Belantamab mafodotin with pomalidomide and dexamethasone for previously treated multiple myeloma [ID6211]

PART 1 for PROJECTOR – contains no confidential information

Technology appraisal committee B 2nd meeting [5 November 2025]

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Draft guidance consultation

Belantamab mafodotin (Blenrep)

- **Marketing authorisation (Apr 2025):** BEL+POM+DEX for MM after at least 1 prior therapy including LEN
  - BEL: via IV infusion in a 4-week cycle: 2.5 mg/kg once (cycle 1), 1.9 mg/kg once every 4 weeks (cycle 2 onwards) until progression or unacceptable toxicity
- **Company positioning:** 2L in LEN-exposed population
- **Comparators:** CAR+DEX, DAR+BOR+DEX, SEL+BOR+DEX (categorised into DAR eligible or ineligible)
- **DREAMM-8:** 100% LEN-exposed, 81% LEN-refractory, ~50% had treatment beyond 2L, ~25% had prior DAR, younger (66 vs 75 years in NHS)

*Link to Appendix – Background

RECAP

Preliminary recommendation

Belantamab mafodotin plus pomalidomide and dexamethasone should **not** be used to treat multiple myeloma in adults who have had at least 1 treatment including lenalidomide

DG consultation responses

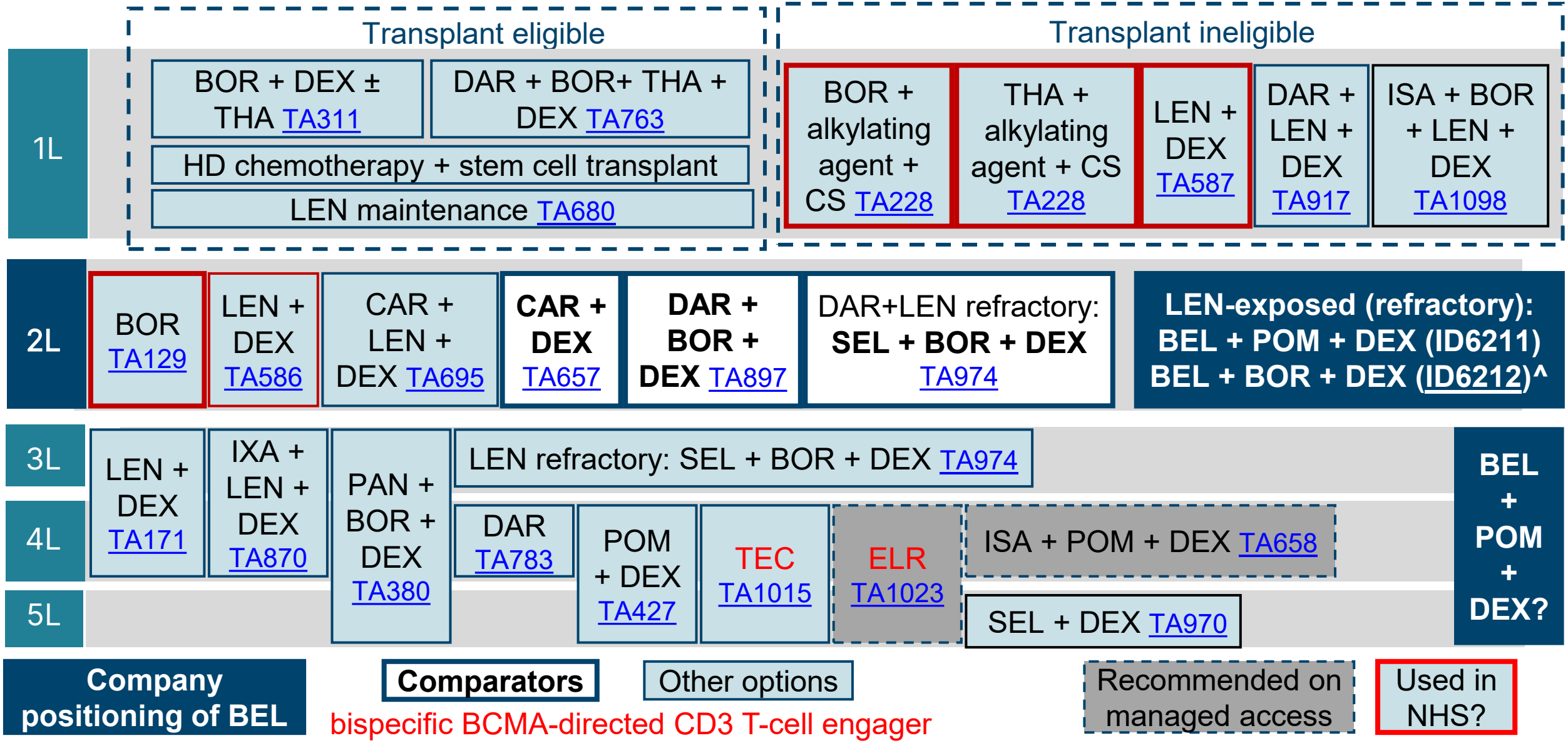
- Company: new evidence and analyses, updated base case with new PAS
- Patient organisations: Myeloma UK, UK Myeloma Society
- Commentator: Menarini Stemline (manufacturer of selinexor)

- In company's DGC response, it states positioning is in LEN-**unsuitable**, only at 2L. Please clarify. Relevant comparators for people choosing not to have LEN at 2L would include LEN-containing options.

Abbreviations: 2L, 2nd line; Apr, April; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; DGC, draft guidance consultation; IV, intravenous; LEN, lenalidomide; MM, multiple myeloma; PAS, patient access scheme; POM, pomalidomide; RR, relapsed or refractory; SEL, selinexor

Treatment pathway and company positioning of BEL

RECAP



- Are TA228, TA587 and TA129 used in NHS clinical practice?
- What proportion of people would normally have had DAR at 1L in the NHS? 25% or 50%?

Committee considerations at ACM1

Committee considerations and preferences (DG section)	Company's DGC response
Uncertainty in clinical effectiveness of BEL+POM+DEX (3.7) • No statistically significant differences in OS with comparators in DREAMM-8 or in NMAs (methodological limitations) • No NMAs using data for target 2L LEN-exposed • Unknown impact of BEL dose modifications on clinical effectiveness (no KM plots comparing PFS in people having longer 8 and 12-weekly BEL treatment vs 4-weekly; 3.8)	**NMA for 2L LEN-exposed:** not feasible (little publicly-available data). Maintains ITT population most appropriate (81% LEN-refractory, data aligned with comparator trials' populations) **See slides 6 to 7**
OS benefit modelling (3.6 & 3.11) • Use OS SACT data for DAR+BOR+DEX to estimate absolute baseline curve, with relative effects of comparators from updated NMA that addresses limitations • Explore MAIC for all comparators • Clarification on adjustment method for subsequent treatments in OPTIMISMM and other trials in NMA • Scenario using unadjusted HR 0.94	• **MAIC:** limited data unlikely resolve uncertainty • **Adjustment methods:** no access to information for OPTIMISMM; other RCTs NR • **Scenario HR 0.94:** maintains adjusted HR 0.74 is appropriate (58.3% in BOR+DEX had subsequent POM, so relative OS benefit of POM+BOR+DEX is diluted) **See slides 8 to 13**
Health state utilities (3.18): apply same utilities from wholly 2L population, regardless of treatment (EAG's base case)	**See slide 14**
Monitoring cost of eye-related AEs (3.16): include hospital-based ophthalmology services	**See slide 15**

Other committee considerations (DG section)	Company's DGC response	EAG comments
Disutility of eye-related AEs (3.18) Scenario with disutility applied	Scenario showed little impact on overall QALY for BEL ([redacted])	Disutilities appropriately calculated and included in model
Medication use and drug costs (3.14) • Evidence of consistency between IPD and RDI-based costs for comparators • Scenario with all available IPD	• Provided evidence of consistency for DAR and POM **(see Appendix – medication use and costs)** • No scenario	None
Cost of subsequent treatments (3.15) Scenario: use SACT data to model subsequent treatments in NHS and include TEC at 4L (see Appendix)	• No SACT data available • **Scenario 1 (clinical advice):** 75% have 3L, 50% have 4L • **Scenario 2:** TEC at 4L	Including cost of TEC but not benefits will lead to biased estimates
Model maximum dose interruption interval of 6 months for BEL (3.12)	• Excluded: [redacted] had interruptions ≥6 months, but PFS similar to ITT • Inequitable to limit gaps to 6 months See slide 7	• No data to support 6-month dose interruptions – unknown impact on efficacy • DREAMM-8 included people with >6-month treatment gaps

- Should disutility of eye-related AEs be included in the base case?
- Is the company's original approach to modelling medication use appropriate? That is, using IPD for BEL and RDI for all other medicines.
- How should cost of subsequent treatments be modelled? Company's original base case (81% have 3L, 34% have 4L) vs Company's DGC response scenarios 1 or 2?

Clinical effectiveness of BEL+POM+DEX: DREAMM-8 results

Company: BEL+POM+DEX increases PFS compared with POM+BOR+DEX at latest data cut in June 2025. Results for 2L LEN-refractory subgroup consistent with full ITT at June 2024 data cut

Table 1. DREAMM-8 results in ITT and 2L LEN-refractory populations

	Full ITT population (LEN-exp for all LoT)		2L LEN-refractory	
	BEL+POM+DEX (n=155)	POM+BOR+DEX (n=147)	**BEL+POM+DEX (n=66)^**	**POM+BOR+DEX (n=53)^**
PFS at Jan 2024 data cut (median follow up 21.8 months)				
Median (95% CI), months	NR (20.6 to NR)	12.7 (9.1 to 18.5)	**NR (21.1 to NR)**	**13.1 (9.1 to 19.8)**
HR (95% CI)	0.52 (0.37 to 0.73), p<0.001		**0.43 (0.25 to 0.75)**	
PFS at Jun 2025 (median follow up 28 months)				
Median (95% CI), months	**32.6 (n=NR)**	**12.5 (n=NR)**		
HR (95% CI)	**0.49 (0.35 to 0.68)**			
OS at Jan 2024 data cut (median follow up 21.8 months)				
Median (95% CI), months	NR (33.0 to NR)	NR (25.2 to NR)	**NR (NR to NR)**	**NR (22.2 to NR)**
Estimated HR (85% CI)	0.77 (0.53 to 1.14), p=0.095		**0.72 (0.37 to 1.41)**	
TTD at Jan 2024 data cut (median follow up 21.8 months)				
Median (95% CI), months	[redacted]	[redacted]	-	-

Company's new data provided in DGC response in bold

*Link to Appendix – 2L LEN-refractory

Abbreviations: ^assumed from CS (see Appendix – DREAMM-8); 2L, 2nd line; BEL, belantamab mafodotin; BOR, bortezomib; CI, confidence interval; DEX, dexamethasone; DGC, draft guidance consultation; HR, hazard ratio; ITT, intention-to-treat; LEN, lenalidomide, LoT, line of treatment; NR, not reported; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; TTD, time to treatment discontinuation

DREAMM-8 results: impact of BEL dose interruptions

Company: dose interruptions do not affect BEL+POM+DEX efficacy – results consistent with ITT

Eye-related AEs in BEL+POM+DEX led to frequent dose reductions, delays and interruptions:

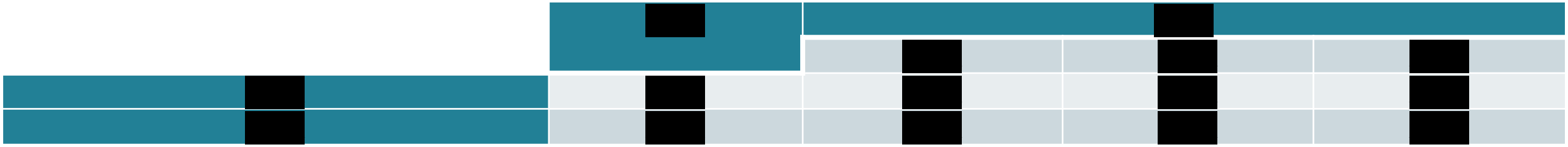
- 99% had ≥1 dose delay lasting a median of 53 days
- 74% had ≥3 dose delays
- 70% had dose reductions from 1x every 4 weeks to 1x every 8 weeks

*Link to Appendix – KM dose delays

Table 2. Best response before and during/after first BEL dose delay of ≥8 weeks

Before 1st dose delay >8 weeks (n=83)		During/after 1st dose delay of >8 weeks	
Best response	**n (%)**	**Best response**	**n (%)**
≤ partial response	37 (45)	**≥ very good partial response**	27 (73)
		≥ partial response	34 (92)
≥ very good partial response	46 (55)	**(stringent) complete response**	36 (78)
		≥ very good partial response	45 (98)

Table 3. Impact of dose interruptions in BEL+POM+DEX arm at Jan 2024 data cut



- Has committee seen any new evidence to change its views about the uncertainty of the clinical effectiveness of BEL+POM+DEX in the 2L LEN-refractory population and because of dose interruptions?
- Should a maximum dose interruption interval of 6 months for BEL+POM+DEX be modelled?

Key issue: Limitations of OS NMA

Company conducted IPTW analysis and integrated in NMA

Committee considerations at ACM1

- Concerns about credibility of company's long-term OS estimates because of methodological limitations of NMA
  - Impact of subsequent treatments (type or frequency) on OS and generalisability to NHS not considered
    - OPTIMISMM (common comparator linking DREAMM-8 to network via POM+BOR+DEX)
      - Company preferred adjusted HR 0.76 vs EAG preferred unadjusted HR 0.94
  - Not restricted to 2L LEN-exposed; 25% had prior DAR
  - Not adjusted for TEMS specifically prior LoT, ECOG PS and ISS stage

Company

Used IPD and inverse-probability-of-treatment weighting (IPTW)

- Matched DREAMM-7 control arm (DAR+BOR+DEX; key comparator and current standard care) with DREAMM-8 treated arm (BEL+POM+DEX)
- Estimated relative OS of BEL+POM+DEX vs DAR+BOR+DEX

Used IPTW-integrated FE NMA for LEN-exposed + ITT population to derive PFS and OS outcomes

- IPTW connects BEL+POM+DEX to DAR+BOR+DEX and network – provides more direct path with less connections to reach relevant comparators (validated by 2 statistical experts)

Abbreviations: 2L, 2nd line; ACM, appraisal committee meeting; BEL, belantamab mafodotin; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FE, fixed effects; HR, hazard ratio; IPD, individual patient data; IPTW, inverse probability of treatment weighting; ISS, International Staging System; ITT, intention-to-treat; LEN, lenalidomide, LoT, line of treatment; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; TEMS, treatment-effect modifiers; TTD, time to treatment discontinuation

Company network diagram from original NMA and using IPTW

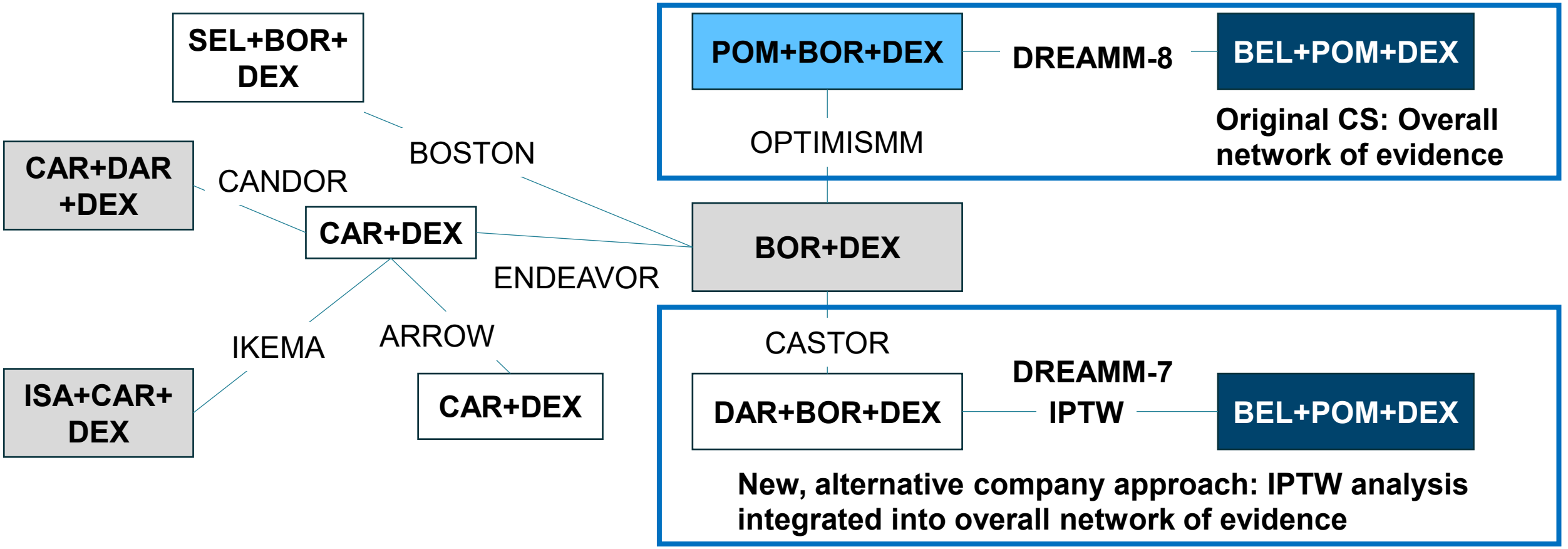


Figure 1. Network diagram of original NMA using OPTIMISMM and new IPTW approach using DREAMM-7

EAG comments

IPTW OS analysis integrated in company's previous NMA

- Methodological issues with NMA still exists (subsequent therapies in trials not adjusted, centrality of OPTIMISMM in linking BEL+POM+DEX to SEL+BOR+DEX)

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; CS, company submission; DAR, daratumumab; DEX, dexamethasone; IPTW, inverse probability of treatment weighting; ISA, isatuximab; NMA, network meta-analysis; OS, overall survival; POM, pomalidomide; SEL, selinexor

IPTW analyses: results

Table 4. OS effect of BEL+POM+DEX vs 2L comparators from IPTW-integrated NMA and original NMA

	HR (95% CrI) for BEL+POM+DEX vs	
	IPTW-integrated NMA	Global DREAMM-8 NMA (original)
CAR+DEX	[redacted]	[redacted]
SEL+BOR+DEX	[redacted]	[redacted]
DAR+BOR+DEX	[redacted]	[redacted]

Figure 2. IPTW OS KM plot for BEL+POM+DEX vs DAR+BOR+DEX

EAG comments

- **IPTW analysis:** company did not test PH assumption, but OS KM IPTW data suggests HR changes over time and data is immature (only 24 months of data not heavily censored)
- IPTW OS HRs in line with original NMA HRs (remains [redacted])
- Modelling any specific difference in OS between BEL+POM+DEX and any comparator is poorly supported by current evidence ([redacted], immature data, potential for PH assumption to be violated) – maintains base case

- Does PH assumption hold for DREAMM-8 OS data?
- Does the company's IPTW-integrated NMA address the methodological limitations of the original NMA?
- Should an OS benefit be assumed?

Key issue: SACT OS data

Committee considerations at ACM1

- To address uncertainty in relative estimates of OS, base case should use analysis with OS data from SACT for DAR+BOR+DEX to estimate absolute baseline curve, with relative effects of comparators applied from amended NMA

Company: DAR+BOR+DEX SACT baseline curve

- Identified paper on SACT data for DAR+BOR+DEX use in NHS for 275 people at 2L LEN-exposed (Mar 2019 to Jun 2021 and follow-up until Aug 2023; Lawton et al 2024)
- **KM curve extracted**, digitised and validated against IPTW curve. SACT OS KM curve and extrapolated Weibull used in model, with relative effect of BEL+POM+DEX vs DAR+BOR+DEX baseline from IPTW OS HR
- OS HR of other comparators (SEL+BOR+DEX and CAR+DEX) derived from IPTW integrated NMA
- PFS and TTD are aligned to original NMA where HRs are applied to POM+BOR+DEX baseline (OPTIMISMM)
- Only treatment-free survival (TFS) data available from SACT: scenario with TFS as proxy for PFS

EAG comments: DAR+BOR+DEX SACT baseline curve

- Company chosen Weibull distribution for extrapolated DAR+BOR+DEX OS SACT is acceptable
- Company scenario with TFS has limited relevance

Other considerations

- Lawton et al. refers to time to next treatment (TTNT), available in SACT (used as surrogate for PFS)
- TFS = PFS-TTD (TTD and PFS are not available in SACT)

- Please clarify whether TFS or TTNT was used from Lawton et al.?

IPTW OS HR using SACT DAR+BOR+DEX baseline: results

Figure 3. Relative OS of BEL+POM+DEX vs SACT DAR+BOR+DEX baseline (Weibull) by applying OS HR ([redacted]) from IPTW analysis

EAG comments

DAR+BOR+DEX SACT baseline curve

- PFS and TTD were modelled by extrapolating DREAMM-8 data
  - OS, PFS and TTD should be taken from same data source, as it is unclear exactly which population is being modelled
- Do not think extrapolated SACT OS data should be used in base case, even if they may be more generalisable to NHS

- Should OS data from SACT for DAR+BOR+DEX be used to estimate absolute baseline curve?
- Or should company's original approach of using POM+BOR+DEX OS data from DREAMM-8 be used for the baseline curve?

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; IPTW, inverse probability of treatment weighting; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; SACT, Systemic Anti-Cancer Therapy; TTD, time to treatment discontinuation

Summary of extrapolations used in company base case and scenarios

Company original base case

BEL+POM+DEX	**PFS + TTD + OS** DREAMM-8 ITT
DAR+BOR+DEX SEL+BOR+DEX CAR+DEX	**PFS + TTD + OS** NMA HR vs **PBd** baseline

Company updated base case (only OS changed)

BEL+POM+DEX	IPTW HR vs **DBd** baseline
DAR+BOR+DEX	OS SACT baseline (Weibull)
SEL+BOR+DEX CAR+DEX	IPTW NMA HR vs **DBd** baseline

Company scenario 1 (only PFS and TTD changed)

BEL+POM+DEX	DREAMM-8 ITT (Weibull)
DAR+BOR+DEX	IPTW HR vs **BPd** baseline
SEL+BOR+DEX CAR+DEX	IPTW NMA HR vs **BPd** baseline

Company scenario 2 (PFS and TTD changed using SACT data as baseline)

BEL+POM+DEX	**PFS:** IPTW HR vs **DBd** baseline
DAR+BOR+DEX	**PFS:** TFS SACT baseline (Weibull) **TTD:** DREAMM-7 HR vs **TFS SACT** baseline
SEL+BOR+DEX CAR+DEX	IPTW NMA HR vs **DBd** baseline

EAG base case: assumed no difference in OS benefit across treatments and applied company's OS extrapolation for BEL+POM+DEX to comparators

- What is the committee's preferred approach for OS modelling?

Key issue: Health state utilities

Committee considerations at ACM1

- No strong evidence to justify a higher 'progression-free on-treatment' utility for BEL than its comparators
- Apply same utilities from wholly 2L population, regardless of treatment (EAG base case)
  - Company scenario using utilities from ENDEAVOR in TA897 for DAR+BOR+DEX

Company

- ENDEAVOR utilities derived from mapping exercise, not directly elicited EQ-5D data

Updated base case, utilities for health states:

- **PFS:** baseline utility [redacted], independent of treatment from DREAMM-8 (PFS on-treatment utility)
- **PD:** decrement from Hatswell et al. (2019) applied to PFS (approached accepted in ID6212)

EAG comments

- Company preferred Hatswell's PD utility is [redacted] lower than PFS utility from DREAMM-8
  - Small decrement in entirety of PD state utility may not be clinically plausible
- EAG prefer using ENDEAVOR utilities with a difference of 0.072 (corrected from 0.081)

Table 5. Health state utilities in company updated base case, EAG base case and other sources

	Company updated base case	EAG base case: ENDEAVOR (TA897/TA457)	BOSTON (SEL+BOR+DEX vs BOR+DEX; EQ-5D-5L)		Scenario: Hatswell (2019)
	All	All treatments: 2L	Company base case (mean of both arms across all LoTs)	EAG base case: 2L	2L
PF on treatment	[redacted]	**0.737**	0.697	**0.706**	0.620
PD	[redacted]	**0.665**	0.660	**0.668**	0.550

- Which health state utilities should be used in the model?

Key issue: Eye-related adverse event monitoring costs

Committee considerations at ACM1

- Cost of monitoring with BEL likely underestimated as it did not include continued monitoring until resolution of eye-related AEs
- Base case: monitoring costs using hospital-based ophthalmology services
- Scenario: company proposed community-based ophthalmology services

Company

- **Base case:** assumed [redacted] ophthalmology visits (based on DREAMM-8 median TTD) and split between hospital (20%) and community services (80%) – based on advisory board of consultant haematologists, ophthalmologists and optometrist with direct experience in managing people on BEL
- Company's [redacted]

EAG comments

- Considers company's assumptions to be reasonable
- With 100% hospital-based visits, adds ~1% to total cost of BEL+POM+DEX, minimal impact on cost-effectiveness estimates
- Has not amended its base case analysis as costs are likely to be minimal

- How is interval progression after dose interruptions incorporated in the model?
- Is the company's modelling of eye-related adverse events monitoring costs plausible?

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Abbreviations: ACM, appraisal committee meeting; AE, adverse event; BEL, belantamab mafodotin; DEX, dexamethasone; POM, pomalidomide; [redacted]; TTD, time to treatment discontinuation

Summary of company and EAG base case assumptions

Assumption	Company original base case	Company updated base case	EAG base case (unchanged)
OS benefit	Treatment-specific OS benefit from DREAMM-8 and NMA BEL+POM+DEX: unadjusted DREAMM-8 OS extrapolation Comparators: HRs vs POM+BOR+DEX as baseline from LEN-exposed+ITT OS NMA	**BEL+POM+DEX:** IPTW HR vs DAR+BOR+DEX baseline **DAR+BOR+DEX:** OS SACT baseline (Weibull) **SEL+BOR+DEX and CAR+DEX:** IPTW HR vs DAR+BOR+DEX baseline	No difference in OS benefit across treatments → applied company's OS extrapolation for BEL+POM+DEX to comparators
POM cost	[redacted] ([redacted] of list price)		**MPSC price**
Medication usage	BEL: IPD dosing using actual dose received Comparators: dosing based on SmPC label and constant RDI		Used RDI-based approach for all treatments
Health state utility values	PF-on-treatment utilities from DREAMM-8 • BEL+POM+DEX: [redacted] • CAR+DEX; DAR+BOR+DEX; SEL+BOR+DEX: [redacted] PF off-treatment: [redacted] PD: [redacted]	PF on/off treatment: [redacted] PD: [redacted]	PF on/off treatment: 0.737 PD: 0.665

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; IPD, individual patient data; IPTW, inverse probability of treatment weighting; IPD, individual patient data; ITT, intention-to-treat; LEN, lenalidomide; MPSC, medicines procurement and supply chain; NMA, network meta-analysis; OS, overall survival; PD, progressed disease; PFS, progression-free survival; POM, pomalidomide; RDI, relative dose intensity; SEL, selinexor

Other changes to company base case and scenarios

Parameter	Company updated base case	EAG comments
Use starting age from SACT dataset in model	In updated base case (66.1 years in DREAMM-8 vs 70 years from SACT)	• Implemented correctly • Using different start age to efficacy data population in model is inappropriate as DREAMM-8 outcomes may differ
Assume no vial sharing	In updated base case (as in original) and correction of EAG model that assumed no wastage for BOR	None
Exclude wastage of tablets	In updated base case	None

Company also provided scenarios:

- Health state utilities using values from ENDEAVOR
- Included eye-related adverse events disutilities
- Included teclistamab subsequent treatment costs
- Proportion having subsequent treatment based on clinical opinion vs Raab et al. (original base case)
- Ophthalmology test services: 100% hospital or 100% community

- Are any of the scenario assumptions preferable to the company's updated base case?

Abbreviations: BOR, bortezomib; SACT, Systemic Anti-Cancer Therapy

Cost-effectiveness results

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

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Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme

Summary of issues (1)

Treatment pathway (slide 3)

- Are TA228, TA587 and TA129 used in NHS clinical practice?
- What proportion of people would normally have had DAR at 1L in the NHS? 25% or 50%?

Positioning of BEL+POM+DEX (slide 2)

- Which patient population should BEL+POM+DEX be applied to? 2L LEN-exposed and/or LEN-refractory?

Clinical effectiveness of BEL+POM+DEX (slides 6 and 7)

- Has committee seen any new evidence to change its views about the uncertainty of the clinical effectiveness of BEL+POM+DEX in the 2L LEN-refractory population and because of dose interruptions?

Indirect treatment comparisons (slides 8 to 10)

- Does PH assumption hold for DREAMM-8 OS data?
- Does the company's IPTW-integrated NMA address the methodological limitations of the original NMA?
- Should an OS benefit be assumed?

OS modelling (slides 11 to 13)

- Should OS data from SACT for DAR+BOR+DEX be used to estimate absolute baseline curve?
- Or should company's original approach of using POM+BOR+DEX OS data from DREAMM-8 be used for the baseline curve?
- What is the committee's preferred approach for OS modelling?

Abbreviations: 1L/2L, 1st/2nd line; BEL, belantamab mafodotin; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; IPTW, inverse probability of treatment weighting; LEN, lenalidomide; NMA, network meta-analysis; OS, overall survival; PH, proportional hazards; POM, pomalidomide; SACT, Systemic Anti-Cancer Therapy; TA, technology appraisal

Summary of issues (2)

Utilities

- Which health state utilities should be used in the model? **(slide 14)**
- Should disutility of eye-related AEs be included in the base case? **(slide 5)**

Costs

- Is the company's original approach to modelling medication use appropriate? That is, using IPD for BEL and RDI for all other medicines? **(slide 5)**
- How should cost of subsequent treatments be modelled? Company's original base case (81% have 3L, 34% have 4L) vs Company's DGC response scenarios 1 or 2? **(slide 5)**
- Is the company's modelling of eye-related adverse events monitoring costs plausible? **(slide 15)**

Modelling

- How is interval progression after dose interruptions incorporated in the model? **(slide 15)**
- Should a maximum dose interruption interval of 6 months for BEL+POM+DEX be modelled? **(slide 7)**
- Are any of the scenario assumptions preferable to the company's updated base case? **(slide 17)**

Other

- Are there any uncaptured benefits?
- Are there any equality issues to consider?
- **Managed access:** what are the key uncertainties and can they be resolved with further data collection?

Abbreviations: 3L/4L, 3rd/4th line; AE, adverse event; BEL, belantamab mafodotin; DEX, dexamethasone; DGC, draft guidance consultation; IPD, individual patient data; POM, pomalidomide; RDI, relative dose intensity

NICE National Institute for Health and Care Excellence

End of Part 1

Belantamab mafodotin with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6211]

Supplementary appendix

NICE National Institute for Health and Care Excellence

Background

RECAP

RRMM: Incurable, rare, relapsing, remitting cancer of plasma cells of unknown cause

- 4,906 new cases in England in 2020
  - More common in elderly, men and people of African family background
- Relapsed/refractory: MM that is not responsive to treatment or for MM that has had minimal response or better, progression within 60 days of last LoT
- In 2019 in England, 5-year survival for adults diagnosed with MM was 54%
  - Survival likely worse for LEN-refractory MM

Table S1. Information on belantamab mafodotin (Blenrep)

Marketing authorisation	• SmPC: ophthalmic examinations (e.g. visual acuity, slit lamp) must be performed before each of the first 4 BEL doses and during treatment as clinically indicated
Mechanism of action	• Antibody-drug conjugate binds to B-cell maturation antigens (BCMA) on myeloma cells → drug enters cell and destroys it or helps body to destroy it
Administration	**BEL** via IV infusion in a 4-week cycle: 2.5 mg/kg once (cycle 1), 1.9 mg/kg once every 4 weeks (cycle 2 onwards) until progression or unacceptable toxicity **POM:** 4mg 1x/day orally on Days 1 to 21 of 28-day cycles **DEX:** 40mg 1x/day orally on Days 1, 8, 15 and 22 of 28-day cycle
List price	• 1 vial (powder for concentrate for solution): 100mg (£16,848) and 70mg (£11,784) • Patient access scheme available

*Link to Draft guidance consultation

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Abbreviations: BEL, belantamab mafodotin; DEX, dexamethasone; IV, intravenous; LEN, lenalidomide; MM, multiple myeloma; POM, pomalidomide; RR, relapsed or refractory; SmPC, summary of product characteristics

DREAMM-8

Ongoing phase 3 international (5 UK centres) open-label RCT
(Oct 2020 – May 2029)

Population

302 adults with MM, ≥1 prior LoT inc. LEN-containing regimen (LEN ≥2 cycles), progression during or after most recent therapy
- ≤50% ≥2 prior LoTs

Intervention and comparator

BEL+POM+DEX n=155

- Central 1:1 randomisation stratified for prior: BOR, anti-CD38, LoTs (1 vs 2 or 3 vs 4+)
- No treatment cross-over

POM+BOR+DEX n=147

Outcomes

- **Primary endpoint:** PFS^
- **Secondary:**
  - OS^, DoR, MRD
  - TTD^
  - Safety (AEs)^
  - HRQoL (EQ-5D-3L^, EORTC QLQ-C30 / MY20 / IL52)

Characteristics	BEL+POM+DEX	POM+BOR+DEX
LEN-exp (ITT)	155 (100%)	147 (100%)
DAR-exp	36 (23%)	39 (27%)
LEN+anti-CD38 exp	38 (25%)	42(29%)
2L: 1 prior LoT	82 (53%)	77 (52%)
LEN-ref	125 (81%)	111 (76%)
LEN-ref + 2L	[redacted]	[redacted]
Anti-CD38-ref + 2L	[redacted]	[redacted]

Main baseline characteristics for ITT (all 2L)

- Median age: 67 and 68 ([redacted]) years
- **Male:** 60% **([redacted])**
- Ethnicity: 86% ([redacted]) White, 12% ([redacted]) Asian, **0% Black**
- ECOG PS 0 or 1: 95% ([redacted])
- ISS: 59% (60%) I; 26% (28%) II; 15% (12%) III
- Prior LoTs: 52.6% 1; 33.8% 2 or 3; 13.6% 4+

*Link to Draft guidance consultation

Abbreviations: ^used in economic model; 2L, 2nd line; AE, adverse event; anti-CD38 (e.g. DAR); BEL, belantamab mafadotin; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30 / MY20 / IL52, European Organisation for Research and Treatment of Cancer 30-item QoL / Multiple Myeloma Module 20 / disease symptoms domain from MY20; EQ-5D, EuroQoL-5 dimensions; exp, exposed; HRQoL, health-related quality of life; inc, including; ISS, International Staging System; ITT, intention-to-treat; LEN, lenalidomide; LoT, line of treatment; MM, multiple myeloma; MRD, minimum residual disease; n, number; NR, not reported; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; RCT, randomised controlled trial; ref, refractory; TTD, time to treatment discontinuation

Medication use and drug costs – RDI vs IPD

[redacted]

[redacted]

[redacted]

[redacted]

*Link to Committee considerations (2)

Abbreviations: IPD, individual patient data; RDI, relative dose intensity

Cost of subsequent treatments – company original base case

EAG: company's approach to modelling subsequent treatments acceptable

- One-off cost for up to 2 lines of subsequent treatments following disease progression after 2L treatment
- Assumed:
  - people would stay on subsequent treatments for median of 9 months
  - same proportion of people would start 3L (81%) and 4L (34%) treatment
- Used average proportions of subsequent treatment options provided by 3 clinical experts to inform distribution of subsequent treatments:
  - 3L: SEL+BOR+DEX (63.3% to 66.7%) and PAN+BOR+DEX (33.3% to 100%)
  - 4L (in order of preference): POM+DEX (81.1% to 83.3%), DAR monotherapy (16.7%) and PAN+BOR+DEX (2.1% to 2.2%)

*Link to Committee considerations (2)

Abbreviations: 2L/3L/4L, 2nd/3rd/4th line; BEL, belantamab mafadotin; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; PAN, panobinostat; POM, pomalidomide; SEL, selinexor

DREAMM-8 results: 2L LEN-refractory subgroup

Figure S3. PFS in 2L LEN-refractory only

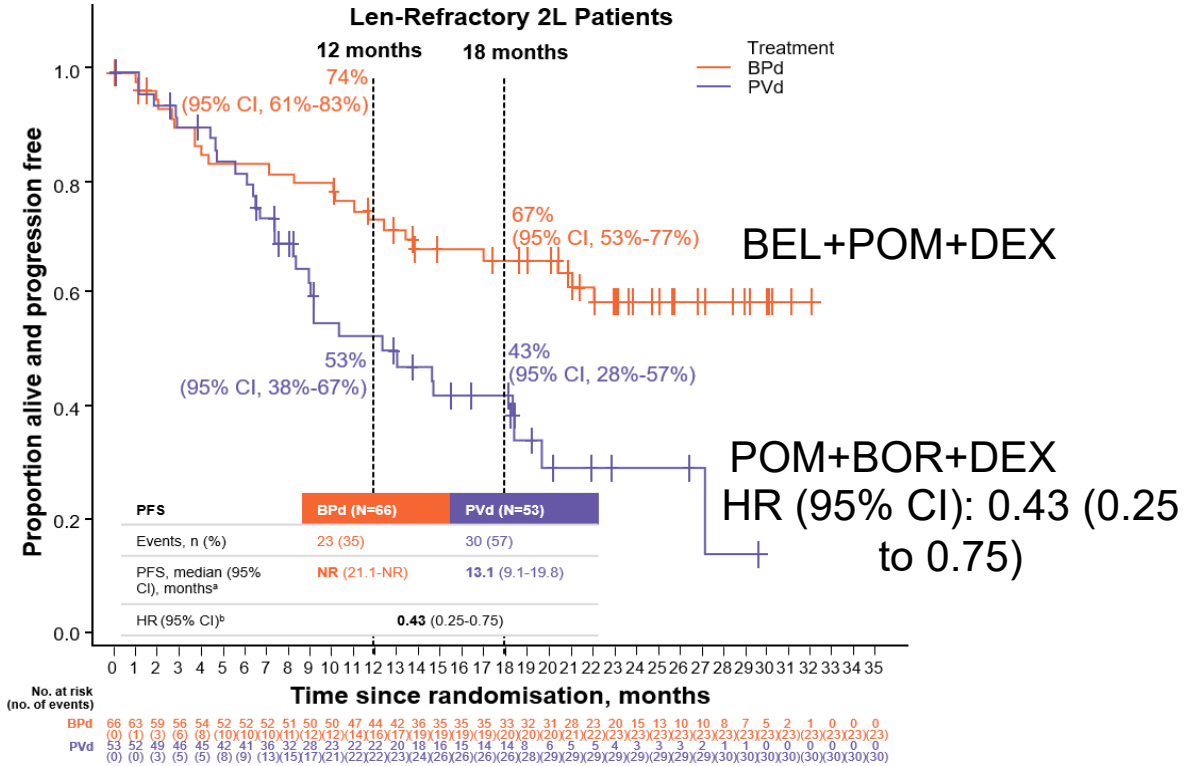
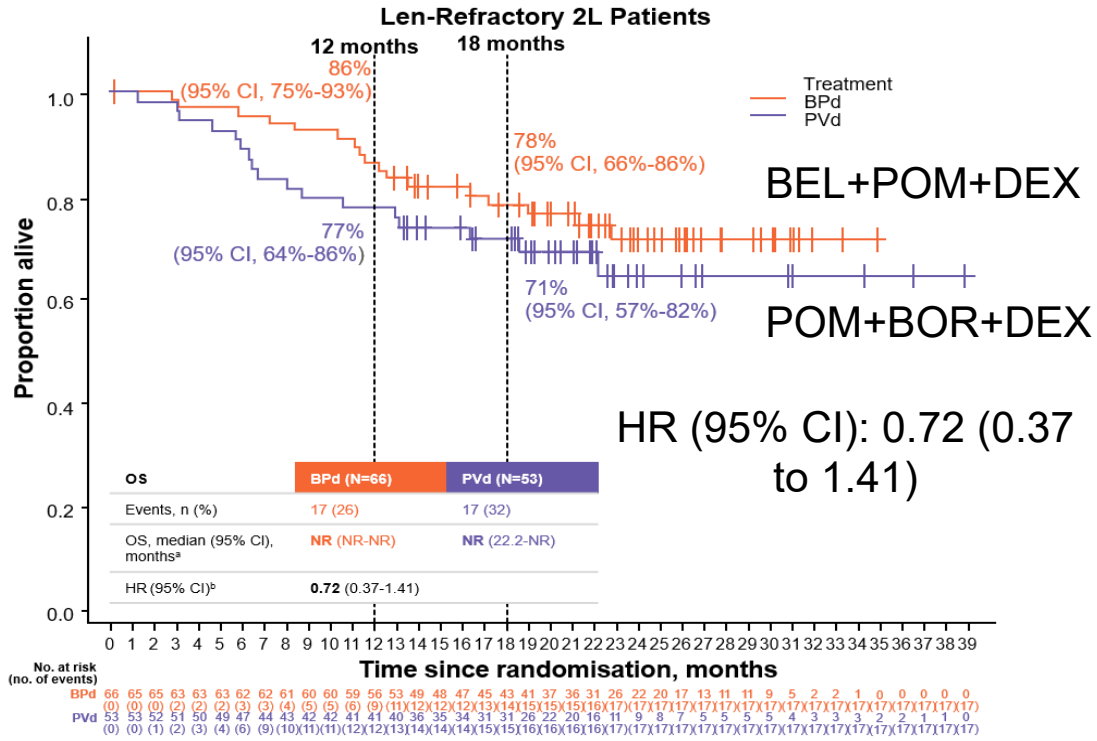


Figure S4. OS in 2L LEN-refractory only

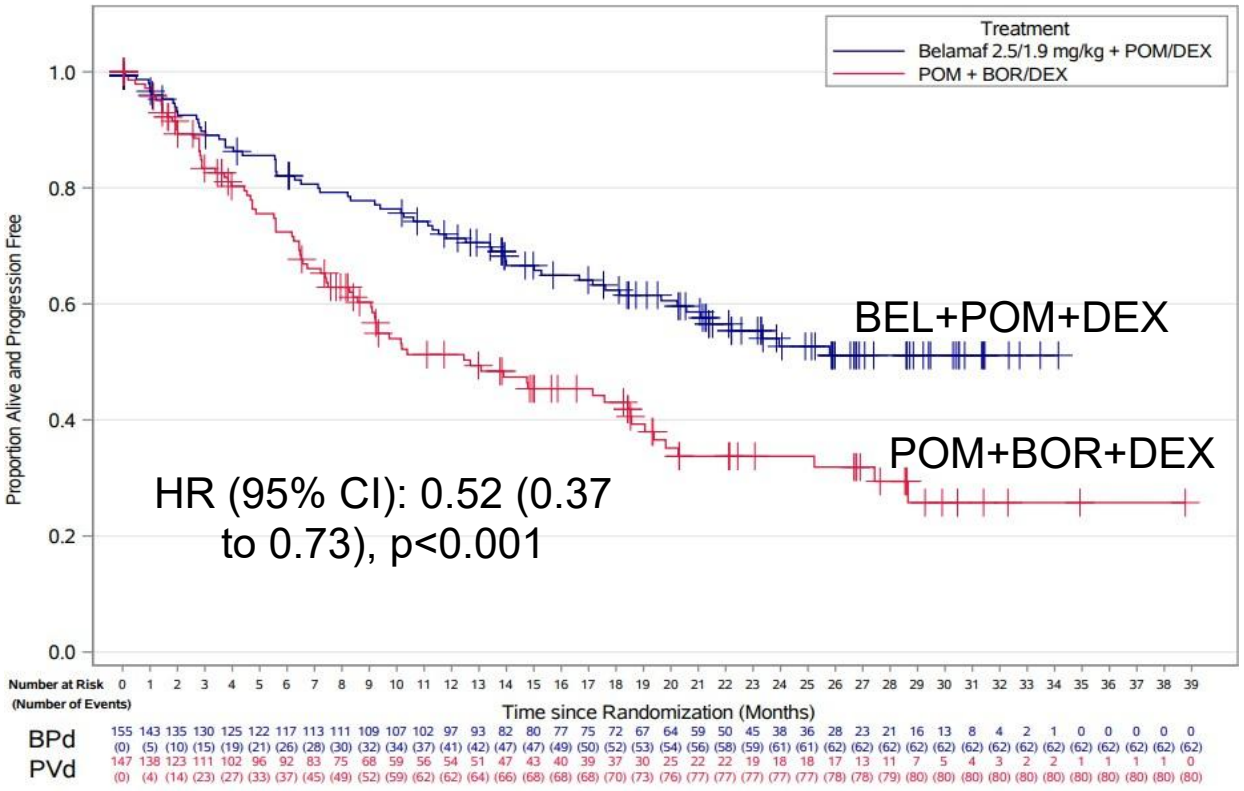


[*Link to Key DREAMM-8 results]

NICE Abbreviations: 2L, 2nd line; BEL, belantamab mafodotin; BOR, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide, OS, overall survival; PFS, progression-free survival; POM, pomalidomide

DREAMM-8: PFS for all LoTs for ITT and LEN-refractory

Figure S5. Kaplan Meier curves of IRC-PFS for ITT (all LoTs)



[redacted]

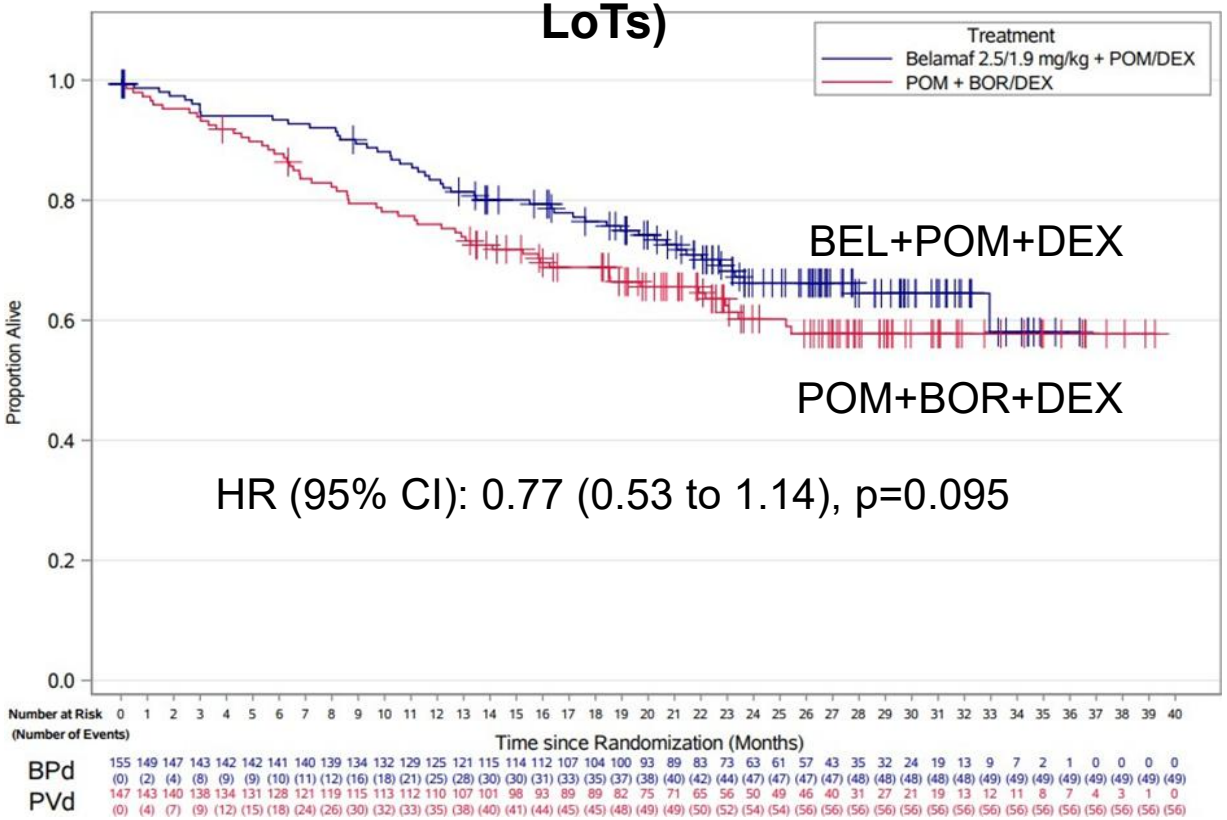
[redacted]

*Link to key DREAMM-8 results

NICE Abbreviations: BEL, belantamab mafadotin; BOR, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; IRC, independent review committee; ITT, intention-to-treat; LEN, lenalidomide; LoT, line of treatment; PFS, progression free survival; POM, pomalidomide

DREAMM-8: OS for all LoTs for ITT and LEN-refractory

Figure S7. Kaplan Meier curves of OS for ITT (all LoTs)



[redacted]

[redacted]

Company: ITT OS has reached [redacted]; overall maturity and information fraction (IF) [redacted], where 217 were planned deaths for OS analysis. [redacted].

*Link to key DREAMM-8 results

NICE Abbreviations: BEL, belantamab mafadotin; BOR, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; IF, information fraction; ITT, intention-to-treat; LEN, lenalidomide; LoT, line of treatment; OS, overall survival; POM, pomalidomide

Kaplan-Meier analyses: dose delays ≥8 and ≥12 weeks after at least 6 months of BEL+POM+DEX

[redacted]

[redacted]

Median PFS for those with dose delays of ≥8 and ≥12 weeks remains [redacted], similar to ITT [redacted].
Suggests extended dose interruptions do not have adverse impact on PFS outcomes

*Link to DREAMM-8 results – dose interruption

Abbreviations: BEL, belantamab mafadotin; DEX, dexamethasone; ITT, intention-to-treat; [redacted]; PFS, progression-free survival; POM, pomalidomide

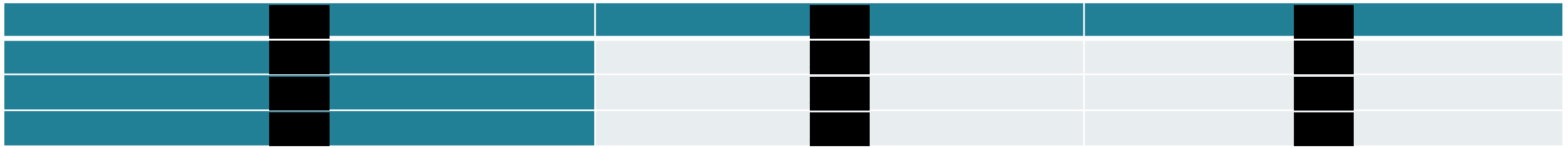
Inverse probability of treatment weighting: datasets

- **IPTW** link BEL+POM+DEX (DREAMM-8) to network via DAR+BOR+DEX (DREAMM-7)
  - Used IPD (study endpoints, treatment group, prognostic/TEM variables)
  - Identified baseline prognostic factors (literature, validated by experts); adjusted using propensity scores
- **Used IPTW-integrated FE NMA for LEN-exposed + ITT population to derive PFS and OS outcomes**
  - IPTW connects BEL+POM+DEX to network (anchored by: DAR+BOR+DEX, BOR+DEX, CAR+DEX)

Table S2. Summary table of exclusion criteria applied to DREAMM-7 and DREAMM-8 for IPTW

Trial	ITT population: adults with RRMM	Exclusion criteria applied for IPTW
DREAMM-7	• At least 1 prior LOT • Not intolerant or refractory to DAR • No more than 50% with 2+ prior LOT	• No prior exposure to LEN • Refractory to POM
DREAMM-8	• Previously treated with LEN & at least 1 prior LOT • Not refractory to POM • No more than 50% with 3+ LOT	• Refractory to any anti-CD38 (including DAR)

[redacted]



NICE

*Link to Limitations of OS NMA

IPTW analysis population: baseline characteristics

[redacted]

[redacted]	[redacted]			[redacted]		
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Link to Limitations of OS NMA

Abbreviations: BEL, belantamab mafadotin; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IPTW, inverse probability of treatment weighting; ISS, International Staging System; LEN, lenalidomide, LoT, line of treatment; POM, pomalidomide; ref, refractory; std, standard

IPTW results: PFS and TTD

Figure S11. KM plot of PFS with BEL+POM+DEX vs DAR+BOR+DEX from IPTW analysis

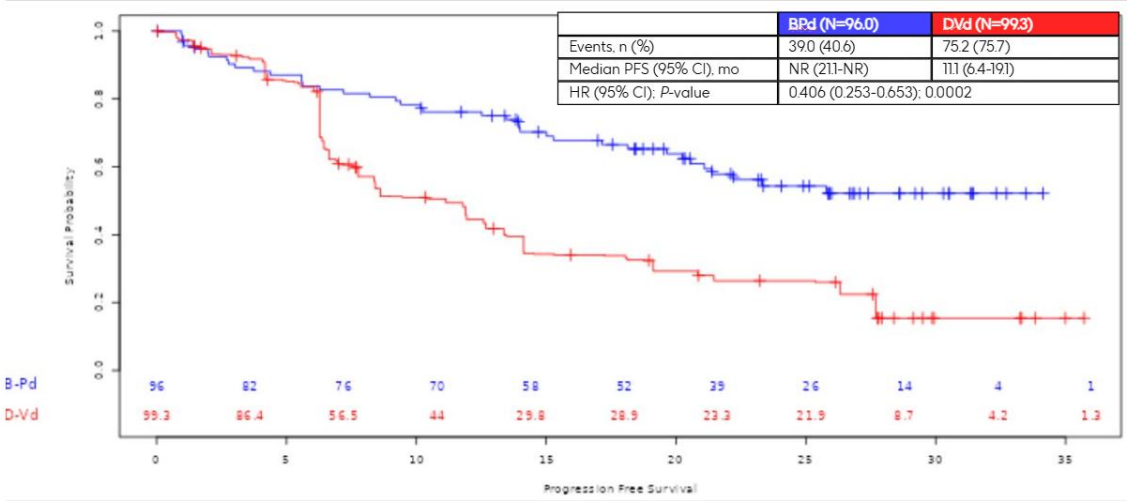
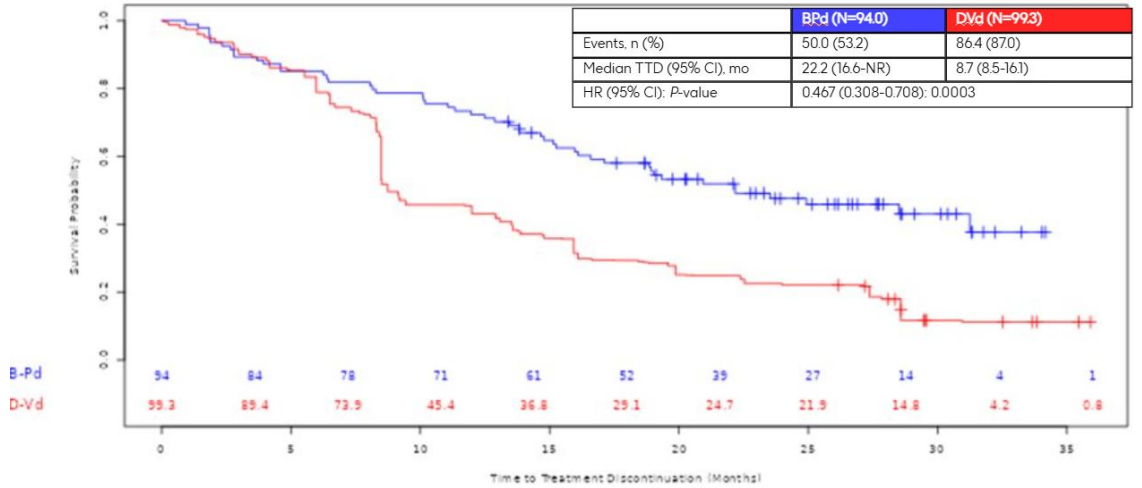


Figure S12. KM plot of TTD with BEL+POM+DEX vs DAR+BOR+DEX from IPTW analysis



- Company did sensitivity analysis excluding 4 people assigned with high weight to account for notable drop in PFS and TTD KM curves of DAR+BOR+DEX at around month 6-7
- Results consistent with initial analyses. A clinical expert suggested drop in PFS may be related to fixed duration of BOR+DEX (~6 months). At this point, people transition from triplet therapy to DAR monotherapy, potentially losing initial PFS benefits from triplet regimen

*Link to IPTW analyses: results

NICE Abbreviations: BEL, belantamab mafadotin; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; IPTW, inverse probability of treatment weighting; KM, Kaplan-Meier; PFS, progression-free survival; POM, pomalidomide; TTD, time to treatment discontinuation

DAR+BOR+DEX SACT baseline curve

Figure S13. Digitised SACT data overlaid with the IPTW DAR+BOR+DEX curve

[redacted]

Figure S14. Summary of parametric extrapolations of DAR+BOR+DEX SACT OS data

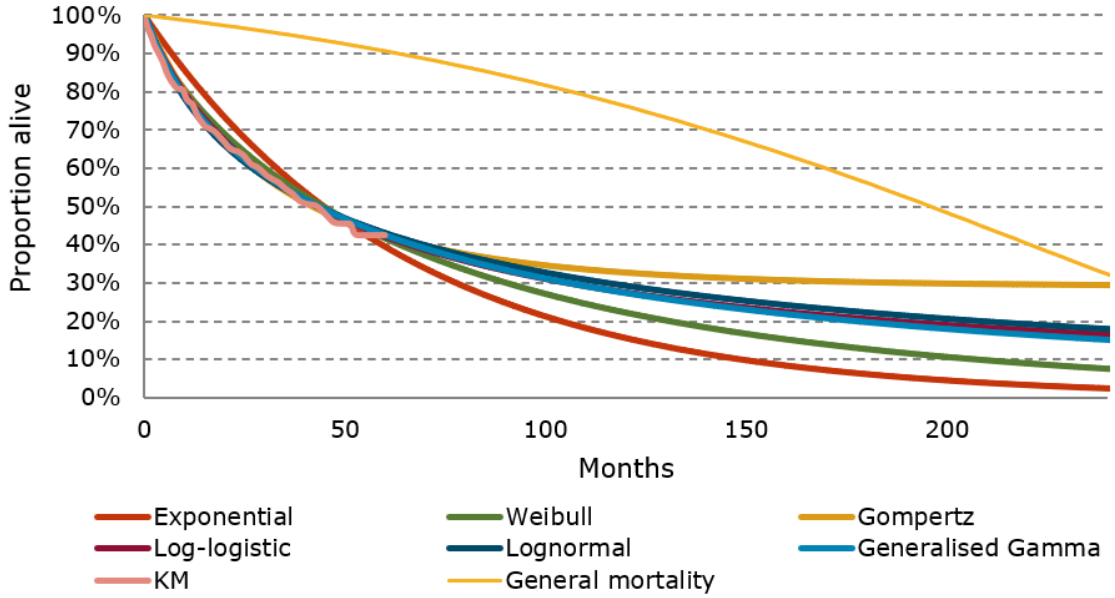


Table S5. DAR+BOR+DEX SACT OS extrapolation versus DREAMM-7 DAR+BOR+DEX clinician validation

Parametric curve (DAR+BOR+DEX)	OS		
	5 years	10 years	15 years
DREAMM-7 clinical validation (average of 3 EE's, most likely %)	[redacted]	[redacted]	[redacted]
DAR+BOR+DEX SACT – Weibull	[redacted]	[redacted]	[redacted]
DAR+BOR+DEX SACT – Exponential	[redacted]	[redacted]	[redacted]

*Link to SACT data to model OS

NICE Abbreviations: BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; KM, Kaplan-Meier; OS, overall survival; SACT, Systemic Anti-Cancer Therapy

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**.

*Link to Summary of issues (2)