PART 1 for PROJECTOR – contains redacted information

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

Technology appraisal committee B [8 January 2025] (Closed meeting)

Chair: Charles Crawley

Lead team: Vanessa Danielson, Andrew Makin, Tony Wootton

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Company: GlaxoSmithKline

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

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

NICE National Institute for Health and Care Excellence

Relapsed or refractory multiple myeloma

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

- **Epidemiology**: 4,906 new cases in England in 2020 (Cancer registration statistics)
  - more common in elderly, men and people of African family background
- **Classification**
  - Relapsed/refractory: MM that is not responsive to treatment or for MM that has had minimal response or better, progression within 60 days of the last LoT
- **Symptoms**: infections, bone pain, fractures, fatigue, hypercalcaemia, kidney issues
- **Prognosis**: In 2019 in England, 5-year survival for adults diagnosed with MM was 54% (Baker and Mansfield 2023)
  - Survival likely worse for LEN-refractory MM
  - Prognosis improving with more new and effective treatments
- **Challenge of treatment**: as MM progresses, resistance to different classes of treatments
  - LoT in UK: 95% diagnosed with MM have 1L, 64% have 2L
  - Company estimates ~3,400 eligible for 2L

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Abbreviations: 1/2L, 1st/2nd line; LEN, lenalidomide; LoT, line of treatment; MM, multiple myeloma

Patient perspectives

Submission from Myeloma UK

Living with RRMM

- Highly individual, variable and complex cancer
- Moderate or high effect on QoL, constant possibility of relapse has huge psychological impact
- Affects all aspects of life for people and carers: social, relationships, financial, physical, emotional
- Switching treatment brings hope, stress in adjusting to possible new side effects and awareness that with each new LoT, options become limited and life expectancy decreases

Current treatments

- Later LoT have worse outcomes (decreased remission times, more side effects; treatments less effective, harder to tolerate)

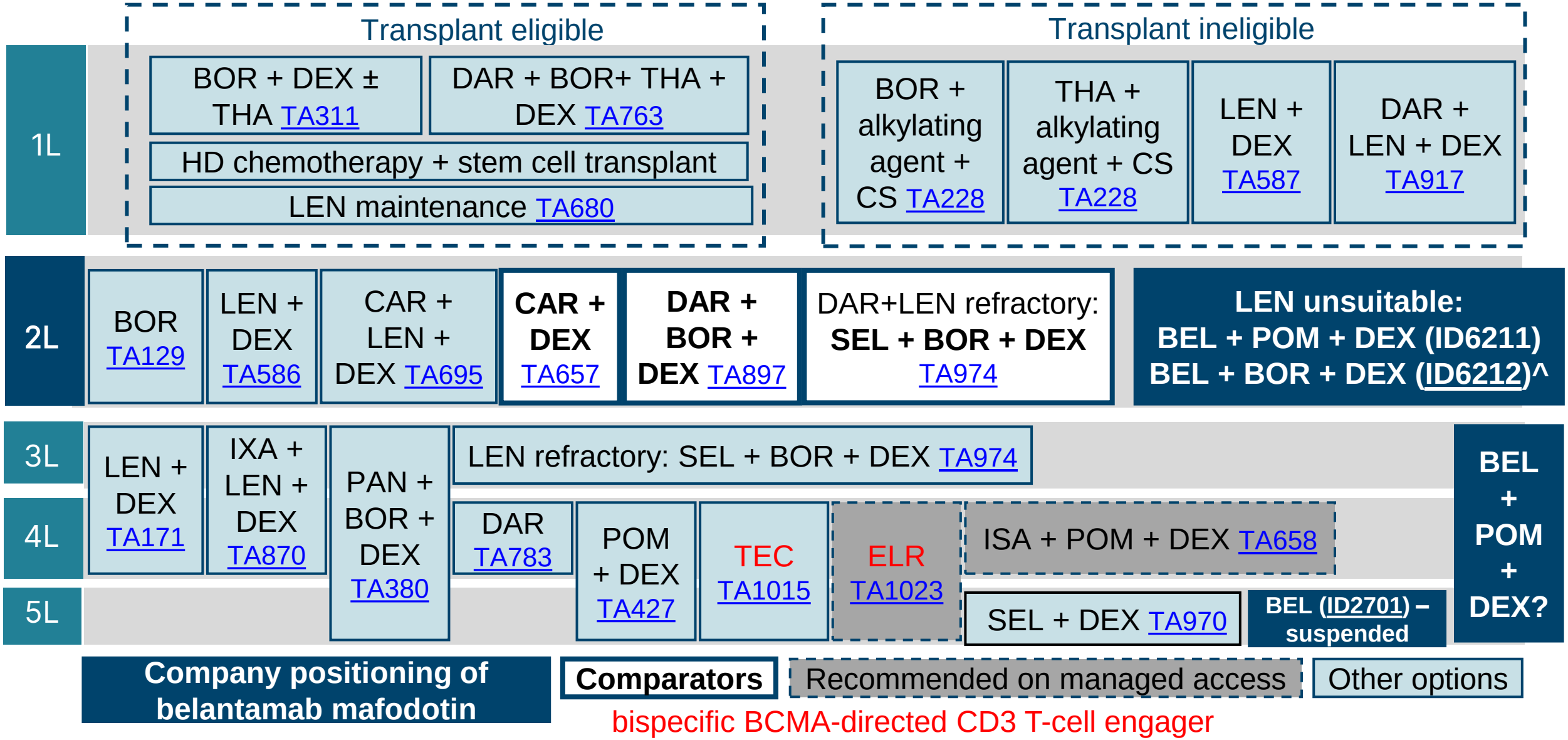
Unmet need

- More options needed with high response rates and good remission times: MM is varied; individual response to treatments affects future options
- BEL: eye-related side effects are tolerable and do not negate overall treatment benefit

Myeloma has impacted a lot. I have a big family and even with close family, a lot of the time they won't even come into the house because they are scared they are going to make me ill

Abbreviations: BEL, belantamab mafodotin; LoT, line of treatment; MM, multiple myeloma; QoL, quality of life; RR, relapsed or refractory

Treatment pathway and company positioning of BEL



Abbreviations: **^BEL+BOR+DEX is being appraised at the same time in the same position (ID6212);** 1/2/3/4/5L, 1st /2nd/3rd/4th/5th line; BCMA, B-cell maturation antigen; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; CS, corticosteroid; DAR, daratumumab (**anti-CD38**); DEX, dexamethasone; ELR, elranatamab; HD, high dose; ISA, isatuximab; IXA, ixazomib; LEN, lenalidomide; PAN, panobinostat; POM, pomalidomide; SEL, selinexor; TEC, teclistamab; THA, thalidomide

Belantamab mafodotin (Blenrep)

Marketing authorisation (MA) – Apr 2025	• BEL+POM+DEX for treatment of MM in adults after ≥1 prior therapy including a LEN-containing regimen • 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 ([redacted]), 70mg ([redacted]) • Patient access scheme available
Other	• Dec 2023: EMA's CHMP recommended not to renew conditional MA for BEL monotherapy for MM after ≥4 previous treatments (recent data had not confirmed BEL's effectiveness and benefits no longer outweighed its risks) • MHRA revoked conditional MA of BEL • NICE TA ID2701 suspended Oct 2024

Abbreviations: Apr, April; BEL, belantamab mafodotin; CHMP, Committee for Medicinal Products for Human Use; Dec, December; DEX, dexamethasone; EMA, European Medicines Agency; LEN, lenalidomide; MHRA, Medicines and Healthcare products Regulatory Agency; MM, multiple myeloma; Oct, October; POM, pomalidomide; RR, relapsed or refractory; SmPC, summary of product characteristics

Positioning of BEL+POM+DEX

Company's positioning at 2L and LEN unsuitable is narrower than its proposed MA. Definition of 'LEN-unsuitable' is unclear. Relevant comparators for people choosing not to have LEN at 2L would include LEN-containing options

Company

- Positioned BEL+POM+DEX at 2L for MM after 1 LoT inc. a LEN-containing regimen, and LEN unsuitable (LEN refractory, contraindicated, not tolerated or other such as individual preference)
  - Believes LEN will be unsuitable for every patient at 2L in NHS → considers most relevant evidence for BEL+POM+DEX is from DREAMM-8 **full ITT** population (all LoT, 81% LEN-refractory, 100% LEN-exposed)
- Presented cost-effectiveness analyses for DAR-eligible and DAR-ineligible subpopulations
  - based on relevant comparators: CAR+DEX, DAR+BOR+DEX and SEL+BOR+DEX only for DAR+LEN refractory
- CS, p20: [redacted]

- What is the company's intended positioning of BEL+POM+DEX?
- Where would BEL+POM+DEX likely be used in the NHS?
- Besides refractoriness, contraindications and intolerance, when would LEN be considered unsuitable?

Abbreviations: 2L, 2nd line; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; inc, including; ITT, intention-to-treat; LEN, lenalidomide; LoT, line of treatment; MM, multiple myeloma; POM, pomalidomide; SEL, selinexor

Treatment pathway and company positioning – EAG comments

Treatment pathway for RRMM is evolving in NHS

Clinical advice to EAG

- 1L DAR seems effective → impact on OS is unknown
  - Transplant eligible: DAR+BOR+THA+DEX then LEN (~30% choose not to have LEN)
  - Transplant ineligible: DAR+LEN+DEX (on disease progression, most likely DAR refractory)
- Uncertain which 2L treatments would become future standard care
  - Limited experience of treating 1L DAR-refractory MM
  - Clinical experience of SEL+BOR+DEX is limited (TA974 published in May 2024)

- Is the treatment pathway reflective of NHS practice?
  - What do most people in the NHS have at 1L? A DAR-containing regimen?
- For people on DAR+LEN+DEX, would they become refractory to LEN and DAR at the same time?
- What are the relevant comparators for the company's positioning at 2L for MM that is **LEN unsuitable**?
- What is the likely impact of using BEL at 2L on subsequent treatments in the pathway such as other BCMA-targeted treatments, TEC and ELR?

Abbreviations: 1/2L, 1st/2nd line; BCMA, B-cell maturation antigen; BEL, belantamab mafodotin; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; ELR, elranatamab; LEN, lenalidomide; MM, multiple myeloma; OS, overall survival; RR, relapsed/refractory; SEL, selinexor; TA, technology appraisal; TEC, teclistamab; THA, thalidomide

Key issues

Issues	Slides	ICER impact
1. DREAMM-8: generalisability to NHS	13	Unknown
2. Indirect treatment comparisons: limitations of PFS and OS NMAs	14 – 16	Unknown
3. Eye-related adverse events: HRQoL and modelling disutility	17 – 19	Unknown
4. Modelling OS benefit: differential OS benefit for BEL+POM+DEX and comparators [company] vs no differential benefit [EAG]	21 – 22	Large
5. Modelling drug costs: POM price, estimating medication usage, wastage of tablets	23 – 24	Large
6. Health state utility values: treatment-specific PF-on-treatment utilities for BEL+POM+DEX (higher) and comparators (lower) [company] vs same health state utilities for all treatments [EAG]	25	Large

Abbreviations: BEL, belantamab mafodotin; DEX, dexamethasone; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; POM, pomalidomide

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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% ([redacted]) I; 26% ([redacted]) II; 15% ([redacted]) III
- Prior LoTs: 52.6% 1; 33.8% 2 or 3; 13.6% 4+

*Back-up slides 34 – 37

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

Key DREAMM-8 results (data cut: 29 Jan 2024)*

Median PFS reached only for comparator. Otherwise, median PFS and OS not reached. Company did not present results for LEN-unsuitable + 1 prior LoT

	Full ITT population (LEN-exp for all LoT)		LEN refractory (all LoT)	
	BEL+POM+DEX (n=155)	POM+BOR+DEX (n=147)	BEL+POM+DEX (n=125)	POM+BOR+DEX (n=111)
Progression-free survival (PFS)				
Median (95% CI), months	NR (20.6 to NR)	12.7 (9.1 to 18.5)	24 (17.6 to NR)	9.2 (7.2 to 12.5)
HR (95% CI)	0.52 (0.37 to 0.73), p<0.001		0.45 (0.31 to 0.65)	
Overall survival (OS)				
Median (95% CI), months	NR (33.0 to NR)	NR (25.2 to NR)	[redacted]	[redacted]
Estimated HR (85% CI)	0.77 (0.53 to 1.14), p=0.095		[redacted]	
Time to treatment discontinuation (TTD)				
Median (95% CI), months	[redacted]	[redacted]	-	-

Progression-free survival (PFS)

*Back-up slides 38 – 40

Subgroup	BEL+POM+DEX	POM+BOR+DEX	HR (95% CI)
2L: 1 prior LoT	25/82	34/77	0.52 (0.31 to 0.88)
Anti-CD38-refractory	20/35	25/36	0.65 (0.36 to 1.18)
LEN+anti-CD38 exposed	22/38	27/42	0.69 (0.39 to 1.21)

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Abbreviations: 2L, 2nd line; anti-CD38 e.g. daratumumab; BEL, belantamab mafodotin; BOR, bortezomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide, LoT, line of treatment; NR, not reported; POM, pomalidomide

Key issue 1: Generalisability of DREAMM-8 results

Company: ITT data representative of LEN-unsuitable population and use of 2L options in NHS. EAG: company did not present data for target population (LEN-unsuitable at 2L)

Company

- Clinical evidence informing economic model: DREAMM-8 full ITT (primary endpoint IRC-PFS met)
  - ITT population is 'predominantly LEN-unsuitable': 81% LEN-refractory; 19% LEN-exposed likely LEN-unsuitable at 2L (clinical expert opinion) [53% at 2L, 47% at 3L+]
- Impact of DAR-refractoriness on 2L options: ITT results still relevant to NHS
  - Implementation of DAR+LEN+DEX (TA917 Oct 2023) in NHS will take time
  - DAR-refractory at 2L likely low in next 3-5 years (DAR long PFS: at 56.2 months, mPFS not reached)
  - NHS: ≤10% DAR-refractory, likely rise to 15-20% in 2025 and 50-60% in 2027 (clinical advice)

EAG comments

- DREAMM-8: baseline characteristics balanced between arms; population generally comparable to NHS patients but DREAMM-8 mean age 66.1 years greater than NHS average 70 years
  - ~53% had 1 prior LoT (2L) – baseline characteristics similar to ITT population
  - ~[redacted] LEN-refractory and 2L
  - ~25% had prior DAR, [redacted] anti-CD38 refractory and 2L → limits generalisability to NHS. Majority likely have DAR at 1L moving forwards. Impact of prior DAR on BEL+POM+DEX's efficacy unknown
- DREAMM-8's data is immature and company did not present data for specific target population only

- Is DREAMM-8 ITT data representative of company's target population in NHS?
- What DREAMM-8 data should be used to inform economic model?

Abbreviations: 2/3+L, 2nd/3rd+ line; anti-CD38 e.g. DAR; BEL, belantamab mafodotin; DAR, daratumumab; DEX, dexamethasone; ITT, intention-to-treat; IRC, independent review committee; LEN, lenalidomide, LoT, line of treatment; mPFS, median progression-free survival; POM, pomalidomide

Company NMA FE results*

BEL+POM+DEX showed longer PFS than CAR+DEX (in LEN-exposed and LEN-refractory) and longer PFS than SEL+BOR+DEX (in LEN-exposed)

	HR (95% CrI) for BEL+POM+DEX vs		
	CAR+DEX	DAR+BOR+DEX	SEL+BOR+DEX
LEN-exposed: PFS	[redacted]	[redacted]	[redacted]
LEN-exposed: OS	[redacted]	[redacted]	[redacted]
LEN-exposed+ITT: OS	[redacted]	[redacted]	[redacted]
LEN-refractory: PFS	[redacted]	[redacted]	[redacted]
LEN-refractory+ITT: OS	[redacted]	[redacted]	[redacted]

- Primary analysis: DREAMM-8 ITT and LEN-exposed populations from comparator studies
- Secondary analysis: primary analysis and data from other studies' ITT populations, not specifically LEN-exposed

EAG overall comments

- NMAs correctly implemented. Agree with using FE NMAs for base case
- **LEN-exposed PFS NMA:** LoTs mixed, impact of TEMS not explored → caution in interpreting results
- **LEN-exposed + ITT OS NMA:** heterogenous populations – unclear if results generalisable to company's target population in NHS
  - Considers an inappropriate HR used to link BEL+POM+DEX with all comparators (OPTIMISMM). Company did not adjust for impact of subsequent treatments on effectiveness of comparators – see Key issue 2

*Back-up slides 41 – 44

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; CrI, credible interval; DAR, daratumumab; DEX, dexamethasone; FE, fixed effects; HR, hazard ratio; ITT, intention-to-treat; LEN, lenalidomide, LoT, line of treatment; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; SEL, selinexor; TEM, treatment-effect modifier

Key issue 2: Limitations of PFS and OS NMAs – EAG comments

High levels of uncertainty in NMA results. OS HR from OPTIMISMM used to link BEL+POM+DEX with all other comparators uncertain

EAG comments

- Subsequent treatments: impact of type and frequency on OS not considered
  - Evidence of importance of subsequent treatments from OPTIMISMM trial in NMA (common comparator – POM+BOR+DEX)
    - Company used unpublished conference presentation with pre-planned exploratory OS analysis applying Cox PH model adjusted for stratification factors and subsequent therapy as time-dependent covariate: **HR 0.76**; 95% CI: 0.62 to 0.93 – used in LEN-exp+ITT OS NMA
      - Published (conference abstract) ITT OS analysis: **HR 0.94**; 95% CI 0.77 to 1.15
  - Unclear if subsequent treatments in studies are representative of NHS practice
- For some comparator studies, PFS and OS PH assumptions may not hold (see back-up slides 45 – 46)
- Limited reporting of baseline characteristics → difficult to assess between study heterogeneity and transitivity/inconsistency assumption
- NMAs not adjusted for TEMS specifically prior LoT, ECOG PS and ISS stage
- Populations: mixed with different LoTs, DAR and LEN exposure
- Immature OS DREAMM-8 data

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; CI, confidence interval; DAR, daratumumab; DEX, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; exp, exposed; HR, hazard ratio; 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; PH, proportional hazards; POM, pomalidomide; TEM, treatment-effect modifier

Key issue 2: Limitations of PFS and OS NMAs – company response

Use of adjusted HR for OS from OPTIMISMM methodologically necessary and appropriate

Company's response to issues raised by EAG

- Impact of subsequent treatments
  - OPTIMISMM Cox PH analysis: methodologically necessary and appropriate, accounting for unique high rates of unintended cross-over of patients from assigned interventions (POM+BOR+DEX and BOR+DEX)
    - 79.1% BOR+DEX and 68.3% POM+BOR+DEX had subsequent therapy; >66% in BOR+DEX had POM
  - Adjusting for subsequent treatments impact on comparators' efficacy may not be appropriate for all trials
- DREAMM-8 ITT data used to align with included studies' populations (mixed prior LEN use and LoTs)
  - Agrees difficulty in fully assessing between-study heterogeneity which "underscores need for cautious interpretation of NMA results"
- Acknowledges limitation of maturity of DREAMM-8 data

- Should the adjusted HR for OS from OPTIMISMM be used in the LEN-exp+ITT OS NMA?
- Are the PFS and OS NMAs robust for decision making?
- Are the PFS and OS NMAs results generalisable to the NHS?
- Is BEL+POM+DEX clinically effective compared with 2L LEN-sparing comparators?

Abbreviations: 2L, 2nd line; BEL, belantamab mafodotin; BOR, bortezomib; DEX, dexamethasone; exp, exposed; ITT, intention-to-treat; LEN, lenalidomide, LoT, line of treatment; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; POM, pomalidomide

DREAMM-8: Eye-related adverse events in BEL+POM+DEX (n=150)*

Company: most eye-related side effects could be resolved with dose interruption. Dose changes based on keratopathy visual acuity scale (lower RDI for BEL+POM+DEX than POM+BOR+DEX)

BEL: [redacted] dose reductions, 86% interruptions or delays, 9% discontinuations

^median (range) days

	Bilateral worsening of BCVA in patients with normal baseline (20/25 or better in ≥ 1 eye)	
	20/50	20/200
Patients, n/N (%)	51/150 (34%)	2/150 (1%)
Time to onset of **1st event**^	112 (28 – 761)	351 (29 – 673)
Duration of 1st event^	29 (7 – 196)	25.5 (22 – 29)
First event resolved, n (%)	47 (92%)	2 (100%)
Duration of **last event**^	[redacted]	[redacted]
Last event resolved, n (%)	[redacted]	[redacted]

Events per KVA scale	
Any event, n (%)	[redacted]
Grade 2, n (%)	[redacted]
Grade ≥3, n (%)	[redacted]
Time to **1st event** (≥ grade 2)^	[redacted]
Duration of 1st event^	[redacted]
First event resolved, n/N (%)	[redacted]
Events per visual acuity changes	
Any event, n (%)	[redacted]
Grade 2, n (%)	[redacted]
Grade ≥3, n (%)	[redacted]
Time to **1st event** (≥ grade 2)^	[redacted]
Duration of 1st event^	[redacted]
First event resolved, n/N (%)	[redacted]

Normal Vision (20/20)

Blurred Vision (20/50)

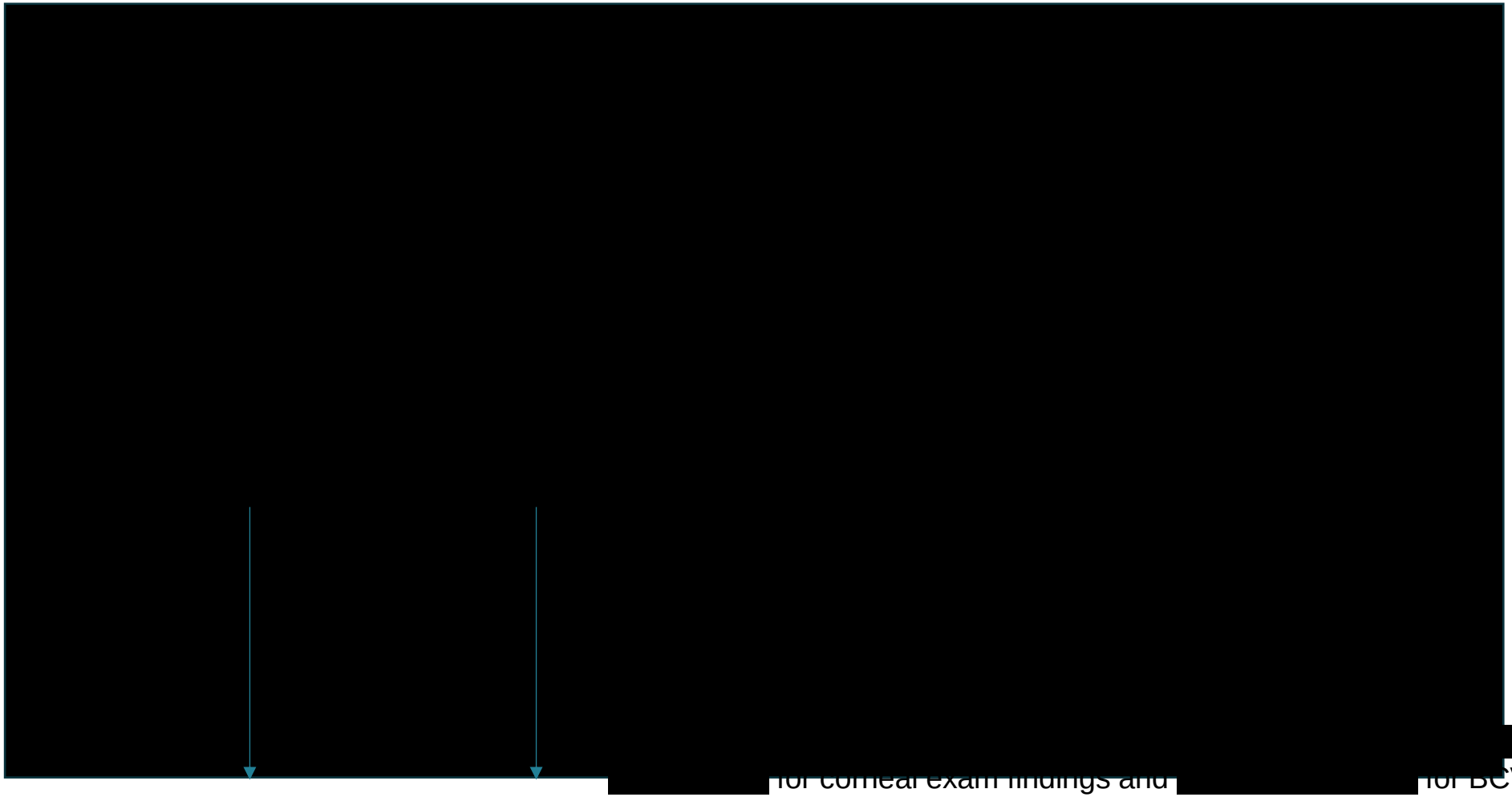
Vision Impaired (20/200)

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; BCVA, best corrected visual acuity; DEX, dexamethasone; KVA, keratopathy visual acuity; n, number; N, total sample; POM, pomalidomide; RDI, relative dose intensity

*Back-up slide 47

DREAMM-8 (ITT): EQ-5D-3L results

Company: despite higher incidence of eye-related side effects in BEL+POM+DEX, overall HRQoL did not differ between arms over time



Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; DEX, dexamethasone; EQ-5D, EuroQoL-5 dimensions; HRQoL, health-related quality of life; ITT, intention-to-treat; POM, pomalidomide

; overall KVA grade

for corneal exam findings and for BCVA events

- Are eye-related adverse events disutility likely captured in the EQ-5D-3L?
- Does BEL+POM+DEX improve HRQoL compared with POM+BOR+DEX?

Key issue 3: eye-related adverse events

≥5% Grade 3+ TEAEs in economic model. Company: given regularity of eye-related AEs in BEL+POM+DEX, DREAMM-8 EQ-5D-3L likely account for HRQoL impact so no additional disutility is applied as it is already reflected in treatment-specific utilities for PFS health state

Incidence of AE	BEL+POM+DEX	CAR+DEX	DAR+BOR+DEX	SEL+BOR+DEX	Disutility
Source	DREAMM-8	Usmani 2023	DREAMM-7	Bahlis 2018	^TA695; ^^TA897
Neutropenia	0.42	0.07	[redacted]	0.19	0.15^
Anaemia	0.10	0.16	[redacted]	0.04	0.31^
Thrombocytopenia	0.24	0.16	0.35	0.31	0.31^
Lymphopenia	[redacted]	0.07	[redacted]	-	0.07^^
Pneumonia	0.17	0.09	0.04	-	0.19^
Peripheral neuropathy	[redacted]	0.01	[redacted]	-	0.07^^
Hypertension	[redacted]	0.18	[redacted]	-	0^
Fatigue	0.06	0.05	[redacted]	0.23	0.12^
Keratopathy	[redacted]	-	-	-	Captured in EQ-5D-3L
Blurred vision	0.17 per cycle	-	-	-	
Dry eyes	0.08 per cycle	-	-	-	

- What is the impact of BEL's eye-related adverse events on patients?
- How are eye-related adverse events managed?
- What is the impact of dose modifications on BEL+POM+DEX's effectiveness?
- How should treatment-related adverse events be modelled?

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; EQ-5D, EuroQoL-5 dimensions; HRQoL, health-related quality of life; PFS, progression-free survival; POM, pomalidomide; SEL, selinexor; TEAE, treatment-emergent adverse event

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Key issue 4: Modelling OS benefit (1)

Large impact

Company assumes differential OS benefit across treatments; EAG assumes none

Background

- Company base case: OS with BEL+POM+DEX is longer than OS with comparators
  - BEL+POM+DEX: used unadjusted DREAMM-8 OS extrapolation
  - Comparators: HRs vs POM+BOR+DEX as baseline from LEN-exposed+ITT OS NMA (see slides 14 – 16)

EAG comments

- OS data in DREAMM-8 is immature and uncertain
- Company's OS NMA credible intervals all crossed 1
- OS benefit includes varying impact of subsequent therapies after progression
  - Using a different (published) HR from OPTIMISMM (common comparator POM+BOR+DEX) in LEN-exposed+ITT OS NMA would result in all HRs (vs BEL+POM+DEX) being closer to 1
  - If OS does not vary by treatment, as time in PFS-on-treatment health state is longer with BEL+POM+DEX, time on subsequent treatments is likely shorter than with comparators
    - Company and EAG preferred base cases: assumed time on subsequent treatment is independent of 2L treatments → BEL+POM+DEX's total costs may be overestimated and/or comparators' total costs may be underestimated
- EAG base case: no difference in OS across treatments → applied company's OS extrapolation for BEL+POM+DEX to comparators

Abbreviations: 2L, 2nd line; BEL, belantamab mafodotin; BOR, bortezomib; DEX, dexamethasone; HR, hazard ratio; ITT, intention-to-treat; LEN, lenalidomide, NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; POM, pomalidomide

*Back-up slide 48 – 49

Key issue 4: Modelling OS benefit (2)

Large impact

Company reiterates there is evidence of OS benefit with BEL+POM+DEX

Company's response to issues raised by EAG

- Presented evidence that supports an OS improvement for BEL+POM+DEX:
  - Uncertainty surrounding OS HRs is accounted for in model through PSA, which provides an unbiased, probabilistic interpretation of results (i.e., distribution of ICERs) incorporating the uncertainty
  - Company's surrogacy report (CS, Appendix O.4) demonstrates a clear relationship between strong PFS result and OS extrapolations
  - Evidence from DREAMM-7 (BEL+BOR+DEX) demonstrates a statistically significant OS benefit
- Considers EAG's assumption of equal OS between treatments is an extreme scenario

- How should OS benefit be modelled? Using company's differential OS benefit approach or using EAG's assumption of no difference between treatments?

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; CS, company submission; DEX, dexamethasone; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; PSA, probabilistic sensitivity analysis

Large impact

Key issue 5: Modelling drug costs (1)*

Company assumed a reduction in POM list price, applied different approaches to estimating medication usage for BEL and comparators, and assumed wastage on 100% of administrations including tablets

Background

- To calculate drug costs, company's model consider acquisition costs, dosing and wastage
  - **Acquisition costs:** because POM's patent is due to expire in 2024, company assumes a [redacted] reduction in list price of POM (pack of 21 x 4mg tablets from £8,884 to [redacted])
  - **Estimated medication usage:** based on label using RDI to account for dose reductions or delays **or** based on IPD without RDI (option to use actual dose received or closest SmPC dose)
  - **Wastage:** when wastage is assumed, method of moments calculations derive number of vials needed per cycle based on weight or body surface area
- Company base case
  - **POM:** assumes acquisition cost of [redacted]
  - **Medication usage**
    - BEL: IPD dosing using actual dose received
    - Comparators: dosing based on SmPC label and constant RDI
  - **Wastage:** 100% of administrations including tablets (POM, SEL, DEX)

*Back-up slides 50 – 51

Abbreviations: BEL, belantamab mafodotin; DEX, dexamethasone; IPD, individual patient data; POM, pomalidomide; RDI, relative dose intensity; SEL, selinexor; SmPC, summary of product characteristics

Key issue 5: Drug costs (2)

Large impact

EAG base case: POM current list price, used RDI to estimate medication usage for all treatments, excluded wastage of tablets

EAG comments

- **POM:** in line with NICE HTE manual 2022, EAG has used POM's current list price in its base case
- **BEL usage:** EAG acknowledges IPD is more accurate than RDI-based costs but
  - Using IPD, total cost of BEL+POM+DEX is lower by [redacted] ([redacted]) than using RDI → same RDI-based approach should be applied for BEL and comparators
- **Wastage:** consider all tablets allow dose reductions without wastage → excluded from base case

Company's response to issues raised by EAG

- Regular dose modifications due to eye-related side effects is unique to BEL → using mean RDI would artificially inflate costs by assuming time varying trends do not exist and does not account for trends in trial data of increasing dose reductions and delays over time. Use of mean RDI skews towards earlier points in follow up where more patients are on treatment and dose intensity is higher
- CS p85 "A significantly higher rate of dose interruptions and reductions in BEL+POM+DEX led to a notably lower RDI in actual clinical practice than might be inferred from the trial dosing schedule"

- What price of POM should be used?
- How should BEL usage be estimated? IPD or RDI?
- Should wastage of tablets be included or excluded in the model?

Abbreviations: BEL, belantamab mafodotin; DEX, dexamethasone; IPD, individual patient data; POM, pomalidomide; RDI, relative dose intensity

Key issue 6: Health state utility values

Large impact

Company

- **Base case:** in line with NICE reference case, used DREAMM-8 ITT EQ-5D-3L data for health state utilities (age-adjusted)
- Assumed PFS off treatment = PFS on treatment
- ^Assumed PFS for all comparators = PFS for POM+BOR+DEX
- Considers eye-related adverse events captured in EQ-5D-3L and no specific disutility is applied

EAG comments

- 48% on BEL+POM+DEX in DREAMM-8 had Grade ≥3 eye-related AE → EQ-5D-3L unlikely to capture HRQoL detriment (visual 'bolt on' EQ-5D-V available)
- EAG base case: used ENDEAVOUR utilities from TA897 (DAR+BOR+DEX for MM with 1 prior LoT that included LEN or LEN was unsuitable at 2L)

Health state	ID6211 (BEL+POM+DEX)			TA974 (SEL+BOR+DEX)		
	Company base case: DREAMM-8 EQ-5D-3L		EAG base case: ENDEAVOR (TA897/TA457)	BOSTON (SEL+BOR+DEX vs BOR+DEX; EQ-5D-5L)		Scenario: Hatswell (2019)
	BEL+POM+DEX	POM+BOR+DEX^	All treatments: 2L	Company base case (mean of both arms across all LoTs)	EAG base case: 2L	2L
PF on treatment	[redacted]	[redacted]	0.737	0.697	**0.706**	0.620
PF off treatment	[redacted]	[redacted]	0.737	-	**-**	-
PD	[redacted]	[redacted]	0.665	0.660	**0.668**	0.550

- How should utilities be modelled? Should BEL+POM+DEX apply a different PF-on-treatment utility whereas all comparators apply the same utility as POM+BOR+DEX?

Abbreviations: 2L, 2nd line; AE, adverse event; BEL, belantamab mafodotin; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; EQ-5D, EuroQoL-5 dimensions; HRQoL, health-related quality of life; ITT, intention-to-treat; LEN, lenalidomide; LoT, line of treatment; MM, multiple myeloma; PD, progressed disease; PFS, progression-free survival; POM, pomalidomide; SEL, selinexor

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
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	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)	List price £8,884
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
Wastage	Included for tablets	Excluded for tablets
Health state utility values	PF-on-treatment utilities based on DREAMM-8 EQ-5D-3L • BEL+POM+DEX: [redacted] • CAR+DEX; DAR+BOR+DEX; SEL+BOR+DEX: [redacted] PF off-treatment: [redacted] PD: [redacted]	Same PF-on-treatment utilities across all treatments based on utilities from TA897 PF on/off treatment: 0.737 PD: 0.665
Vial sharing	Scenario only: 100% vial sharing	Scenario only: 100% vial sharing

- Should vial sharing be modelled? If so, what proportion of vial sharing should be modelled?

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; EQ-5D, EuroQoL-5 dimensions; HR, hazard ratio; IPD, individual patient data; ITT, intention-to-treat; LEN, lenalidomide; NMA, network meta-analysis; OS, overall survival; PD, progressed disease; PFS, progression-free survival; POM, pomalidomide; RDI, relative dose intensity; SEL, selinexor; SmPC, summary of product characteristics

Cost-effectiveness results

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

- Company and EAG base case ICERs: >£30,000 per QALY
- All scenarios >£30,000 per QALY

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Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

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

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

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Other considerations

Severity modifier

- Does not meet severity weighting threshold

Company's perspective of uncaptured benefits

- Growing DAR-refractory population at 2L
- Patient preferences not captured in partitioned survival modelling approaches → POM+DEX advantages such as oral treatments and well tolerated
- Increase therapeutic options for subsequent LoTs

Equality considerations

- No potential issues raised by stakeholders
- MM is more common in men, older people and people of African and Caribbean family background

Managed access (see slide 52)

- Company has not submitted a managed access proposal but notes in its submission that "managed access could be considered if this was an appropriate route to ensure patient access"

- Are there any uncaptured benefits?
- Are there any equality issues to consider?
- What are the uncertainties and can they be resolved with further data collection?

Abbreviations: 2L, 2nd line; DAR, daratumumab; DEX, dexamethasone; LoT, line of treatment; MM, multiple myeloma; POM, pomalidomide

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

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

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Key issues

Issues	Slides	ICER impact
1. DREAMM-8: generalisability to NHS	13	Unknown
2. Indirect treatment comparisons: limitations of PFS and OS NMAs	14 – 16	Unknown
3. Eye-related adverse events: HRQoL and modelling disutility	17 – 19	Unknown
4. Modelling OS benefit: differential OS benefit for BEL+POM+DEX and comparators [company] vs no differential benefit [EAG]	21 – 22	Large
5. Modelling drug costs: POM price, estimating medication usage, wastage of tablets	23 – 24	Large
6. Health state utility values: treatment-specific PF-on-treatment utilities for BEL+POM+DEX (higher) and comparators (lower) [company] vs same health state utilities for all treatments [EAG]	25	Large

Abbreviations: BEL, belantamab mafodotin; DEX, dexamethasone; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; POM, pomalidomide

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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

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DREAMM-8 design (NCT04484623)	Ongoing (completion ~May 2029), phase 3, international (95 centres in 18 countries; 5 in UK), open-label, central randomisation (stratified for prior BOR, anti-CD38, LoTs (1 vs 2 or 3 vs ≥4); no treatment cross-over First patient in on 13 October 2020 to database lock date on 19 February 2024
Population	302 adults (≥18 years) with MM (confirmed IMWG criteria), ≥1 prior LoT, including LEN-containing regimen (LEN ≥2 consecutive cycles) and documented disease progression during or after most recent therapy. Up to 50% with ≥2 prior LoTs enrolled No prior POM or anti-BCMA, not refractory or intolerant to BOR. ECOG PS 0-2 **100% LEN-exposed; prior LoT 1: 52.6%; 2 or 3: 33.8% 4+: 13.6%**
Interventions	BEL+POM+DEX n=155 (81% LEN-refractory) **vs** POM+BOR+DEX n=147 (76% LEN-refractory) Comparator POM+BOR+DEX: NICE terminated appraisal TA602 (no company submission)
Primary outcome	PFS according to IMWG criteria or death due to any cause (assessed by blinded IRC) Primary endpoint: 173 PFS events Primary analysis data cut-off: 29 January 2024 (median study follow-up 21.8 months)
Secondary outcomes	**Key:** OS, DoR, MRD negative status **Other:** TTD, ORR, AEs, eye-related AEs, HRQoL
Pre-planned subgroup analysis of PFS	Age; sex; race; ethnicity; race groups; region; baseline ECOG; baseline EMD; cytogenetic risk; number of prior LoTs; prior anti-CD38; prior BOR; prior SCT; prior LEN and anti-CD38 mAb; triple-exposed (PI, immunomodulator, anti-CD38); LEN-refractory; refractory to anti-CD38; time to relapse after starting 1st LoT

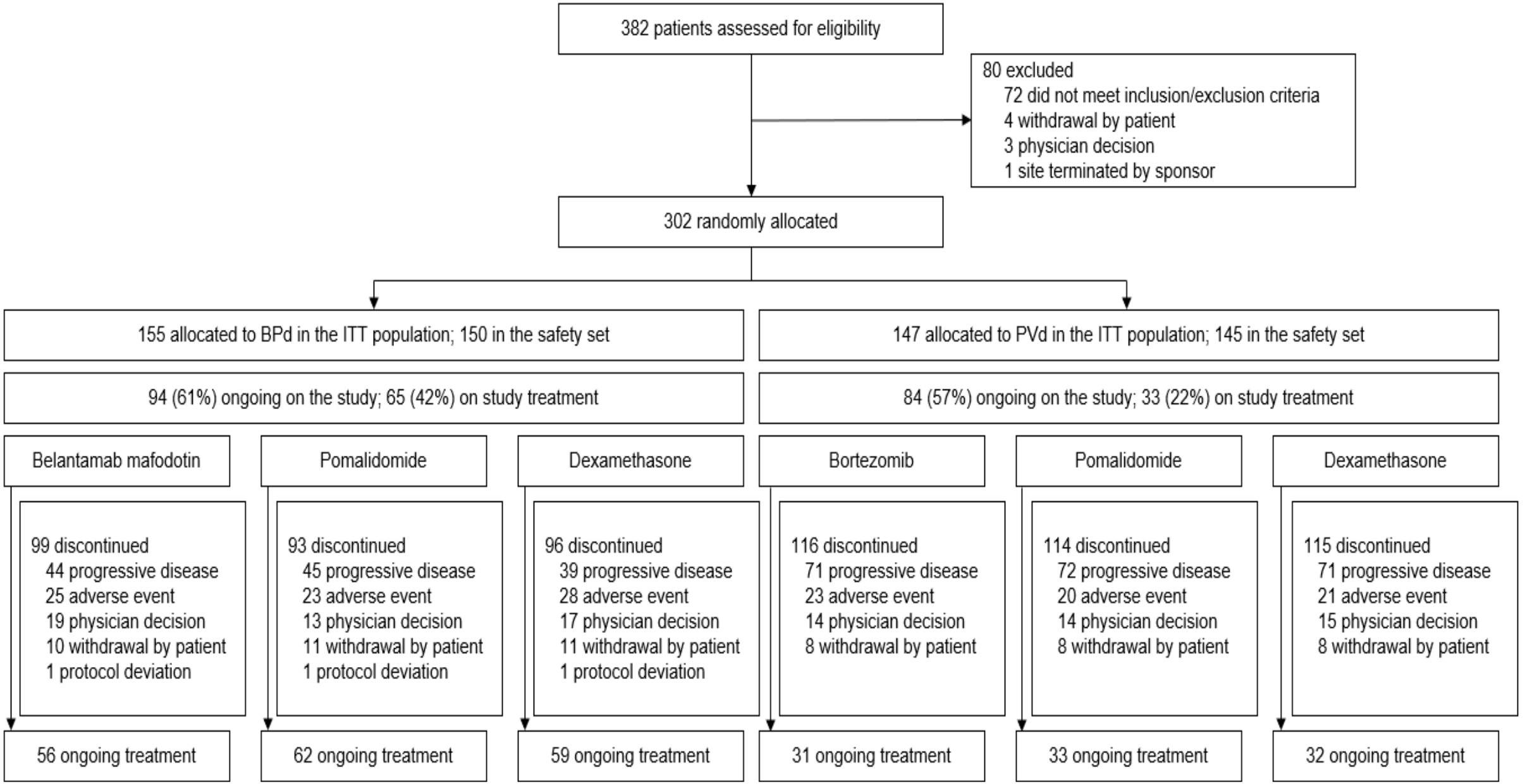
Abbreviations: AE, adverse event; BCMA, B-cell maturation antigen-targeted; BEL, belantamab mafadotin; BOR, bortezomib; DEX, dexamethasone; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EMD, extramedullary disease; HRQoL, health-related quality of life; IMWG, International Myeloma Working Group; IRC, independent review committee; LEN, lenalidomide; LoT, line of treatment; MM, multiple myeloma; MRD, minimum residual disease; n, number; ORR, overall response rate; OS, overall survival; PFS, progression free survival; PI, proteasome inhibitor; POM, pomalidomide; SCT, stem cell transplant; TTD, time to treatment discontinuation

Link to slide 11

DREAMM-8 baseline characteristics	ITT		2L	
	BEL+POM+DEX (n=155)	POM+BOR+DEX (n=147)	BEL+POM+DEX (n=82)	POM+BOR+DEX (n=77)
Age, median (range), years[a]	67.0 (40 - 82)	68.0 (34 - 86)	[redacted]	[redacted]
≥75 years, n (%)	19 (12)	35 (24)	[redacted]	[redacted]
Male, n (%)	99 (64)	82 (56)	[redacted]	[redacted]
ECOG PS ≤1, n/N (%)[b]	146/150 (98)	140/145 (97)	-	-
R-ISS stage at screening I, n (%)	93 (60)	85 (58)	[redacted]	[redacted]
R-ISS stage at screening II, n (%)	39 (25)	40 (27)	[redacted]	[redacted]
R-ISS stage at screening III, n (%)	22 (14)	22 (15)	[redacted]	[redacted]
Time since diagnosis, median (range), years	4.04 (0.4 - 16.7)	3.43 (0.4 - 17.7)	-	-
Cytogenetic high risk, n (%)	52 (34)	47 (32)	[redacted]	[redacted]
Extramedullary disease, n (%)	20 (13)	11 (7)	[redacted]	[redacted]
1 prior LoT, n (%)	82 (53)	77 (52)	[redacted]	[redacted]
2 or 3 prior LoT, n (%)	54 (35)	48 (32)	[redacted]	[redacted]
4+ prior LoT, n (%)	19 (12)	22 (15)	[redacted]	[redacted]
Prior bortezomib, n (%)	134 (86)	130 (88)	-	-
Prior carfilzomib, n (%)	34 (22)	37 (25)	-	-
Prior lenalidomide, n (%)	155 (100)	147 (100)	-	-
Prior daratumumab/[redacted], n (%)	36 (23)	39 (27)	[redacted]	[redacted]
Prior SCT, n (%)	99 (64)	82 (56)	[redacted]	[redacted]
Prior chemotherapy, n (%)	108 (70)	87 (59)	-	-
Refractory to bortezomib, n (%)	16 (10)	8 (5)	-	-
Refractory to carfilzomib, n (%)	18 (12)	23 (16)	-	-
Refractory to lenalidomide, n (%)	125 (81)	111 (76)	[redacted]	[redacted]
[redacted], n (%)	-	-	[redacted]	[redacted]

Abbreviations: BEL, belantamab mafadotin; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, international staging system; LoT, line of treatment; n, number; POM, pomalidomide; SCT, stem cell transplant

DREAMM-8 participant flow diagram



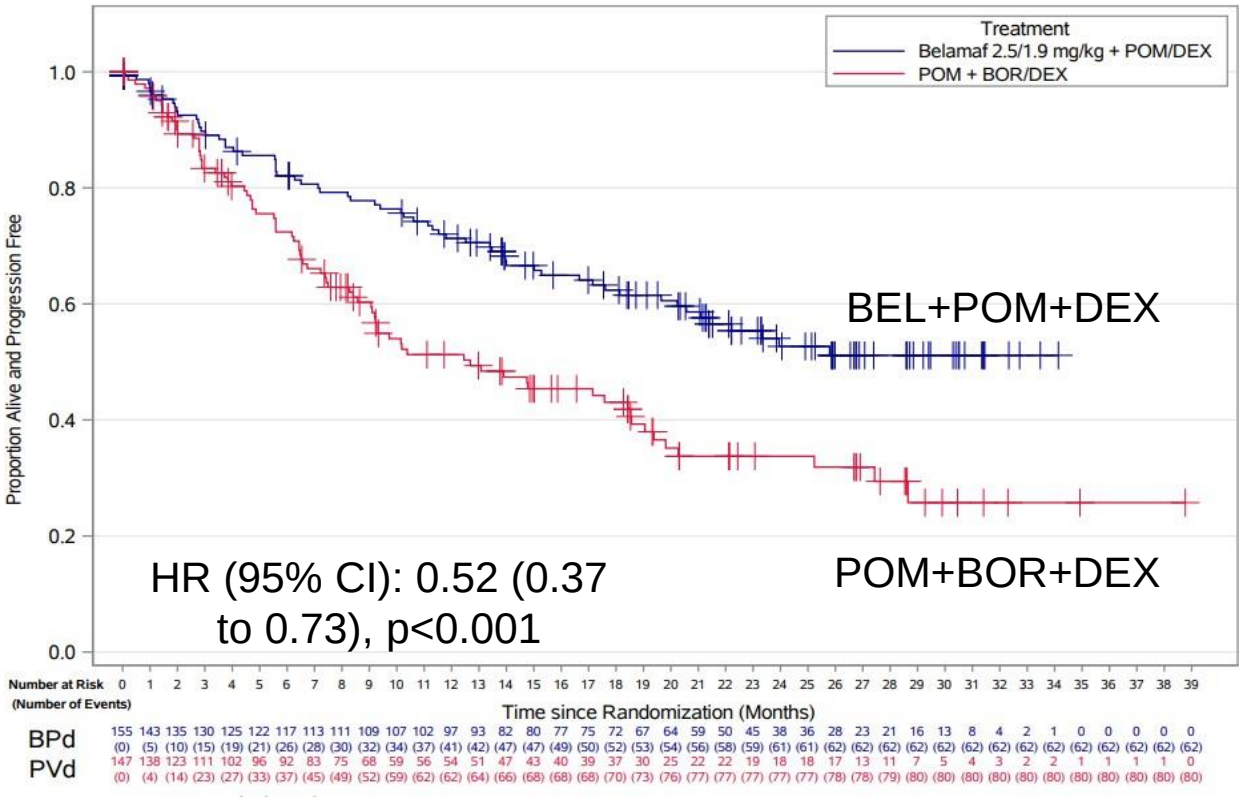
DREAMM-8 (ITT): Subsequent treatments

Drug Class, n (%)	BEL+POM+DEX (n=155)	POM+BOR+DEX (n=147)
Steroids	37 (24%)	59 (40%)
mAb	24 (15%)	51 (35%)
Anti-CD38 antibodies	23 (15%)	49 (33%)
Other mAb	4 (3%)	2 (1%)
Proteasome inhibitor	26 (17%)	36 (24%)
Immunomodulator	14 (9%)	29 (20%)
Chemotherapy	16 (10%)	25 (17%)
BsAb	6 (4%)	16 (11%)
Other	5 (3%)	7 (5%)
Antibody-drug conjugate	0	10 (7%)
Stem cell transplant	1 (<1%)	5 (3%)

	BEL+POM+DEX (n=155)	POM+BOR+DEX (n=147)	Total (n=302)
Number of subjects[a]	[redacted]	[redacted]	[redacted]
Any anti-myeloma therapy			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Subsequent anti-myeloma therapy	[redacted]	[redacted]	[redacted]
NHS-aligned[b]	[redacted]	[redacted]	[redacted]
Non-NHS aligned	[redacted]	[redacted]	[redacted]
Subsequent anti-myeloma therapy	[redacted]	[redacted]	[redacted]
ADC, mAB, BsAb	[redacted]	[redacted]	[redacted]
Other anti-myeloma therapy	[redacted]	[redacted]	[redacted]

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

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



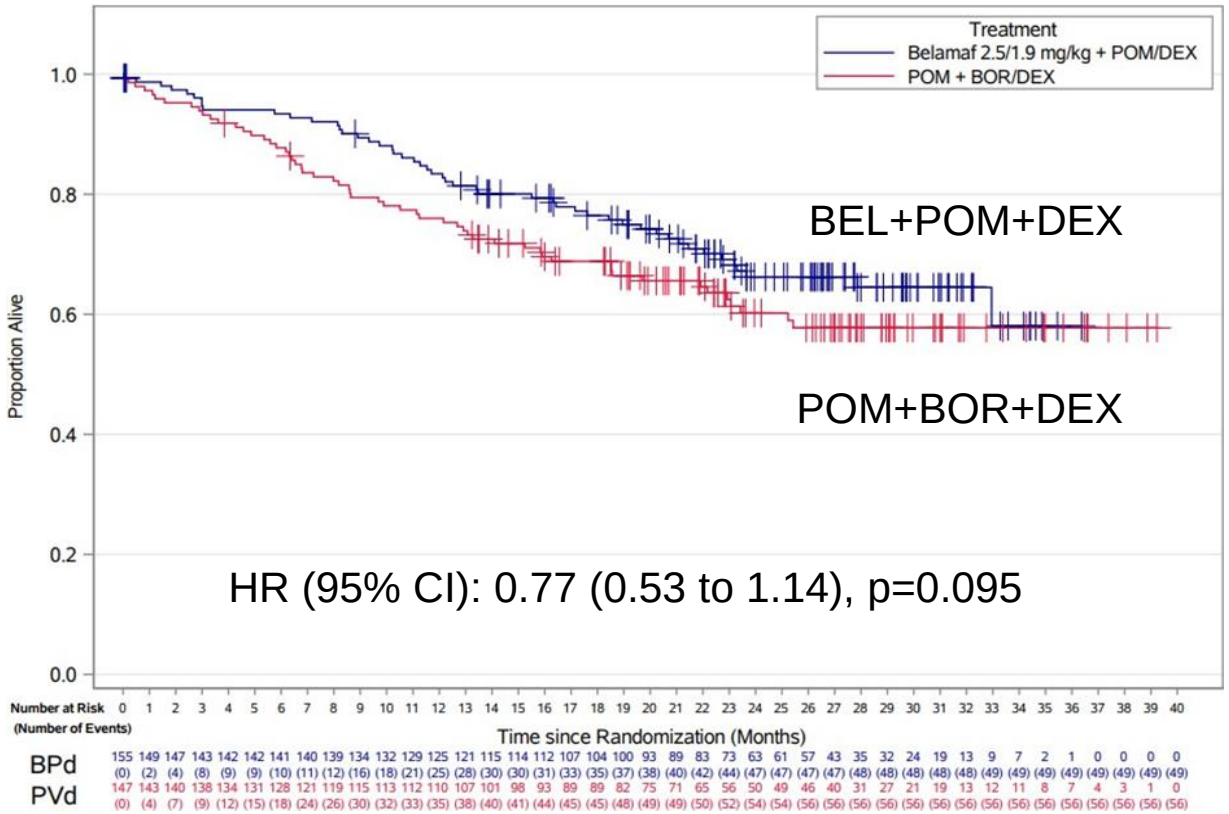
[redacted]

Link to slide 12

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

Kaplan Meier curves of OS for ITT (all LoTs)

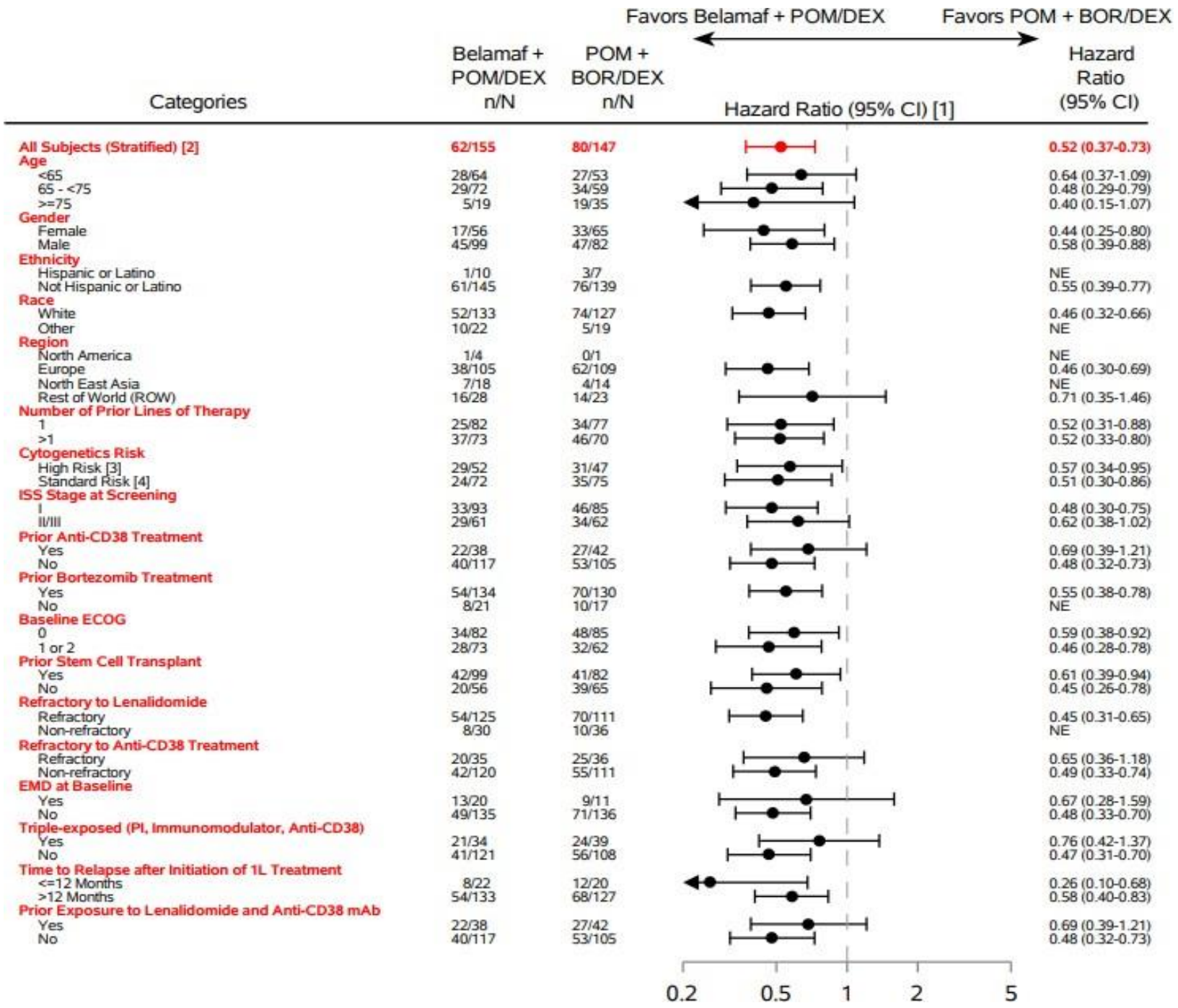


[redacted]

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

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

DREAMM-8 subgroup analysis: PFS



Categories	Belamaf + POM/DEX n/N	POM + BOR/DEX n/N	Hazard Ratio (95% CI)
All Subjects (Stratified) [2]	**62/155**	**80/147**	**0.52 (0.37-0.73)**
Age			
<65	28/64	27/53	0.64 (0.37-1.09)
65 - <75	29/72	34/59	0.48 (0.29-0.79)
>=75	5/19	19/35	0.40 (0.15-1.07)
Gender			
Female	17/56	33/65	0.44 (0.25-0.80)
Male	45/99	47/82	0.58 (0.39-0.88)
Ethnicity			
Hispanic or Latino	1/10	3/7	NE
Not Hispanic or Latino	61/145	76/139	0.55 (0.39-0.77)
Race			
White	52/133	74/127	0.46 (0.32-0.66)
Other	10/22	5/19	NE
Region			
North America	1/4	0/1	NE
Europe	38/105	62/109	0.46 (0.30-0.69)
North East Asia	7/18	4/14	NE
Rest of World (ROW)	16/28	14/23	0.71 (0.35-1.46)
Number of Prior Lines of Therapy			
1	25/82	34/77	0.52 (0.31-0.88)
>1	37/73	46/70	0.52 (0.33-0.80)
Cytogenetics Risk			
High Risk [3]	29/52	31/47	0.57 (0.34-0.95)
Standard Risk [4]	24/72	35/75	0.51 (0.30-0.86)
ISS Stage at Screening			
I	33/93	46/85	0.48 (0.30-0.75)
II/III	29/61	34/62	0.62 (0.38-1.02)
Prior Anti-CD38 Treatment			
Yes	22/38	27/42	0.69 (0.39-1.21)
No	40/117	53/105	0.48 (0.32-0.73)
Prior Bortezomib Treatment			
Yes	54/134	70/130	0.55 (0.38-0.78)
No	8/21	10/17	NE
Baseline ECOG			
0	34/82	48/85	0.59 (0.38-0.92)
1 or 2	28/73	32/62	0.46 (0.28-0.78)
Prior Stem Cell Transplant			
Yes	42/99	41/82	0.61 (0.39-0.94)
No	20/56	39/65	0.45 (0.26-0.78)
Refractory to Lenalidomide			
Refractory	54/125	70/111	0.45 (0.31-0.65)
Non-refractory	8/30	10/36	NE
Refractory to Anti-CD38 Treatment			
Refractory	20/35	25/36	0.65 (0.36-1.18)
Non-refractory	42/120	55/111	0.49 (0.33-0.74)
EMD at Baseline			
Yes	13/20	9/11	0.67 (0.28-1.59)
No	49/135	71/136	0.48 (0.33-0.70)
Triple-exposed (PI, Immunomodulator, Anti-CD38)			
Yes	21/34	24/39	0.76 (0.42-1.37)
No	41/121	56/108	0.47 (0.31-0.70)
Time to Relapse after Initiation of 1L Treatment			
<=12 Months	8/22	12/20	0.26 (0.10-0.68)
>12 Months	54/133	68/127	0.58 (0.40-0.83)
Prior Exposure to Lenalidomide and Anti-CD38 mAb			
Yes	22/38	27/42	0.69 (0.39-1.21)
No	40/117	53/105	0.48 (0.32-0.73)

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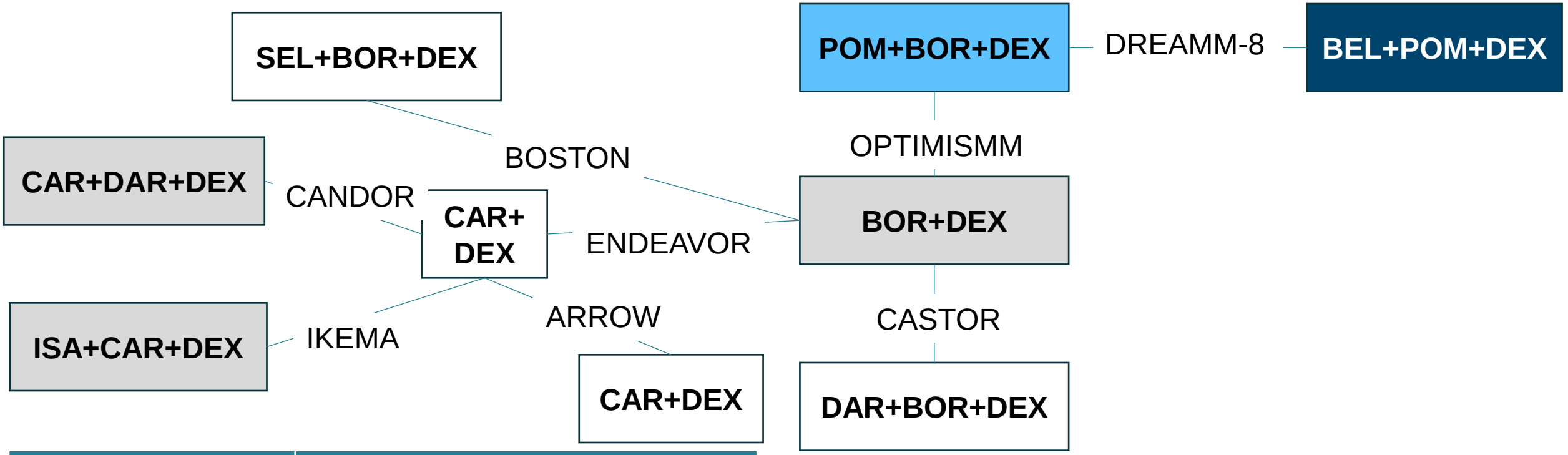
NMA methodology: company comments

- Bayesian NMA using MCMC simulation in Stan through R using RStudio interface and 'multinma' package
- 4 MCMC chains and 10,000 iterations
- Model convergence assessed using Gelman-Rubin statistic
- RE and FE NMAs on PFS and OS
- Goodness-of-fit summary statistics: little difference between FE and RE NMAs: FE chosen for base case
- TEMs: published literature and clinical expert opinion identified potential TEMs (≥1 prior LoT, prior IMD, LEN refractory, refractoriness, ISS stage, cytogenetic risk profile, EMD, creatine clearance, time since diagnosis, age, sex, ethnicity, comorbidities, ECOG PS)
  - Company conducted analyses on included studies to assess whether PFS (primary endpoint of DREAMM-8) varied between subgroups for potential TEMs: prior LoT, prior IMD, prior BOR, prior LEN, ISS stage, ECOG, cytogenic risk profile using ITT data. Imbalances between studies indicated variables were TEMs. Company unable to adjust for any of 7 potential TEMs
  - Of the 12 studies in the full network, 8 reported subgroup results in LEN-exposed population
  - Identified TEMs: prior LoT, ISS stage, ECOG PS. PFS treatment effect will reduce (HRs will increase) with more prior LoTs and higher ISS stages

Abbreviations: BOR, bortezomib; ECOG PS, Eastern Cooperative Oncology Group performance status; EMD, extramedullary disease; FE, fixed effects; HR, hazard ratio; IMD, immunomodulatory drug; ISS, international staging system; ITT, intention-to-treat; LEN, lenalidomide; LoT, line of treatment; MCMC, Markov Chain Monte Carlo; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; RE, random effects; TEM, treatment-effect modifier

Link to slide 14

Company non-outcome-specific network diagram



Outcome and population	BEL+POM+DEX vs		
	DAR+BOR+ DEX	SEL+BOR +DEX	CAR+DEX
PFS: LEN-exposed	✓	✓	✓
OS: LEN-exposed	X	X	✓
PFS: LEN-refractory	✓	X	✓
OS: LEN-refractory	X	X	X
PFS: 2L	X	X	X
OS: 2L	X	X	X

Secondary analysis	Population		
	DAR+BOR+ DEX	SEL+BOR+ DEX	CAR+DEX
PFS: LEN-ref	LEN-ref	ITT	LEN-ref
OS: LEN-exp+ITT	ITT	ITT	LEN-exp
OS: LEN-ref+ITT	ITT	ITT	ITT

Abbreviations: 2L, 2nd line; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; exp, exposed; ISA, isatuximab; ITT, intention-to-treat; LEN, lenalidomide; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; ref, refractory; SEL, selinexor

Baseline characteristics of NMA studies

Studies	Median age (years)	Male (%)	White (%)	ECOG PS (%)			ISS stage (%)				Cytogenetic high risk (%)
				0	1	2	I	II	III	unknown	
BOSTON	66.5	57.5	NR	36	54.5	9	NR				NR
ENDEAVOR	65	50.5	0.755	49	44.5	6.5	44	56	-	-	22.5
CANDOR	64.25	58	NR	95	-	5	49	32	19	0	16
IKEMA	64	55.5	0.7	56	39	5	54	30	15.5	1	24
ARROW	66	54.5	NR	49	50	<1	40.5	33.5	24.5	1	17
CASTOR	64	NR	NR	NR			38.95	39	22.05	-	24.43
OPTIMISMM	67.5	54	NR	51	43	6	51.5	31	17.5	-	20

Studies	% with prior									Refractory status (%)		
	Line of treatment (LoT)					BOR	LEN	THA	DAR	IMD	PI	Last LoT
	1	2	3	4+	Median							
BOSTON	**49.5**	32	18.5	NR	NR	69.5	**38**	NR	**4.5**	NR	NR	NR
ENDEAVOR	**50**	32.5	17.5	0.21	2	54	**38**	49	**NR**	25.3	3.7	82.5
CANDOR	**45.5**	NR	NR	NR	2	89.5	**43.5**	NR	**NR**	34	29.5	82.5
IKEMA	**44.5**	32.5	21	2	2	NR	**44**	NR	**0.5**	45.5	33.5	54.5
ARROW	**0**	50.5	49.5	0	NR	99	**84**	50	**NR**	74.5	42	-
CASTOR	**47.15**	28.95	13.85	10.05	2	65.5	**42.05**	49.4	**NR**	36	NR	32.35
OPTIMISMM	**40.5**	39.5	20	NR	2	72.5	**100**	NR	**NR**	70.5	13	68

Abbreviations: BOR, bortezomib; DAR, daratumumab; ECOG PS, Eastern Cooperative Oncology Group performance status; IMD, immunomodulatory drug; ISS, international staging system; LEN, lenalidomide; NR, not reported; PI, proteasome inhibitor; THA, thalidomide

Treatment effect modifiers: PFS by study and subgroups

Study	n	HR	95% CI	n	HR	95% CI	n	HR	95% CI
Intention-to-treat									
BOSTON	402	0.7	0.53, 0.93	-	-	--	-	-	-
CASTOR	498	0.39	0.28, 0.53	-	-	--	-	-	-
ENDEAVOR	929	0.53	0.44, 0.65	-	-	--	-	-	-
OPTIMISMM	559	0.61	0.49, 0.77	-	-	--	-	-	-
Prior line of treatment	1 prior line			2 prior lines			3 prior lines		
BOSTON	198	0.63	0.41, 0.96	-	-	--	-	-	-
CASTOR	235	0.21	0.15, 0.31	144	0.5	0.28, 0.89	69	0.66	0.31, 1.41
ENDEAVOR	460	0.45	0.33, 0.61	-	-	--	-	-	-
OPTIMISMM	226	0.54	0.36, 0.82	221	0.67	0.48, 0.94	-	-	-
Prior immunomodulatory drug	Prior exposure				No prior exposure				
CASTOR	377	0.8	0.27, 0.55	121	0.50	0.24,1.04	-	-	-
ENDEAVOR	673	0.60	0.48, 0.75	256	0.38	0.25, 0.58	-	-	-
International staging system	ISS stage I				ISS stage II			ISS stage III	
CASTOR	194	0.25	0.13, 0.48	194	0.37	0.23, 0.61	110	0.55	0.31, 0.98
ENDEAVOR	409	0.45	0.32, 0.63	-	-	--	-	-	-
OPTIMISMM	287	0.56	0.40, 0.78	175	0.68	0.46, 0.99	97	0.72	0.46, 1.15
ECOG PS	ECOG PS: 0				ECOG PS: 1			ECOG PS: 2	
ENDEAVOR	453	0.51	0.38, 0.68	414	0.60	0.45, 0.81	-	-	-
OPTIMISMM	286	0.62	0.45, 0.87	-	-	--	-	-	-
Cytogenetic risk	High cytogenetic risk								
BOSTON	141	0.73	0.47, 1.14	-	-	--	-	-	-
CASTOR	131	0.4	0.24, 0.65	-	-	--	-	-	-
ENDEAVOR	210	0.65	0.45, 0.92	-	-	--	-	-	-
OPTIMISMM	NR	0.56	0.35, 0.90	-	-	--	-	-	-

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; n, number; PFS, progression-free survival

PFS hazard functions for comparators

Link to slide 15

OS hazard functions for comparators

Link to slide 15

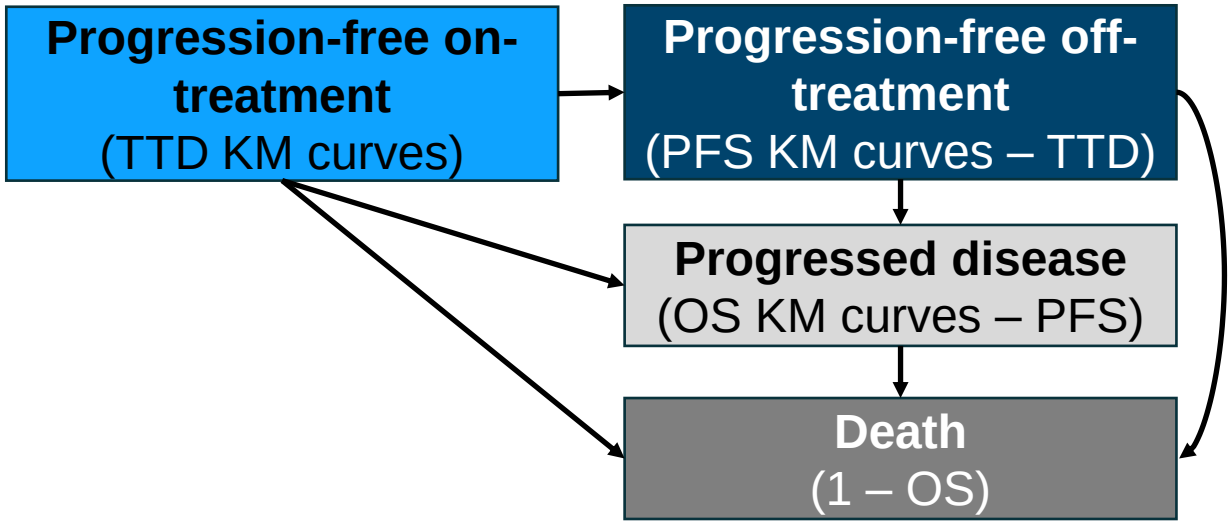
DREAMM-8: adverse events

	BEL+POM+DEX (n=150)	POM+BOR+DEX (n=145)
Any AE, n (%)	149 (>99)	139 (96)
AE related to any study treatment	143 (95)	118 (81)
Grade 3/4 AE	136 (91)	106 (73)
EAIR, per 100 person-years	66	78
Related to any study treatment	120 (80)	85 (59)
AEs leading to permanent stopping of treatment	22 (15)	18 (12)
EAIR, per 100 person-years	11	13
AEs related to any study treatment leading to permanent stopping of any study treatment	19 (13)	9 (6)
BEL stopping due to eye-related event	14 (9)	-
AEs leading to dose reduction	92 (61)	88 (61)
EAIR, per 100 person-years	44	65
BEL dose reduction due to eye-related event	88 (59)	-
AEs leading to dose interruption/delay	136 (91)	109 (75)
EAIR, per 100 person-years	66	80
BEL dose interruption / delay due to eye-related event	124 (83)	-
Any SAE	95 (63)	65 (45)
EAIR, per 100 person-years	46	48
Related to any study treatment	45 (30%)	21 (14%)
Fatal SAEs	17 (11)	16 (11)
Related to any study treatment	3 (2)	0

NICE Abbreviations: BEL, belantamab mafadotin; DEX, dexamethasone; EAIR, exposure-adjusted incidence rates; POM, pomalidomide; SAE, serious adverse event

Link to slide 17

Company's model overview



- PSM with 4 health states (PF divided into on or off treatment, toxicity dependent)
- Start in PFS and start 2L (on treatment)
- % in HS: extrapolations of PFS, OS and TTD, using standard parametric distributions fitted to DREAMM-8 KM data
- 1 week cycle; no half cycle correction; 33.9-year time horizon; NHS/PSS perspective; 3.5% discount rate
- Baseline characteristics (DREAMM-8 ITT): 66.1 years, 60% male, [redacted] weight, [redacted] BSA
- Cost-effectiveness results presented for DAR eligible/ineligible populations

Link to slide 21

 Abbreviations: 2L, 2nd line; BSA, body surface area; DAR, daratumumab; HS, health state; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; PSM, partition survival model; TTD, time to treatment discontinuation

Company base case assumptions

Category	Assumption	Justification
Clinical effectiveness	In the absence of TTD data for non-trial comparators, PFS HRs from the NMA applied to POM+BOR+DEX TTD are used as a proxy for treatments given until progression.	PFS HRs applied to POM+BOR+DEX TTD was determined to be the most conservative assumption to estimate non-trial comparator TTD.
Costs and resource use	The proportion of patients receiving subsequent treatment is informed by the literature.	Proportion of patients who received a 1st and 2nd line of subsequent treatment was informed by Raab (2019) in base-case (scenario using estimates from Yong 2016)
	The distribution of patients in each subsequent treatment is informed by clinical expert opinion.	The average subsequent treatments estimates provided by 3 three clinical experts used in base case
	Subsequent treatments are being modelled through a one-off cost upon disease progression.	In line with previous HTA appraisals, a one-off cost upon disease progression is applied for 2 lines of subsequent therapy.
	Costs associated with the delivery of second subsequent treatment were assumed to incur at the same time as costs related to the first subsequent line of treatment (i.e., upon disease progression)	Patients were assumed to incur a one-off cost associated with both first and second line of subsequent treatments, upon disease progression
	End-of-life care costs is applied as a one-off cost in the cycle in which patients die.	Patients accrue end-of-life care costs before they die and therefore, they are applied within the cycle that patients die in the model death.

Abbreviations: BOR, bortezomib; DEX, dexamethasone; HR, hazard ratio; PFS, progression-free survival; POM, pomalidomide; TTD, time to treatment discontinuation

Relative dose intensity

Company used IPD to estimate BEL dose intensity and for comparators used constant RDI from sources in table

[redacted]

Constant relative dose intensity (used for comparators)

Drug	RDI	Source
BEL 100mg	[redacted]	DREAMM-8 CSR
BEL 70mg	[redacted]	
BOR	[redacted]	
DEX	[redacted]	
POM	[redacted]	
DAR	[redacted]	DREAMM-7 CSR
CAR	90.7%	TA695
SEL	78.9%	TA974

*Link to slide 23

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; CSR, clinical study report; DAR, daratumumab; DEX, dexamethasone; IPD, individual patient data; POM, pomalidomide; RDI, relative dose intensity; SEL, selinexor

DREAMM-8: Impact of adverse events on relative dose intensity

	BEL+POM+DEX (n=150)			POM+BOR+DEX (n=145)		
Median (range) total duration of exposure, months	[redacted]			[redacted]		
Treatments	BEL	POM	DEX	POM	BOR	DEX
Median (range) number of cycles	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range) average daily dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dose intensity, Measure, Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative dose intensity Median (%) (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; DEX, dexamethasone

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 slide 29