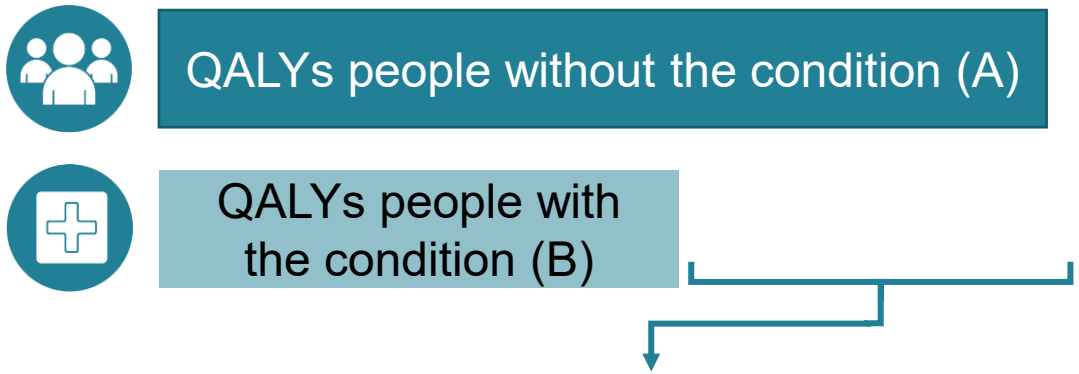
Other assumptions – additional changes with small ICER impact

Assumption	Company base case	EAG base case
Subsequent treatment Incident progression	Newly progressed	Fixed proportion of PFS events
Subsequent treatment duration cap	Capped by expected progressed disease years	Capped by progressed disease life years conditioned on proportion assumed to progress
Cost for treating grade 3-4 infections	£431 – NICE TA567	£2,512 – pneumonia HRG codes
Include administration cost of IVIG	None – assumed included in AE cost	£208 – simple parenteral chemotherapy admin at 1st attendance (outpatient)
Apply IVIG as one-off cost in first cycle	No – applied as per cycle cost	Yes
EOL care cost	£961.67 – 1 week of care	£5,231.30 – 90 days of care
RDI – POM + DEX	90% - MM-003	95.94% - TA427
TTD extrapolation elranatamab	Log normal	As per company
Severity weighting	1.2	1.2

Abbreviations: AE, adverse event; EAG, External Assessment Group; EOL, end-of-life; HRG, healthcare resource group; ICER, incremental cost-effectiveness ratio; IVIG, intravenous immunoglobulin; PFS, progression-free survival; POM + DEX, pomalidomide plus dexamethasone; RDI, relative dose intensity; TA, technology appraisal; TTD, time-to-treatment-discontinuation.

QALY weightings for severity (1/2)

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Abbreviations: QALY, quality-adjusted life year

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QALY weightings for severity (2/2)

Company

Table 1: Company's QALY shortfall analysis

Component	QALYs / shortfall
Expected total QALYs for the general population	10.22
Total QALYs that people living with a condition would be expected to have with current treatment (POM + DEX)	0.89
QALY shortfall (absolute)	9.33
QALY shortfall (proportional)	90.27%

Proportional shortfall is between 0.85 and 0.95 therefore a severity weighting of 1.2 applies

EAG comments

- Agrees with the company that a weighting of 1.2 should apply

Abbreviations: QALY, quality-adjusted life year; POM + DEX, pomalidomide plus dexamethasone.

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Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.