Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

Technology appraisal committee B [3 September 2025]

FOR PROJECTOR – information **REDACTED**

Chair: Charles Crawley

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Company: GlaxoSmithKline

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- ✓ **Recap from ACM1**
- ❑ Consultation response
- ❑ Company response and EAG critique
- ❑ Cost effectiveness results

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Appraisal timeline

May 2024
Company submission:
BEL+BOR+DEX positioned at 2L when LEN is 'unsuitable'

Feb - May 2025
Company submits additional info:
Updated base case with committee's preferred assumptions, updated OS data and full 2L population (LEN suitable subpopulation added)

July 2025, consultation phase
Company provided updated analyses comparing BEL+BOR+DEX with CAR+LEN+DEX in LEN suitable population

EAG critique & lead team consideration

January 2025, ACM1:
Committee concluded:
- want to consider full 2L population or 2L & 3L with previous LEN
- Other modelling assumptions confirmed

April 2025
UK MA received

June 2025
Draft Guidance published:
- BEL+BOR+DEX recommended* for adults at 2L, when 1L contained LEN, and refractory to / cannot tolerate LEN (*optimised rec.*)
- Not cost effective in LEN suitable population

Aug 25, ACM2:
Committee to consider LEN suitable population

*(vs CAR + DEX, DAR + BOR + DEX and SEL + BOR + DEX)

Abbreviations: 1L, 1st line; 2L, 2nd line; ACM, appraisal committee meeting; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; EAG, External Assessment Group; LEN, lenalidomide; MA, marketing authorisation; OS, overall survival; SEL, selinexor;

Draft guidance: preliminary recommendations

Recommendation:

Belantamab mafodotin plus bortezomib and dexamethasone (BEL+BOR+DEX) can be used as an option to treat multiple myeloma in adults if they have had 1 previous line of treatment only, which contained lenalidomide, and:

- Their condition is refractory to lenalidomide, or
- They cannot tolerate lenalidomide

Recap from ACM1:

- Company proposed population was 2L only; compared against all relevant 2L comparators
- BEL-BOR-DEX not cost-effective vs all comparators, so only recommended 2L after LEN
- Committee would prefer to evaluate BEL-BOR-DEX in its full MA and in accordance with trial data (2L+)
- Restricting the recommendation to 2L may disadvantage people at 3L and later
  - ↳ Clinical and patient experts agreed that BEL-BOR-DEX would be beneficial as an option at 3L
- Restricting the recommendation to people who had not had LEN would disadvantage people who had not been offered this treatment at 1L

Consultation responses received from:

The company (GlaxoSmithKline), Myeloma UK, The UK Myeloma Society, Menarini Stemline, Johnson & Johnson and 4 web comments

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Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; ACM, appraisal committee meeting; BEL, belantamab mafodotin; BOR, bortezomib; DEX, dexamethasone; LEN, lenalidomide;

Company response to committee preferred assumptions

Committee's preferred assumptions at ACM1	Implemented in company base case?	For discussion?
Using individual patient data for BEL-BOR-DEX and RDI for other comparators	Yes	No
Using a baseline age that is reflective of the NHS population, from the SACT dataset	No – (scenario provided) Company says using different data sources for starting age and clinical effectiveness introduces bias. Aligns with EAG critique post ACM1.	No
Using DAR-BOR-DEX SACT data to inform the baseline OS curve with relative effects applied for BEL-BOR-DEX and other comparators	No - RWE/SACT baseline data not available for comparison of BEL+BOR+DEX vs CAR+LEN+DEX	No
Using treatment-independent utilities	Yes	No
include ocular AE's disutilities for BEL-BOR-DEX	Yes	No
Including teclistamab as 4L treatment	Yes	No

Could SACT data (or other RWE) be used to inform the baseline OS curve for CAR+LEN+DEX?

Abbreviations: 4L, 4th line; ACM, appraisal committee meeting; AE, adverse event; BEL, belantamab mafodotin; BOR, bortezomib; DEX, dexamethasone; EAG, External Assessment Group; OS, overall survival; RDI, relative dose intensity; SACT, Systemic Anti-Cancer Therapy;

Key issues identified by the EAG for ACM2

Issue	ICER impact
MAIC limitations	Large
Modelling OS for CAR+LEN+DEX	Large
Modelling TTD for CAR+LEN+DEX	Small

EAG comments

- Broadly agrees that the company's approach to assessing the cost-effectiveness of BEL+BOR+DEX vs. CAR+LEN+DEX in the LEN-suitable population is appropriate, apart from issues listed above

Abbreviations: ACM, appraisal committee meeting; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; OS, overall survival; TTD, time to treatment discontinuation;

Belantamab mafodotin with bortezomib and dexamethasone

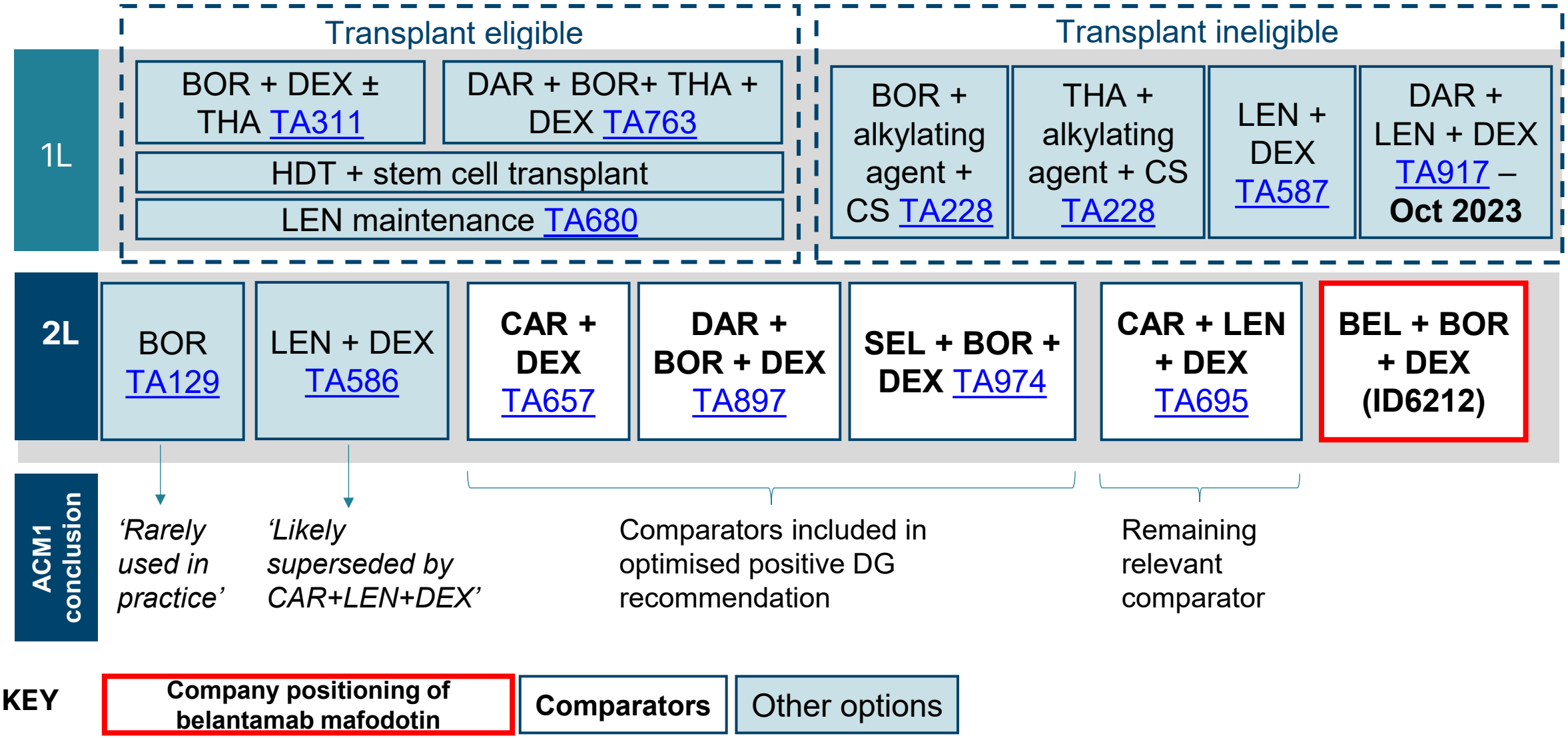
Marketing authorisation	• Belamaf in combination with bortezomib and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy
Mechanism of action	• An antibody-drug that targets and binds to B-cell maturation antigen (BCMA), which is highly expressed on the surface of malignant plasma cells. • Bound belamaf is internalised by the malignant cell, where the cytotoxic drug is released and leads to cell cycle arrest and apoptosis. • While bound to BCMA, it enhances recruitment and activation of immune effector cells, inducing antibody-dependant cellular cytotoxity and phagocytosis.

Administration	• 3 week cycle:
	  • Belamaf: 2.5 mg/kg IV infusion on day 1
	  • Bortezomib: 1.3 mg/m^2 subcutaneously on days 1, 4, 8, and 11 (first 8 cycles only)
	  • Dexamethasone 20 mg IV or oral on both the day of and day after bortezomib (8 doses, first 8 cycles only)
	• Treatment should be continued until disease progression or unacceptable toxicity.

Price	• The list price for belantamab mafodotin is £16,848 per 100-mg vial and £11,784 per 70-mg vial • Patient access scheme in place.

Abbreviations: IV, intravenous;

Treatment pathway and positioning of BEL+BOR+DEX



BEL+POM+DEX is being appraised at ACM2 later this year in 2L population with prev. len (ID6211)

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; CS, corticosteroid; DAR, daratumumab; DEX, dexamethasone ELR, elranatamab; ISA, isatuximab; IXA, ixazomib; LEN, lenalidomide; PAN, panobinostat; POM, pomalidomide; SEL, selinexor; TEC, teclistamab; THA, thalidomide

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Consultation responses to draft guidance (1/3)

Consultation response: Myeloma UK

Disappointed that the recommendation in the draft guidance does not provide access at 2L for patients who have not had LEN

- ↳ Clinical evidence demonstrates that BEL+BOR+DEX can improve OS and PFS in people that have not received LEN
- ↳ Due to rapidly evolving myeloma pathway some people have not had LEN 1L; they would now miss out on a clinically effective treatment for a second time
- ↳ Transplant ineligible patients are typically older and may not have been treated with LEN regimens or LEN maintenance at diagnosis

Restricting BEL+BOR+DEX to 2L means that patients who have LEN at 2L (rather than 1L) would not be able to have BEL at 3L

Note: *Committee concluded at ACM1 that they would like to see BEL+BOR+DEX appraised for the widest possible population (in line with MA and trial data)*

- ↳ *However, the company has chosen to only provide analyses at 2L (by subgroups)*

Abbreviations: 1L, 1st line; 2L, 2nd line; 3L, 3rd line; ACM, appraisal committee meeting; BEL, belantamab mafodotin; BOR, bortezomib; DEX, dexamethasone; LEN, lenalidomide; MA, marketing authorisation; OS, overall survival; PFS, progression free survival;

Consultation responses to draft guidance (2/3)

Consultation response: The UK Myeloma Society

Data from DREAMM-7 could suggest that the LEN suitable population may benefit more

- ↳ Median PFS: ITT population 36.6 months, LEN refractory population 25 months

Patients should be able to access BEL+BOR+DEX at 3L

- ↳ 49% of patients in DREAMM-7 that took BEL+BOR+DEX had already received >1 line of therapy, so the excellent PFS benefit observed (36.6 months) would have included patients who had received 2 or 3 lines of therapy
- ↳ There's a gap in effective therapies at 3L

Consultation response: Menarini Stemline

DG (section 3.20) does not make clear why SEL+BOR+DEX and CAR-LEN-DEX are not considered relevant comparators (BEL+BOR+DEX is not cost-effective against either)

- ↳ CAR+LEN+DEX can be assumed not to be a comparator given that it contains LEN, and the current recommendation is for a population that is refractory to or can't tolerate LEN
- ↳ Unclear why SEL+BOR+DEX is not a comparator

Abbreviations: 3L, 3rd line; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; ITT, intention-to-treat; LEN, lenalidomide; PFS, progression free survival; SEL, selinexor;

Consultation responses to draft guidance (3/3)

Web comments

RCOphth: surprised RCOphth was not invited to be stakeholder given nature of ocular AEs and the proposed recommendation for ophthalmic surveillance; proposed pathway for implementing surveillance is unclear.

↳ *Company has since implemented an independent screening service*

Equalities issues raised:

The recommendation is unfair to patients that were not offered LEN at 1L (which may be linked to age and transplant eligibility)

Abbreviations: 1L, 1st line; AE, adverse event; LEN, lenalidomide; RCOphth, Royal College of Ophthalmologists;

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Company response to draft guidance

Company

- Patients who started treatment before LEN was available 1L will be unable to access BEL+BOR+DEX
  - ↳ Broadening access to 2L patients will ensure equitable access
- At first relapse there is a high unmet need for effective treatments with novel mechanisms of action
  - ↳ Well-established principle in myeloma that most effective therapy should be used as early as possible to maximize benefit

Updates to base case for ACM2

- Company base case includes committee's preferred assumptions post ACM1
- Have provided additional analyses for BEL+BOR+DEX vs CAR+LEN+DEX (not cost effective at ACM1)
- For the 2L LEN suitable population, CAR+LEN+DEX is the only remaining relevant comparator
- Company notes that over the next few years virtually all patients will have LEN 1L, so 2L population eligible for CAR+LEN+DEX will diminish over time
- Key difference in company base case since ACM1:
  - ↳ Independent extrapolation of CAR+LEN+DEX and BEL+BOR+DEX curves weighted by MAIC (rather than applying relative effects of the MAIC to unadjusted BEL+BOR+DEX trial data)
  - ↳ Alternative approach to estimating TTD for CAR+LEN+DEX

Abbreviations: 1L, 1st line; 2L, 2nd line; ACM, appraisal committee meeting; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; TTD, time to treatment discontinuation;

Key issue 1: MAIC limitations (1/2)

Company used a MAIC inform treatment effectiveness due to lack of direct evidence

Background:

- Evidence directly comparing BEL+BOR+DEX with CAR+LEN+DEX is not available.
- Effectiveness of BEL+BOR+DEX vs CAR+LEN+DEX (OS & PFS) was assessed using an unanchored MAIC
  - ↳ BEL+BOR+DEX (DREAMM - ITT) weighted towards CAR+LEN+DEX (ASPIRE - ITT)

Company

- The weighted PFS and OS BEL+BOR+DEX KM curves are clinically plausible
- TEMs & PFs were identified through discussions with clinical experts and targeted literature searches
- TEMs & PFs ranked based on importance as potential sources of heterogeneity which could lead to bias
- Sensitivity analysis was performed to explore the impact uncertainties caused by high variation in certain PFs & TEMs (R-ISS stage, β2-microglobulin, cytogenetic risk profile and ≥4 prior LoT)
  - ↳ For all 4 sensitivity analyses PFS HRs were aligned with the MAIC base-case results
  - ↳ Analysis including R-ISS resulted in a higher median OS HR than all the other analyses, but is unlikely to provide meaningful insights due to the large proportion of missing data and inadequate matching
- MAICs are widely accepted and used in HTAs
- A STC would produce similar results as key PFs & TEMs are well balanced

*See appendix - PF & TEM comparison and Key MAIC results

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; HR, hazard ratio; HTA, health technology assessment; LEN, lenalidomide; LoT, line of treatment; MAIC, matching-adjusted indirect comparison; OS, overall survival; PF, prognostic factor; PFS, progression free survival; R-ISS, revised international staging system; STC, simulated treatment comparison; TEM, treatment effect modifier;

Key issue 1: MAIC limitations (2/2)

EAG says that limitations in the MAIC introduce considerable uncertainty

EAG:

- MAIC associated with unavoidable uncertainty that must be considered
- Unanchored nature of MAIC and failure to balance important covariates leads to considerable uncertainty
  - ↳ Excluding R-ISS from the matching process may be appropriate given the level of missing data
  - ↳ Not matching for R-ISS potentially introduced bias favouring BEL+BOR+DEX, as the ASPIRE trial included a higher proportion of stage III R-ISS patients
- ASPIRE trial population may not be generalisable to NHS clinical practice
  - ↳ ASPIRE participants were younger and treatment was 3L+ for 53.5% of patients
  - ↳ People who previously had LEN (19.8% in ASPIRE) and patients who had not received BOR in a previous line (34.1% in ASPIRE) would not receive CAR+LEN+DEX in the NHS

Is the unanchored MAIC suitable for decision making?

Abbreviations: 3L, 3rd line; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; EAG, External Assessment Group; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; R-ISS, revised international staging system;

Key issue 2: Modelling CAR+LEN+DEX OS: Choice of approach

Company says ACM1 approach was too conservative; EAG has concerns on new approach

	Company approach
February 2025 (post ACM1, pre-DG)	MAIC relative treatment effect (CAR+LEN+DEX vs BEL+BOR+DEX) applied to DREAMM-7 BEL+BOR+DEX (*assumes PH holds*)
ACM2 company base case	Weighted BEL+BOR+DEX[1] modelled independently; exponential CAR+LEN+DEX modelled independently: generalized gamma
Other approaches explored	Other extrapolation curves for CAR+LEN+DEX explored

Company justification of new approach:

- Previous analysis underestimates benefits of BEL+BOR+DEX: PH assumption removes long-term benefit
- MAIC results fit better to modelling the BEL+BOR+DEX and CAR+LEN+DEX arms independently
- Hazard plots suggests PH doesn't hold

EAG comments :

- Cannot rule out that PH holds; still important to consider analyses which includes PH assumption
- Hazard rate towards tail of KM curve is highly uncertain (particularly for weighted BEL+BOR+DEX curve)
- MAIC matching was limited (esp R-ISS), so unclear if all relevant covariates adjusted for
- Important to consider impact of weighting BEL+BOR+DEX according to alternative covariates (w/wo R-ISS)

1. BEL+BOR+DEX population weighted from MAIC to match patient characteristics in ASPIRE

Abbreviations: ACM, appraisal committee meeting; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; DG, draft guidance; EAG, External Assessment Group; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; OS, overall survival; PH, proportional hazard; R-ISS, revised international staging system; w/wo, with/without;

Key issue 2: Modelling CAR+LEN+DEX OS: Choice of curve

Company and EAG disagree on the most appropriate CAR+LEN+DEX OS extrapolation

Company	EAG
Generalised gamma (Company base case)	
• 3/5 CEs stated plausible • AIC indicated one of the best statistical fits	• Not satisfied it is the most appropriate extrapolation • Implied HR trend is consistent with the observed data, but observed data towards end of tail is highly uncertain • Greater treatment effect than Weibull for most of the time horizon
Gompertz	
• 3/5 CEs stated plausible • AIC/BIC indicated one of the best statistical fits • Implausible due to likely PH violation	• BIC indicates better statistical fit than generalised gamma • Does not result in a PH violation
Weibull (Company scenario)	
• 3/5 CEs stated plausible • AIC/BIC indicated one of the best statistical fits • Implausible due to likely PH violation	• AIC/BIC indicates better statistical fit than generalised gamma • Does not result in a PH violation
Exponential (Company scenario)	
• BIC indicated one of the best statistical fits • 3/5 CEs considered 15-year tail clinically implausible (but 2/5 CEs said was the most plausible curve) • Implausible due to likely PH violation	• PH assumed but treatment effect is greater than the effect implied by the MAIC HRs

*See appendix - Statistical goodness-of-fit and landmark survival rates

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CAR, carfilzomib; CE, clinical expert; DEX, dexamethasone; EAG, External Assessment Group; HR, hazard ratio; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; OS, overall survival; PH, proportional hazard;

Key issue 2: Modelling OS for CAR+LEN+DEX: HRs

EAG comments

- Assessment of implied HRs over time for different approaches is informative when assessing the clinical plausibility of OS projections → Assuming PH holds suggests smaller treatment effect

Figure: Implied OS HRs over time for the different modelling approaches

Figure: Hazard rate plots for OS: weighted DREAMM-7 and ASPIRE KM curves

Underlying hazard rates were not constrained by the general population mortality hazards

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CAR, carfilzomib; DEX, dexamethasone; EAG, External Assessment Group; HR, hazard ratio; KRd, carfilzomib in combination with lenalidomide, and dexamethasone; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; OS, overall survival; PF, prognostic factor; PH, proportional hazard; R-ISS, revised international staging system; TEM, treatment effect modifier;

Key issue 2: Modelling CAR+LEN+DEX OS: Benefit in PD state

EAG questions if large BEL+BOR+DEX benefit in progressed state is clinically plausible

EAG comments

- LY gain considerably longer in progressed disease state than progression-free state in all approaches but one
  - ↳ Suggests the survival benefit of BEL+BOR+DEX accrued largely beyond disease progression, under all but the most pessimistic survival assumptions (requires validation by clinical experts)
- Possible incremental LY benefit in PD state due to differences in subsequent treatments between trials

Incremental difference in expected LY gain for BEL+BOR+DEX vs CAR+LEN+DEX with alternative approaches:

	BEL+BOR+DEX: OS and PFS exponential (MAIC weighted curves) CAR+LEN+DEX: PFS exponential			BEL+BOR+DEX: OS and PFS exponential (unweighted curves) MAIC adjusted HR	
	OS Gen gamma	OS Weibull	OS Exponential	Without R-ISS	With R-ISS
PFD (on & off treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- Should approaches that rely on PH assumption holding be considered? (e.g. exponential)
- Should analyses using the HRs from MAIC to derive OS curves for CAR+LEN+DEX be considered?
- If modelling CAR+LEN+DEX OS independently, which curve is preferred?
- Is it plausible for BEL+BOR+DEX benefit to be larger in PD state vs PF state (vs CAR +LEN+DEX)?
- Has survival in PD state been influenced by differences in subsequent treatments?

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; EAG, External Assessment Group; HR, hazard ratio; LEN, lenalidomide; LY, life years; MAIC, matching-adjusted indirect comparison; OS, overall survival; PD, progressed disease; PFD, progression free disease; PFS, progression free survival; R-ISS, revised international staging system;

Key issue 3: Modelling TTD for CAR+LEN+DEX (1/3)

Company says ACM1 approach was overly conservative, so have updated TTD modelling

Company

- Approach for CAR+LEN+DEX TTD after ACM1 (CAR+LEN+DEX vs BEL+BOR+DEX PFS HR applied to BEL+BOR+DEX TTD extrapolation) overestimated CAR+LEN+DEX discontinuation
- Relationship between PFS and TTD for BEL+BOR+DEX is atypical as a substantial proportion remain PF while off-treatment (DREAMM-7: BEL+BOR+DEX; PFS and TTD curves diverge while for DAR+BOR+DEX curves are closely aligned)
- Data wasn't available to inform a MAIC for TTD

Base case: DAR+BOR+DEX HR (TTD vs PFS) from DREAMM-7 applied as proxy to extrapolated CAR+LEN+DEX PFS CURVE

↳ Approach replicates the method used to derive TTD for CAR+DEX and SEL+BOR+DEX at ACM1 (PFS HR used as a proxy for TTD HRs which were then applied to the DAR+BOR+DEX TTD curve)

- Two additional approaches considered

EAG comments

- Agree BEL+BOR+DEX TTD shouldn't be used to estimate CAR+LEN+DEX TTD (ACM1 approach)
- Preference is the company's approach using ASPIRE median PFS and median treatment duration for LEN

↳ Using available summary treatment data from ASPIRE for components of CAR+LEN+DEX is preferable and ensures consistency between evidence sources in the model

Abbreviations: ACM, appraisal committee meeting; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; EAG, External Assessment Group; HR, hazard ratio; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; PFS, progression free survival; TTD, time to treatment discontinuation;

Key issue 3: Modelling TTD for CAR+LEN+DEX (2/3)

Table: Methods of extrapolating TTD for CAR+LEN+DEX

Company preference **EAG preference**

Approach	Ratio	Applied to	Source	Uncertainties / limitation
Observed DAR+BOR+DEX HR used as a proxy	Observed DAR+BOR+DEX TTD:PFS (HR [redacted])	CAR+LEN+DEX PFS curve	DREAMM-7 ITT	EAG: Unlike the OS and PFS data the data used to determine the HR was not adjusted for the ASPIRE characteristics → Approach may overestimate TTD compared to ASPIRE treatment durations and the LEN / CAR TTD extrapolations from TA695
Estimated HR using median treatment duration (LEN) and median PFS	Estimated CAR+LEN+DEX TTD:PFS (HR: [redacted])	CAR+LEN+DEX PFS curve	ASPIRE	Company: Relationship between CAR and LEN TTD is uncertain → CAR duration is influenced by a stopping rule (doesn't apply to LEN+DEX) EAG: Prefer to use ASPIRE to be consistent with source of efficacy data
PFS=TTD	TTD:PFS HR = 1	CAR+LEN+DEX PFS curve	ASPIRE	Conservative as people can discontinue treatment while remaining PF

Abbreviations: BOR, bortezomib; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; EAG, External Assessment Group; HR, hazard ratio; LEN, lenalidomide; OS, overall survival; PF, progression free; PFS, progression free survival; TTD, time to treatment discontinuation;

Key issue 3: Modelling TTD for CAR+LEN+DEX (3/3)

Table: Comparison of TTD landmarks over time and median TTD between analyses and data sources

Time (years)	0.5	1	2	3	4	5	6	7	8	9	10	Median (weeks)
DAR+BOR+DEX HR (PFS and TTD) as a proxy	[redacted]											
ASPIRE median PFS to median treatment duration	[redacted]											
TA695 LEN TTD extrapolation (Fig 10, response to PfCs and Fig 23, CS)	~80%	~65%	~45%	30%	20%	~15%	<10%	~5%	<5%	<5%	<5%	~91
TA695 CAR TTD extrapolation (Figure 23, CS)	~85%	70%	0%	0%	0%	0%	0%	0%	0%	0%	0%	72
LEN treatment duration ASPIRE trial												85
CAR treatment duration ASPIRE trial												72

Company preference

EAG preference

What is the committee's preference for modelling TTD for CAR+LEN+DEX?

Abbreviations: BOR, bortezomib; CAR, carfilzomib; CS, company submission; DAR, daratumumab; DEX, dexamethasone; EAG, External Assessment Group; LEN, lenalidomide; PfC, points for clarification; PFS, progression free survival; TTD, time to treatment discontinuation;

Previous and updated company base-case

Table: Key differences between the company's previous (February 2025) and updated base-case (July 2025) parametrisation for BEL+BOR+DEX vs. CAR+LEN+DEX

	February 2025	ACM2
Starting age	70 years – source: SACT	[redacted] years (DREAM-7 ITT MAIC weighted) *(scenario provided using SACT age)*
Survival modelling	Applying estimated treatment effect from the unanchored MAIC (HR for CAR+LEN+DEX vs. BEL+BOR+DEX) to unweighted BEL+BOR+DEX extrapolated survival curve (DREAMM-7 IA2 ITT).	Independently fitted extrapolation curves to: • BEL+BOR+DEX KM curve (DREAMM-7 IA2 ITT) weighted by the unanchored MAIC to reflect the ASPIRE ITT population • CAR+LEN+DEX KM curve (ASPIRE ITT)
TTD for CAR+LEN+DEX	Ratio of CAR+LEN+DEX PFS vs BEL+BOR+DEX PFS ([redacted]) applied to BEL+BOR+DEX TTD curve	Ratio of DAR+BOR+DEX TTD vs. PFS ([redacted]) applied to CAR+LEN+DEX PFS curve (informed by ASPIRE ITT)
CAR+LEN+DEX stopping rule	None	Maximum of 18 cycles for CAR

Abbreviations: ACM, appraisal committee meeting; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; HR, hazard ratio; ITT, intention-to-treat; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; PFS, progression free survival; SACT, Systemic Anti-Cancer Therapy;

Key issues identified by the EAG for ACM2

Issue	ICER impact
MAIC • Is the unanchored MAIC suitable for decision making?	Large 
Modelling OS for CAR+LEN+DEX • Should approaches that rely on PH assumption holding be considered? (e.g. exponential) • Should analyses using the HRs from MAIC to derive OS curves for CAR+LEN+DEX be considered? • If modelling CAR+LEN+DEX OS independently, which curve is preferred? • Is it plausible for BEL+BOR+DEX benefit to be larger in PD state vs PF state (vs CAR +LEN+DEX)? • Has survival in PD state been influenced by differences in subsequent treatments?	Large 
Modelling TTD for CAR+LEN+DEX • What is the committee's preference for modelling TTD for CAR+LEN+DEX?	Small 

Abbreviations: ACM, appraisal committee meeting; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; EAG, External Assessment Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; OS, overall survival; PD, progressed disease; PF, progression free; TTD, time to treatment discontinuation;

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Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

comparator PAS discounts

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Supplementary appendix

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Key clinical trial data

	BEL+BOR+DEX	CAR+LEN+DEX
Name	DREAMM-7	ASPIRE
Design	Phase III, multicentre, randomised, open-label trial	Phase III, multicentre, randomised, open-label trial
Population	Adults (≥18 years) with RRMM who have had at least 1 prior LoT	Adults with relapsed MM who had received 1 to 3 prior LoT
Intervention	BEL+BOR+DEX (n=243)	CAR+LEN+DEX (n=396)
Comparator	DAR+BOR+DEX (n=251)	LEN+DEX (n-396)
Median follow-up	7th October 2024; median follow-up 39.4 months	April 28 2017 data cutoff, PFS 48.8 month OS was 67.1 months
1° outcome	PFS	PFS
Key 2° outcomes	OS, RR, HRQoL (measured by EQ-5D-3L, EORTC QLQ-C30 and EORTC IL52), AEs	OS, ORR, Disease control rate, Duration of response, Duration of disease control, QLQ-C30, AEs

No direct evidence comparing BEL+BOR+DEX with CAR+LEN+DEX, so company conducted MAIC

Abbreviations: AE, adverse event; BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; EORTC IL52, , European Organisation for Research and Treatment of Cancer IL52; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer 30-item Quality of Life Questionnaire; EQ-5D-3L, European Quality of life-5 Dimensions 3 levels; HRQoL, health-related quality of life; LEN, lenalidomide; LoT, line of treatment; MAIC, matching-adjusted indirect comparison; MM, multiple myeloma ORR, overall response rate; OS, overall survival; PFS, progression free survival; RR, response rate; RRMM, relapsed refractory multiple myeloma;

Link to - MAIC

Prognostic Factors & Treatment effect modifiers comparison (1/3)

Table: Comparison of ranked PFS and TEMS based on baseline characteristics in DREAMM-7 and ASPIRE

Study	DREAMM-7 BVd (N=243)	ASPIRE KRd (N=396)
Prior LoT (n, %)	1: 124 (51.0%) 2-3: 89 (36.6%) ≥4: 30 (12.3%)	1: 184 (46.5%) 2-3: 211 (53.3%) ≥4: 1 (0.3%)
Refractory status to the specific agent used in the study (n, %): - IMiDs - Lenalidomide	IMiDs: 94 (38.7%) Lenalidomide: 79 (32.5%)	IMiDs: 85 (21.5%) Lenalidomide: 29 (7.3%)
R-ISS stage (n, %)	I-II: 232 (95.4%) III: 9 (3.7%) Unknown: 3 (1.2%) *After adjusting for missingness:* I-II: 96.3% III: 3.7%	I-II: 236 (59.6%) III: 37 (9.3%) Unknown: 123 (31.1%) *After adjusting for missingness:* I-II: 86.4% III: 13.6%
Cytogenetic risk profile (n, %)	Standard: 175 (72.0%) High: 67 (27.6%) Unknown: 1 (0.4%) *After adjusting for missingness:* Standard: 72.4% High: 27.6%	Standard: 147 (37.1%) High: 48 (12.1%) Unknown: 201 (50.8%) *After adjusting for missingness:* Standard: 75.4% High: 24.6%

NICE

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KRd, carfilzomib in combination with lenalidomide, and dexamethasone; LoT, line of treatment; PF, prognostic factor; R-ISS, revised international staging system; TEM, treatment effect modifier;

Link to - MAIC

Prognostic Factors & Treatment effect modifiers comparison (2/3)

Table: Comparison of ranked PFS and TEMS based on baseline characteristics in DREAMM-7 and ASPIRE

Study	DREAMM-7 BVd (N=243)	ASPIRE KRd (N=396)
Creatinine clearance/eGFR (n, %)	<50 ml/min: 38 (15.6%)	<50 ml/min: 25 (6.3%) ≥50 ml/min: 370 (93.4%) Unknown: 1 (0.3%) *After adjusting for missingness:* <50 ml/min: 6.3%
ECOG PS (n, %)	0 or 1: 232 (95.5%) 2: 10 (4.1%) Unknown: 1 (0.4%) *After adjusting for missingness:* 0 or 1: 95.9% 2: 4.1%	0 or 1: 356 (89.9%) 2: 40 (10.1%)
Age (mean years, SD)	64.5 (9.47)	63.3 (9.21)
Gender (number of males, %)	128 (52.6%)	215 (54.3%)
Race, number (%)	White (combined): 206 (84.8%) Asian (combined): 28 (11.5%) Black / African American: 8 (<0.1%) Mixed race: 0 (0.0%)	White: 377 (95.2%) Black 12 (3.0%) Asian: 1 (0.3%) Other: 6 (1.5%)

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; KRd, carfilzomib in combination with lenalidomide, and dexamethasone; PF, prognostic factor; SD, standard deviation; TEM, treatment effect modifier;

Link to - MAIC

Prognostic Factors & Treatment effect modifiers comparison (3/3)

Company

- EMD was identified as a key TEM but was not reported in ASPIRE so could not be compared across studies → This may introduce bias of unknown direction into the MAIC results
- The proportion of patients that were refractory to LEN was lower in ASPIRE than in DREAMM-7 so adjustment was required
- R-ISS stage was unknown for a large proportion of patients in ASPIRE → ASPIRE data was adjusted based on the assumption that R-ISS data was missing completely at random → After adjustment there were fewer R-ISS III patients in DREAM-7 (3.7%) than in ASPIRE (13.6%) → R-ISS was excluded from the base-case analysis as the difference would likely to lead to unstable estimates
  - ↳ Sensitivity analysis explored including R-ISS stage in the matching process / using serum β2-microglobulin as a proxy (based on clinical expert opinion)
- Cytogenic risk data and creatine clearance data were assumed missing completely at random
  - ↳ Sensitivity analysis explored uncertainty introduced by the assumption that cytogenetic risk data was missing completely at random
- In ASPIRE only 0.3% of patients had ≥4 prior LoT compared to 12.4% DREAMM-7
  - ↳ Sensitivity analysis truncated the LoT data by excluding ≥4 prior LoT from the matching process
- Adjusting for all PFs and TEMs (excluding R-ISS stage) results in an ESS of 126.4 (within the threshold (>60) for sufficient overlap in populations)

NICE

Abbreviations: EMD, extramedullary disease; ESS, effective sample size; LEN, lenalidomide; LoT, line of treatment; MAIC, matching-adjusted indirect comparison; PF, prognostic factor; R-ISS, revised international staging system; TEM, treatment effect modifier;

Link to - MAIC

Key MAIC results (1/2)

MAIC results (base case) - BEL+BOR+DEX improves PFS compared to CAR+LEN+DEX

Figure: MAIC base-case results - PFS

Table: MAIC base-case results - PFS

Treatment Arm	Sample Size	Median PFS (Months)	BEL+BOR+DEX vs CAR+LEN+DEX HR (95% CI)
Weighted BEL+BOR+DEX	126.42	[redacted]	[redacted]
Unweighted BEL+BOR+DEX	243.00	[redacted]	[redacted]
CAR+LEN+DEX	396.00	26.30	N/A

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; PFS, progression free survival;

Link to - MAIC

Key MAIC results (2/2)

MAIC results (base case) - BEL+BOR+DEX improves OS compared to CAR+LEN+DEX

Figure : MAIC base-case results - OS

Table: MAIC base-case results - OS

Treatment Arm	Sample Size	Median OS (Months)	BEL+BOR+DEX vs CAR+LEN+DEX HR (95% CI)
Weighted BEL+BOR+DEX	126.42	[redacted]	[redacted]
Unweighted BEL+BOR+DEX	243.00	[redacted]	[redacted]
CAR+LEN+DEX	396.00	48.3	N/A

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; OS, overall survival;

Link to - MAIC

Key MAIC results – Sensitivity analysis

OS HR for BEL+BOR+DEX vs CAR+LEN+DEX is sensitive to the inclusion of R-ISS in the matching process

Table: MAIC sensitivity analyses results vs base-case

Analysis	PFs and TEMs included in the matching process of the DREAMM-7 BEL+BOR+DEX arm	BEL+BOR+DEX arm sample size	BEL+BOR+DEX vs CAR+LEN+DEX	
			PFS HR (95% CI)	OS HR (95% CI)
Base-case	Adjusting for all feasible TEMs and PFs, except for R-ISS	[redacted]	[redacted]	[redacted]
Sensitivity analysis 1	Exclusion of cytogenetic risk profile from the matching process	[redacted]	[redacted]	[redacted]
Sensitivity analysis 2	Adjusting for all feasible TEMs and PFs, including R-ISS	[redacted]	[redacted]	[redacted]
Sensitivity analysis 3	Truncated population, excluding ≥4 prior LoT in the matching process	[redacted]	[redacted]	[redacted]
Sensitivity analysis 4	Adjusting for all feasible TEMs and PFs, including β2-microglobulin	[redacted]	[redacted]	[redacted]
Unweighted comparison	-	[redacted]	[redacted]	[redacted]

Abbreviations: BEL, belantamab mafodotin; BOR, bortezomib; CAR, carfilzomib; CI, confidence interval; DEX, dexamethasone; HR, hazard ratio; LEN, lenalidomide; LoT, line of treatment; MAIC, matching-adjusted indirect comparison; OS, overall survival; PF, prognostic factor; PFS, progression free survival; R-ISS, revised international staging system; TEM, treatment effect modifier;

Link to - Modelling OS for CAR+LEN+DEX

Proportional hazard diagnostic plots

Figure: Cumulative log-log plot for OS

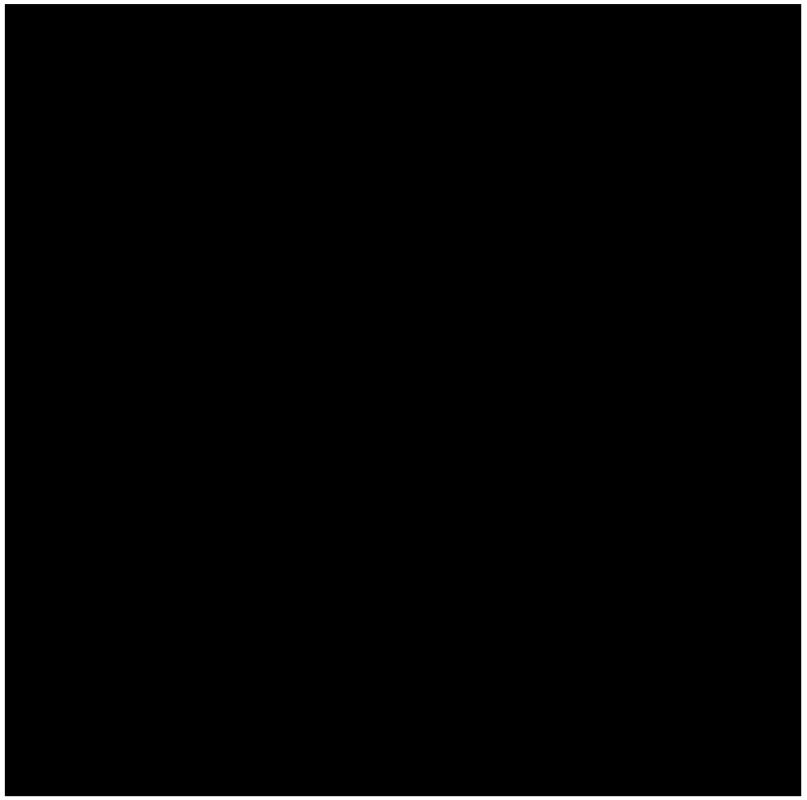


Figure: Schoenfeld residuals plot for OS

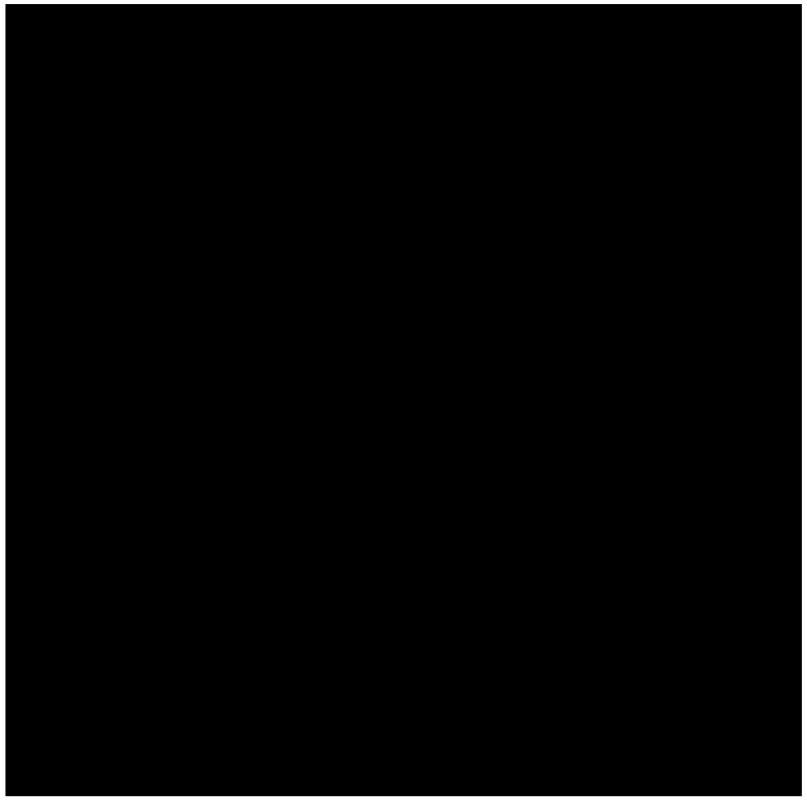
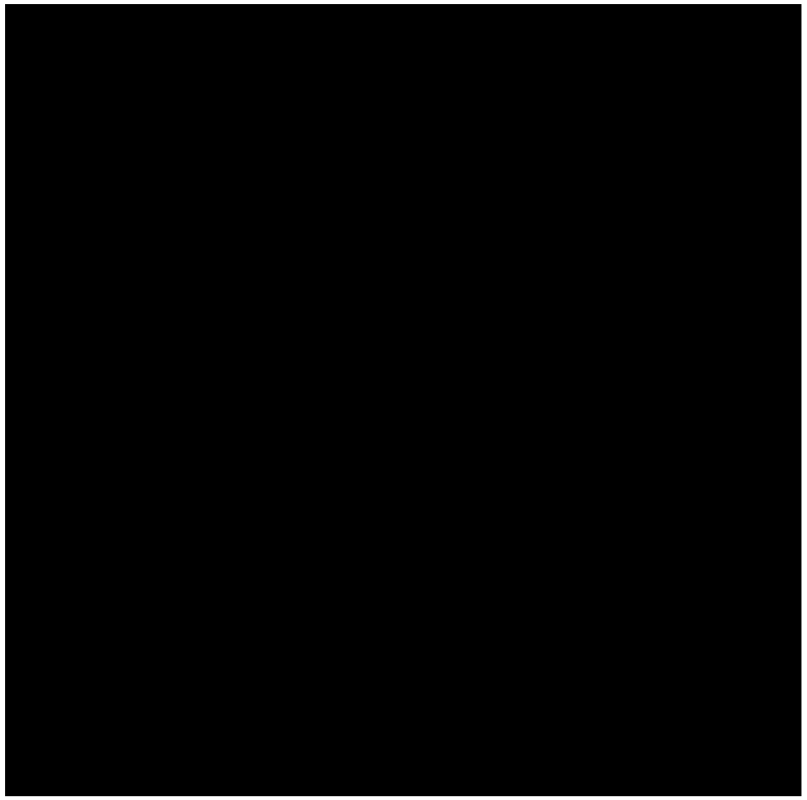


Figure: Quantile-quantile plot for OS



Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CAR, carfilzomib; DEX, dexamethasone; KRd, carfilzomib in combination with lenalidomide, and dexamethasone; LEN, lenalidomide; OS, overall survival; PFS, progression free survival;

Link to - Modelling OS for CAR+LEN+DEX

Statistical goodness-of-fit and landmark survival rates

Table: AIC and BIC statistical goodness-of-fit data for OS

Distribution	Weighted BEL+BOR+DEX		Unweighted CAR+LEN+DEX	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	2616.61	2620.59
Weibull	[redacted]	[redacted]	2611.58	2619.54
Gompertz	[redacted]	[redacted]	2612.91	2620.88
Log-logistic	[redacted]	[redacted]	2617.68	2625.64
Log-normal	[redacted]	[redacted]	2648.50	2656.47
Generalised Gamma	[redacted]	[redacted]	2613.36	2625.30

Table: Unweighted CAR+LEN+DEX landmark survival rates (OS)

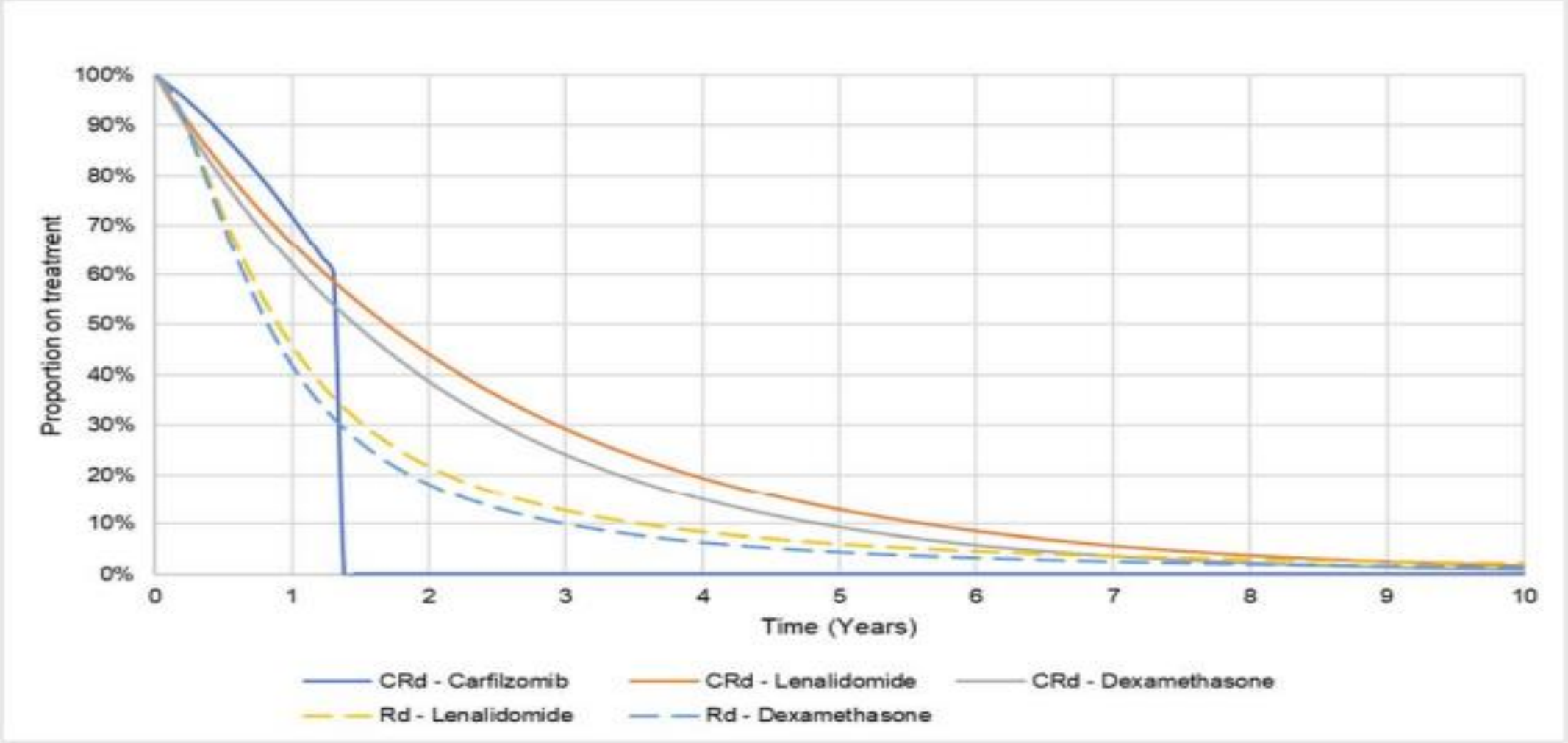
	OS (%) at landmark timepoints, Years					
	1	2	5	10	15	20
Exponential	84	70	41	17	7	3
Weibull	87	73	40	13	4	1
Gompertz	86	73	40	10	1	0
Log-logistic	87	72	41	20	13	9
Log-normal	84	69	42	24	16	11
Generalised Gamma	87	73	40	12	3	1

Abbreviations: AIC, Akaike information criterion; BEL, belantamab mafodotin; BIC, Bayesian information criterion; BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; LEN, lenalidomide; OS, overall survival;

Link to - Modelling TTD for CAR+LEN+DEX (3/3)

Time to treatment discontinuation TA695

Figure: Figure 23 from TA695 CS (Base case TTD curves for components of CAR+LEN+DEX and LEN+DEX



Abbreviations: CAR, carfilzomib; CRd, carfilzomib/lenalidomide/dexamethasone; CS, company submission; DEX, dexamethasone; LEN, lenalidomide; Rd, lenalidomide/dexamethasone; TTD, time to treatment discontinuation;