Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

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

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Consultation on the draft guidance document – deadline for comments 5pm on Thursday 3 July. Please submit via NICE Docs.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	GlaxoSmithKline Ltd

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not applicable
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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Cost-effectiveness results, section 3.17 (page 24):** "For the comparison with Car-Len-Dex, when lenalidomide is an option at second line, the deterministic and probabilistic ICERs for Bel-Bor-Dex were above the range considered to be a cost-effective use of NHS resources."

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	• As noted in the Positioning section, 3.2 (page 6) and Equality section, 3.18 (page 24), the Company had updated its proposed population to be second line only, which included all comparisons against relevant comparators at second line. • The Company would like to submit additional analyses for consideration ahead of the second Committee meeting which aims to improve the cost-effectiveness of Bel-Bor-Dex compared with Car-Len-Dex. As confirmed with the Associate Director of TA Team 3, the additional analysis will be submitted in two weeks and will investigate independent modelling of Bel-Bor-Dex and Car-Len-Dex and scenarios for time to treatment discontinuation for Car-Len-Dex.

Insert extra rows as needed

Checklist for submitting comments

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Additional evidence for BVd versus KRd based on IA2-updated DREAMM-7 results

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

July 2025

File name	Version	Contains confidential information	Date
ID6212_Belantamab mafodotin with bortezomib and dexamethasone_Additional evidence for BVd versus KRd based on IA2-updated DREAMM-7 results.docx	V1.0	Yes	17 July 2025

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1. Report objectives and summary

Following ACM1 for submission ID6212 (hereafter referred to as the company submission, [CS]), the Committee issued their preferred assumptions. One assumption focused on the final population of belantamab mafodotin in combination with bortezomib and dexamethasone (BVd). The committee issued the following consideration:

"Committee would prefer to evaluate within full market authorization (MA), but if this is not possible, it would prefer adults with multiple myeloma (MM) who have had either:

- only 1 previous treatment (that is, second line only), or
- 1 or 2 previous treatments and have had previous exposure to lenalidomide."

GlaxoSmithKline (GSK, hereafter referred to as the company) share the Committee's desire to make BVd available to the widest possible patient group in second line (2L), where the introduction of BVd will have the greatest impact, and as such in response to preferred assumptions updated the cost-effectiveness model (CEM) to cover adults with relapsed or refractory MM (RRMM) who have had only 1 previous treatment (that is, second line).

Evaluation of comparators daratumumab plus bortezomib and dexamethasone (DVd), selinexor plus bortezomib and dexamethasone (SVd) and carfilzomib plus dexamethasone (hKd) versus BVd have been covered previously as part of the original CS concerning the lenalidomide unsuitable population at 2L. Therefore, carfilzomib plus lenalidomide and dexamethasone (KRd) remains as the only remaining relevant comparator for the corresponding lenalidomide suitable/naïve population, and the only lenalidomide-based triplet available to be assessed to allow for broad recommendation of BVd at 2L. This was reinforced by feedback from the published Draft Guidance for ID6212, which identified KRd as the most relevant comparator for the lenalidomide suitable/naïve population at 2L, based on the EAG's own clinical advice.[1]

Broadening the population to include all patients at 2L is important from an equitable access perspective, as patients diagnosed prior to the introduction of lenalidomide in the front-line setting (transplant-eligible: 2019, TA587; transplant-ineligible: 2021, TA680) are currently ineligible for treatment with BVd based on the recent positive Draft Guidance for lenalidomide-exposed patients at 2L [2]. This position is supported by recently published commentary from Shelagh McKinlay (Myeloma UK) and Martin Kaiser (Myeloma Molecular Therapy Group, Institute of Cancer Research) in *The Lancet Oncology* [3]. GSK would, if possible, like to see access granted for all patients at 2L, irrespective of prior lenalidomide exposure, due to the high unmet need for more effective treatment options with novel mechanisms of action at first relapse and the well-established principle in myeloma of using the most effective therapy as early as possible to maximize benefit.

It is also important to recognize that lenalidomide-naïve patients eligible for KRd at 2L (as per the current Blueteq criteria) [4] represent a small population compared to their lenalidomide-exposed counterparts, who are eligible for DVd, Kd, or SVd. Over the next few years, virtually all 2L patients will have been previously treated with lenalidomide, and thus few patients—if any—will remain eligible for KRd at 2L [5]. As a result, the KRd-eligible population is transient in nature and will diminish over time.

The objective of this report is to provide additional evidence for the relative efficacy and cost-effectiveness of BVd versus KRd, which was assessed through an unanchored matching-adjusted indirect comparison (MAIC). Previously, a simplified approach was presented to NICE, applying relative effects of the MAIC to unadjusted DREAMM-7 data. In addition, highly conservative assumptions were applied elsewhere based on the company's mistaken belief as to the certainty of cost-effectiveness against KRd, in order to aid in rapid decision making. Given the discrepancies pointed out by the EAG and NICE which negatively impacted cost-effectiveness (such as the application of a stopping rule for carfilzomib), the company have revised the analysis against KRd to provide a more comprehensive analysis, aligning to appropriately balanced settings and assumptions throughout the model. Namely, the MAIC results have been assessed and fit better to independent modelling of the BVd and KRd curves, and time to treatment discontinuation (TTD) for KRd has been updated for a more realistic extrapolation. The model is inclusive of changes listed by the EAG and NICE in their critique of the model following the Company's response to the Committee's preferred assumptions, such as including the stopping rule for carfilzomib.

The methods and results of the MAIC conducted to evaluate the comparative effectiveness of BVd to KRd for progression-free survival (PFS) and overall survival (OS) in a population equivalent to the DREAMM-7 intention-to-treat (ITT) population are presented in section 2. The corresponding methods and inputs for the Company's CEA of BVd versus KRd are presented in section 3. It should be noted that the report includes all evidence regarding comparisons of BVd to KRd, including evidence shared previously with NICE post ACM1, in order to summarise the totality of the evidence and aid in review by the EAG and committee.

The key conclusions of the analysis are the following:

- The results of the model demonstrate a large benefit to patient outcomes from treating with BVd compared to KRd for patients suitable for treatment with lenalidomide in 2L therapy ([redacted] LYG, and [redacted] QALY gain).
- The cost-effectiveness analyses in this report has been strengthened following the previous analyses submitted to NICE post ACM1 regarding 2L patients who are suitable for lenalidomide treatment. The previous analyses submitted post ACM1 overestimated KRd discontinuation and underestimated the predicted incremental health benefits of treating with BVd. Rectifying both issues strengthens the cost-effectiveness outcomes of BVd versus KRd and reduces the uncertainty within the analysis.

Overall, the analysis incorporates a carefully considered approach designed to utilise the best available evidence to power cost-effectiveness analysis of BVd versus KRd. In doing so, the results demonstrate that broadening access to all 2L patients is an efficient use of NHS resources.

2. Clinical effectiveness

DREAMM-7 is a pivotal phase III, randomised, multicentre clinical trial designed to compare the efficacy and safety of BVd in adults (≥18 years) with RRMM who have had at least one prior line of treatment (LoT) to DVd, the current 2L standard of care (SoC) within the NICE pathway. The study design, enrolled patient characteristics, planned analyses and a quality assessment of the DREAMM-7 trial were presented in sections B.2.2 to B.2.5 of the CS.

During the appraisal process of the CS, updated DREAMM-7 trial data became available corresponding to a longer median follow-up of 39.4 months. The IA2 trial results for PFS, OS and time to treatment discontinuation (TTD) in the corresponding primary evaluable populations (i.e. ITT for PFS and OS, and safety population for TTD) have been presented within previous communication to NICE. The findings of the IA2 data cut were largely consistent with the IA1 DREAMM-7 results. The IA2 efficacy results from DREAMM-7 were further used to inform the MAIC analysis against the most relevant lenalidomide-containing comparator KRd, as described in detail in section 2.1.

2.1. Matching-adjusted indirect comparison

2.1.1. Overview

As described in the CS, a clinical systematic literature review (SLR) was conducted to identify clinical evidence for therapies used in the management of patients with 2L+ RRMM (section B.2.1, appendix D and company's response at the clarification stage). No direct evidence comparing BVd with the regimens defined in the final scope was identified (besides DREAMM-7). Therefore, the DREAMM-7 trial and the evidence base with the SLR-identified studies was assessed for the feasibility of conducting ITCs to obtain estimates of the relative efficacy of BVd and relevant comparators.

The ITC feasibility assessment was conducted from a global perspective and considered 48 studies, including the 47 eligible studies identified by the SLR plus the DREAMM-7 trial. Of these, 18 studies formed a connected network of evidence, including 17 SLR-identified studies plus the DREAMM-7 trial. Details regarding the studies included in the final network of evidence were outlined in section B.2.9 of the CS. The final network included all relevant comparators used in the management of patients with RRMM who have had at least one prior line of treatment. As KRd could not form part of the connected network of evidence for the NMAs, a population-adjusted unanchored ITC was necessary to obtain relative treatment effects versus BVd.

Of the remaining 30 SLR-identified studies that were not included in a connected network of evidence, ten studies assessed treatments considered to be relevant comparators for BVd from a global perspective. A list of these trials that were assessed for the feasibility of conducting a population-adjusted unanchored ITC can be found in Appendix 1.1. A MAIC was deemed the most appropriate method to obtain relative

efficacy estimates for BVd, as this approach is more widely adopted in HTA appraisals than other methods for population-adjustment, such as a simulated treatment comparison (STC). While STCs may be preferred in situations where there is insufficient overlap between trial populations, both the STC and MAIC methods yield similar results when key prognostic factors (PFs) and treatment effect modifiers (TEMs) are well balanced, which was apparent when comparing BVd in DREAMM-7 and KRd in ASPIRE. Given the acceptable balance between these variables and the greater acceptance and use of MAICs in UK health technology assessments, the MAIC approach was selected for the indirect treatment comparisons involving DREAMM-7 and the relevant comparator trials.[1]

Given the unanchored nature of the population-adjusted ITCs, the company prioritised comparators included in the NICE pathway that were within the scope for this appraisal and were not included in the NMA. As outlined in section 1, KRd is the only remaining relevant comparator to be assessed to allow for broad recommendation of BVd at 2L given prior coverage of other relevant comparators in the original CS for the lenalidomide unsuitable population. The company would like to reiterate here that while Rd is available at 2L, it is not a relevant comparator given extremely low usage. This was substantiated by the clinical expert validation sessions in support of the CS (see also Appendix M of the CS), during which only one out of three clinical experts suggested Rd would have any usage at 2L, and only in 1% of patients [6, 7]. Additionally, the published Draft Guidance for ID6212 identified KRd as the most relevant comparator for the lenalidomide suitable population at 2L, based on the EAG's own clinical advice.[1] The only trial within the ten studies that assessed KRd as an intervention was the ASPIRE trial [8, 9], which was therefore assessed for the feasibility of conducting an unanchored MAIC with the BVd arm of the DREAMM-7 trial. The feasibility assessment and the methodology for the unanchored MAIC are presented in sections 2.1.3 and 2.1.4, respectively. The MAIC results for PFS and OS, that were subsequently used to inform the company's CEA analysis of BVd versus KRd are presented in section 2.1.5.

2.1.2. Real world evidence search

The company has conducted a targeted literature review to identify non-randomised studies of KRd that may support an indirect comparison to BVd and complement the data derived from the ASPIRE trial. The National Cancer Registration and Analysis Service (NCRAS) was explored as a potential source of RWE given the alignment of the inclusion and exclusion criteria to the included patients from to the DREAMM-7 trial.[10] In addition, in line with the company's commitment to support the NICE committee's preference for incorporating SACT data in technology appraisals [11] [12], the company engaged with the [redacted], who confirmed that no audit has been carried out to this date for KRd within the SACT data. Consequently, the company is unable to perform any analysis using SACT data for this evaluation.

To the best of the company's knowledge, NCRAS appears to be the only published UK RWE for KRd. However, the NCRAS dataset includes MM diagnoses from 2013–2020, with follow-up survival data up to October 31, 2022. Given that KRd reimbursement 2L setting (TA695) was approved in 2021, near the end of the NCRAS study period, KRd usage therefore comprises of only 1.6% of the "DREAMM7-like cohort" at 2L. Only 168 patients were identified to have received KRd treatment at 2L, and given the short timeframe, only 12 OS events were recorded, thereby highlighting the immaturity of NCRAS data for KRd. As such, NCRAS data is not suitable for informing the outcomes of KRd in UK clinical practice.

It is important to note that given widespread usage of lenalidomide at 1L, patients eligible for KRd represent a small and transient population, as blueteq criteria 6 for KRd mandates that patients need to be lenalidomide naïve in order to receive this option at 2L.[4] Therefore, it is unlikely that robust UK-specific real world data will become available in the future to appropriately inform an indirect comparison.

Given that NCRAS, the only published UK RWE for KRd is insufficient to support an indirect treatment comparison, the company also explored retrospective studies from other countries and regions (e.g., Spain, South Korea, EU & Israel, France) as potential sources of RWE for KRd [13-16]. However, these were excluded as potential options due to concerns regarding the generalisability of findings to UK clinical practice. Differences in MM patient management and treatment pathways across healthcare systems introduce substantial uncertainty in translating clinical efficacy to the UK setting.

In conclusion, the data from ASPIRE was deemed the only appropriate data source to inform relative differences in outcomes between KRd and BVd.

2.1.3. Feasibility assessment

A feasibility assessment was conducted to identify whether a MAIC was feasible for estimating the comparative efficacy of BVd versus KRd in adult patients with 2L+ RRMM. The level of heterogeneity across the relevant studies was assessed by comparing study designs, PFs and TEMs, treatment arms and outcomes, based on guidance from the Cochrane Handbook for Systematic Reviews of Interventions [17]. Additional details are included in Appendix 1.1.

2.1.3.1. Included studies

ASPIRE was the only relevant study which evaluated outcomes in KRd and therefore was chosen as the comparator study to inform the MAIC of BVd versus KRd (Table 1).

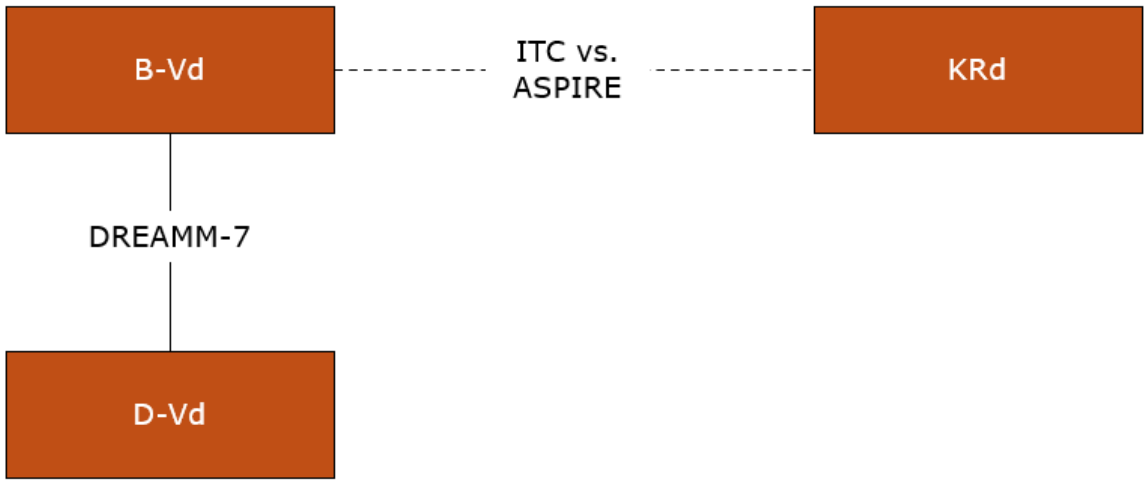
Table 1. Intervention arms of studies considered relevant for inclusion in the MAIC

Study	Intervention	Comparator	Population
DREAMM-7 ***[18]***	**BVd**	**DVd**	ITT*
ASPIRE ***[8, 9]***	**KRd**	**Rd**	ITT*

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; KRd, carfilzomib in combination with lenalidomide, and dexamethasone; MAIC, matching-adjusted indirect comparison; Rd, lenalidomide and dexamethasone.
Note: *The ITT population represents the ITT population of the DREAMM-7 trial
Source: GSK data on file [19]

As there is no common treatment arm between DREAMM-7 and ASPIRE, an unanchored approach was required. The diagram for the study arms considered in the feasibility assessment for an unanchored MAIC is presented in Figure 1.

Figure 1. Indirect network of evidence



Abbreviations: BVd; Belamaf in combination with bortezomib and dexamethasone; DVd, Daratumumab in combination with bortezomib and dexamethasone; ITC, indirect treatment comparison; KRd, carfilzomib in combination with lenalidomide and dexamethasone.

For an unanchored MAIC to be feasible, there must be adequate data and overlap of PFs and TEMs in both the intervention and comparator studies.

2.1.3.2. Prognostic factors and treatment effect modifiers

Based on the NICE technical support document (TSD) 18 [20], the 'conditional constancy of absolute effects' assumption must be met for a MAIC to be feasible. This assumption states that the differences between absolute outcomes that would be observed in each study are entirely explained by imbalances in TEMs and PFs with respect to the chosen scale. As such, the assumption requires all PFs and TEMs to be available.

TEMs and PFs for PFS and OS in MM were identified through discussion with MM clinical experts and supplemented through targeted literature searches. Further clinical validation was undertaken to rank the identified PFs and TEMs based on their importance as potential sources of heterogeneity which could lead to bias in the MAIC.

The list of identified PFs and TEMs and their corresponding ranking based on clinical validation are listed in Table 2.

Table 2. Ranking of identified PFs and TEMs based on clinical validation

Priority	Characteristics	PF	TEM
1	Prior LoT	✓	✓
2	Refractory status to the specific agent used in the study	✓	✓
3	R-ISS stage (% stage I and II, III, unknown)	✓	✓
4	Cytogenetic risk profile	✓	✓
5	EMD	✓	✓
6	Creatinine clearance	x	✓
7	Age	✓	x
8	ECOG PS	✓	✓

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; EMD, Extramedullary disease; ISS, International Staging System; LoT, line of treatment; PF, prognostic factor; TEM, Treatment effect modifier.
Note: (✓) marks indicate whether the patient characteristic is considered a PF and/or a TEM
Source: GSK data on file [19]

The distribution of these PFs and TEMs in the BVd arm of DREAMM-7 was assessed for eligibility of comparison with the KRd arm of ASPIRE. Table 3 shows the corresponding baseline characteristics in the ITT population of the BVd and KRd arms. The Revised International Staging System (R-ISS) was reported in both DREAMM-7 and ASPIRE [8, 9]. Additionally, extramedullary disease (EMD) was not reported in the ASPIRE study and, therefore, could not be compared across the studies [8, 9].

Table 3. Baseline characteristics in DREAMM-7 and ASPIRE

Study	DREAMM-7	ASPIRE
Source	DREAMM-7 IPD	Stewart et al (2015) *[8][21, 22]*
Treatment arm	BVd (N=243)	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, %)	R-ISS stage I-II: 232 (95.4%) III: 9 (3.7%) Unknown: 3 (1.2%) After adjusting for missingness: I-II: 96.3% III: 3.7%	R-ISS stage I-II: 236 (59.6%) III: 37 (9.3%) Unknown: 123 (31.1%) After adjusting for missingness: I-II: 86.4% III: 13.6%

Study	DREAMM-7	ASPIRE
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%
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 or 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; IMiD: immunomodulatory imide drug; R-ISS, Revised International Staging System; IPD, Individual patient data; ITT, intention to treat; KRd, carfilzomib in combination with lenalidomide and dexamethasone; LoT, line of treatment; mL/min, millilitre per minute; NR, not reported; PI, proteasome inhibitor; SD, standard deviation; TEM, treatment effect modifier.
Note 1: ASPIRE reported missing data for R-ISS stage, cytogenic risk profile and creatine clearance, which needed to be adjusted for missingness. Patients were assumed to be missing completely at random (MCAR) and were randomly assigned to an appropriate category.
Note 2: IMiDs include lenalidomide, thalidomide and pomalidomide.
Source: GSK data on file [19]

There were some notable differences identified between certain PFs and TEMs, which were noted as likely to cause unstable estimates. First, the proportion of patients that were refractory to lenalidomide was lower in the KRd arm of ASPIRE (7.3%) than in the BVd arm of DREAMM-7 (32.5%). Therefore, adjustment for this variable was required. Due to the substantial imbalance between the patient populations for this covariate, it was considered that this adjustment might significantly reduce the effective sample size (ESS).

ASPIRE further reported a large proportion of missing cytogenetic risk data (50.8% in the KRd arm) [8, 9]. To allow for matching, missing data was assumed to be missing completely at random and assigned to either standard or high cytogenetic risk, following which values were reweighted to account for missingness. This resulted in 75.4% of patients with standard cytogenetic risk in the KRd arm, which closely aligned with the DREAMM-7 BVd arm (72.4%). The assumption that cytogenetic risk patient data was missing completely at random was expected to introduce uncertainty in the analysis. Therefore, a sensitivity analysis excluding cytogenetic risk as a matching covariate was planned to explore this further.

Similarly to cytogenetic risk, missing data for creatinine clearance from the ASPIRE trial were also assumed to be missing completely at random. However, this covariate was not explored in a sensitivity analysis as only one patient from ASPIRE had missing data (Table 3) and therefore it was not expected to impact results.

A large proportion of patients had unknown R-ISS stage in the KRd arm of ASPIRE (31.1%) [8, 9]. As for cytogenetic risk, R-ISS was assumed to be missing completely at random and data in the KRd arm was reweighted. However, there were still relatively few patients that were R-ISS III in DREAMM-7 (3.7%) compared to the proportions in the KRd arm of ASPIRE both before (9.3%) and after reweighting (13.6%). Given that this difference in the distribution of data was likely to lead to unstable estimates, R-ISS was excluded from the base-case analysis. A sensitivity analysis including R-ISS as a matching covariate was planned to explore the effect of the large difference in distribution of R-ISS data between DREAMM-7 (BVd) and ASPIRE (KRd).

Only R-ISS data were available for ASPIRE and DREAMM-7. Additional staging data were reported for ASPIRE “as reported by investigator” in the appendix of Stewart et al. (2015),[8] however it is unclear which staging system this data corresponds to. To help reduce uncertainty associated with the missing R-ISS data in ASPIRE, the company sought clinical expert opinion, which identified serum β2-microgloblin as a viable proxy. Serum β2-microglobin is a key component of the R-ISS staging system [23] and is strongly correlated with disease burden and prognosis in multiple myeloma [24, 25]. Experts considered it a suitable substitute, as it reflects one of the main determinants of R-ISS staging and could help mitigate some of the limitations arising from the absence of complete R-ISS data. In ASPIRE, 19.4% (N=77) of KRd patients had serum β2-microglobulin <2.5 mg/L at baseline, while the remaining 80.6% (N=319) had serum β2-microglobulin ≥2.5 mg/L [8]. This proportion was slightly higher in the BVd group, with 36.2% (N=88) having <2.5 mg/L and 63.8% (N=155) having ≥2.5 mg/L [26]. Given the prognostic significance of serum β2-microglobulin and the degree of overlap between trials, a MAIC sensitivity analysis was conducted to assess the impact of inclusion of serum β2-microglobulin in the matching process (as presented in Section Appendix 1.4.4).

Another source of substantial imbalance was the distribution of prior LoT. The KRd arm of ASPIRE [8, 9] included only 0.3% of patients with ≥4 prior LoT compared to 12.4% in the BVd arm of DREAMM-7. In addition, grouping of 2-3 prior LoTs was required to align prior LoTs at the DREAMM-7 baseline with the categorisation used

in the ASPIRE study. While this enables a comparison, grouping of prior LoT results in a loss of information on this important factor and is a limitation of the MAIC.

Across DREAMM-7 and ASPIRE, other baseline characteristics (median time since diagnosis, race and gender) that were deemed important but not considered to be a PF or TEM were assessed and considered sufficiently homogenous across the studies.

2.1.4. Methodology

Based on the considerations outlined in section 2.1.3, an unanchored MAIC was deemed feasible between the DREAMM-7 BVd arm and the ASPIRE KRd arm for the endpoints of interest that would be used to inform the company's CEA, namely PFS and OS (see section 3).

MAIC is a non-parametric likelihood reweighting method of comparing treatment effects, while minimizing bias that results from PF or TEM baseline characteristics that are imbalanced across study populations. This is achieved by applying weights to individual patients in a study, where individual patient data (IPD) are available, and matching their weighted summary statistics to those of a comparator study population, where only aggregate data are reported. The methodology is well-established and suggested in the NICE guidelines [20].

The analyses were conducted using the ITT population of the BVd arm from DREAMM-7 (ITT: N = 243), for which IPD were available, and the ITT KRd arm from ASPIRE. Suitability of the PFs and TEMs for matching was assessed by checking the distribution of covariates in each population (outlined in section 2.1.3.2), checking the distribution of weights to identify any outliers, and by assessment of the ESS of the weighted BVd population to determine potential overlap between the populations. The rescaling works by increasing the weights of individuals in the DREAMM-7 BVd arm, who are similar to the aggregate data of the ASPIRE KRd arm, and reducing the weights of individuals who are dissimilar to the aggregate data. Therefore, weights greater than one mean that an individual carries more weight in the reweighted BVd population than in the original study.

Key TEMs and PFs of patients in the DREAMM-7 BVd arm were matched to those of patients in the ASPIRE KRd arm, and reweighted outcomes of the DREAMM-7 BVd arm were compared to the outcomes observed in the ASPIRE KRd arm [8, 9]. Following the NICE TSD 18 [20] recommendation, treatment effects were estimated on the linear predictor scale, with the same link functions that are usually employed for those outcomes:

- Weighted PFS and OS hazard ratios (HRs) from the IPD using Cox regression, and the corresponding standard errors (SEs) using a robust sandwich variance estimator. These were presented alongside naive unweighted estimates.
- Weighted Kaplan-Meier (KM) estimates.

A summary of the conducted analyses is presented in Table 4. The base-case analysis involved adjustment for all feasible PFs and TEMs except for R-ISS, which was excluded from the matching process (see sections 2.1.3.2 and 2.1.5.2). Four sensitivity analyses were conducted to explore uncertainties caused by high variation in certain PFs and TEMs between DREAMM-7 and ASPIRE (Table 4). The first sensitivity analysis excluded cytogenetic risk from the matching process, since half of the patients in the ASPIRE KRd arm had missing data for this covariate (section 2.1.3.2). The second sensitivity analysis included R-ISS in the matching process to assess the impact of the lower R-ISS III proportion in DREAMM-7 compared to ASPIRE. Conversely, a sensitivity analysis (#4) included β2-microglobulin in the matching process to assess the impact of including the variable, as an alternative to matching for R-ISS. Given that the ASPIRE study reported only one patient (0.3%) with ≥4 prior LoT compared to 12.4% in the BVd arm of DREAMM-7, the third sensitivity analysis truncated the LoT data by excluding ≥4 prior LoT from the matching process. Additional information on the statistical analysis plan can be found in Appendix 1.3.

Table 4. Overview of conducted analyses

Analysis	PFs and TEMs included in the matching process of the DREAMM-7 BVd arm	Outcomes
Base-case	Adjusting for all feasible TEMs and PFs excluding R-ISS in the matching process	• Weighted PFS • Weighted OS • Weighted KM estimates
Sensitivity analysis 1	Exclusion of cytogenetic risk profile in the matching process	
Sensitivity analysis 2	Inclusion of R-ISS stage in the matching process	
Sensitivity analysis 3	Truncated population, excluding ≥4 prior LoT in the matching process	
Sensitivity analysis 4	Inclusion of serum β2-microglobulin in the matching process	

Abbreviations: KM, Kaplan-Meier; KRd, carfilzomib in combination with lenalidomide and dexamethasone; LoT, line of treatment, OS, overall survival; PF, prognostic factor; R-ISS, Revised International Staging System; TEM, treatment effect modifier.
Source: GSK data on file [19]

2.1.5. Results

2.1.5.1. Interpretation

For OS and PFS, HRs were estimated to assess the relative efficacy of BVd versus KRd. A median HR<1 suggest a lower probability of the outcome occurring with BVd compared to KRd; values above 1 indicate a higher probability in the outcome occurring with BVd versus KRd. When the 95% confidence intervals (CIs) cross the line of “no difference” or HR=1, this indicates a lack of statistically significant difference in HR between treatments. Large CIs are indicative of low statistical power and uncertain estimates of treatment effects.

The ESS and the distribution of the weights were assessed to determine the level of uncertainty in the MAIC results. Based on the statistical analysis plan (see Appendix 1.3), an ESS >60 would indicate that there is sufficient overlap between the populations for the MAIC to be performed. An ESS of 40-60 suggests that the MAIC can be performed with the caveat that the low ESS indicates limited overlap between the populations, resulting in increased uncertainty. An ESS <40 indicates that there is poor overlap of the populations considered in the MAIC, which would lead to high uncertainty in the results, and therefore the analysis would not be performed.

2.1.5.2. PFs and TEMs before and after weighting for the MAIC base-case

The baseline characteristics for the DREAMM-7 BVd arm before and after weighting for the base-case are presented in Table 5. The weighted BVd baseline characteristics are matched exactly to those of the ASPIRE KRd arm apart from R-ISS, which was not matched in the base-case.

Table 5. BVd baseline characteristics before and after weighting vs KRd – Base-case

TEM or PF	DREAMM-7 BVd (%) at baseline		**ASPIRE KRd (%) at baseline*[21, 22]*
	Before weighting	After weighting	
Mean age (years)	64.4	[redacted]	63.3
1 prior LoT	51.0%	[redacted]	46.5%
2-3 prior LoT	36.6%	[redacted]	53.3%
≥4 prior LoT	12.3%	[redacted]	0.3%
Refractory to IMiD	38.7%	[redacted]	21.5%
Refractory to lenalidomide	32.5%	[redacted]	7.3%
R-ISS 1/2*	96.3%	[redacted]	59.6%
R-ISS 3*	3.7%	[redacted]	9.3%
Standard cytogenetic risk profile	72.4%	[redacted]	75.4%
High cytogenetic risk profile	27.6%	[redacted]	24.6%
ECOG PS 0/1	95.9%	[redacted]	89.9%
ECOG PS 2	4.1%	[redacted]	10.1%
Creatinine clear <50 mL/min	15.6%	[redacted]	6.3%

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance score; IMiD: immunomodulatory imide drug; LoT, line of treatment; KRd, carfilzomib in combination with lenalidomide and dexamethasone; MAIC, matching-adjusted indirect comparison; min, minute; mL, millilitre; PF, prognostic factor; R-ISS, revised International Staging System; TEM, treatment effect modifier.
Note 1: *R-ISS were not matched in the base-case.
Note 2: IMiDs include lenalidomide, thalidomide and pomalidomide.
Note 3: **ASPIRE baseline values have been adjusted for missingness
Source: GSK data on file [19]

The distribution of weights after matching was assessed, including consideration of extreme or highly variable weights. ESS was also assessed, as large reductions in ESS may indicate poor overlap and the resulting comparison may be unstable.

Rescaled weights are presented in Figure 2 for BVd matched to KRd. All patients in the BVd arm were assigned weights below six, indicating relatively stable weightings The rescaled weights indicate that approximately [redacted] of patients were assigned a zero weighting, indicating that they had been excluded from the analysis. Notably, over a third of the ITT patients in the BVd arm (approximately 36%) were assigned a weight close to one, suggesting an overlap and similarities between the trial populations.

The analysis yielded an ESS of 126.42 (BVd arm ITT; N = 243), resulting in a reduction of 48% of the ITT arm sample size. However, the ESS is acceptable according to the pre-specified threshold of 60 (section 2.1.5.1 and Appendix 1.3). Therefore, the analysis was considered to be sufficiently robust to generate meaningful outcomes.

Figure 2. Rescaled weights for BVd in the base-case

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone.

Source: GSK data on file [19]

2.1.5.3. Base-case results

The following section outlines the results of the base-case analysis for PFS and OS of BVd relative to KRd, both before and after matching on the PFs and TEMs presented in section 2.1.5.2.

2.1.4.3.1. Progression-free survival

The base-case analysis for PFS demonstrated that BVd is more efficacious than KRd. Both the weighted (HR: [redacted]) and unweighted (HR[redacted]) results demonstrated a statistically significant benefit for BVd over KRd. It is worth noting that the treatment effect improved after weighting of the BVd population and the ESS of the weighted BVd arm (126.42) was within the threshold (>60) for sufficient overlap in populations. An overview of the PFS HRs for BVd versus KRd before and after matching are presented in Table 6 and Figure 3.

Table 6. MAIC base-case results - PFS

Treatment arm	Sample size	Median PFS (months)	BVd versus KRd	
			HR	95% CI
Weighted BVd	126.42*	[redacted]	[redacted]	[redacted]
Unweighted BVd	243.00*	[redacted]	[redacted]	[redacted]
KRd	396.00*	26.30	N/A	

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; CI, confidence interval; ESS, effective sample size; HR, hazard ratio; ITC: indirect treatment comparison; KRd, carfilzomib in combination with lenalidomide and dexamethasone; MAIC, matching-adjusted treatment comparison; PFS, progession-free survival.
Note: *The weighted BVd sample size corresponds to the ESS after matching for the covariates adjusted in the base-case analysis (section 2.1.5.2). The sample size of the unweighted BVd arm and the KRd arm correspond to the ITT arm sample size.
Source: GSK data on file [19]

Figure 3. Comparison of PFS for BVd vs. KRd

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KM, Kaplan-Meier; PFS, progression-free survival; KRd, carfilzomib in combination with lenalidomide and dexamethasone.
Source: GSK data on file [19]

The KRd PFS KM curve, as well as the weighted and unweighted BVd PFS KM curves are shown in Figure 4. Both the weighted and unweighted BVd curves are above the KRd curve after approximately five months, further underscoring the superior PFS outcomes associated with BVd. It should be noted that the weighted BVd PFS curve structure is closely aligned to the corresponding unweighted curve, with improved PFS after approximately nine months. This is aligned with the MAIC results yielding a statistically significant lower median HR for the weighted BVd arm (Table 6). In addition, these results are consistent with the highest median PFS associated with the weighted BVd arm ( ) compared to the unweighted BVd arm ( ), with both being consistently higher than the median KRd PFS (26.30 months, Table 6).

Figure 4. PFS KM curves, BVd (weighted and unweighted) vs KRd – base-case

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KM, Kaplan-Meier; KRd, carfilzomib in combination with lenalidomide and dexamethasone PFS, progression-free survival.
Note: The number of patients at risk at time zero for the weighted BVd KM curve differs from the ESS. This is due to the ESS being calculated as the sum of the square weights divided by the sum of the weights, whilst the number at risk is simply the sum of the weights.
Source: GSK data in file [19]

2.1.4.3.2. Overall survival

BVd demonstrated a statistically significant OS benefit over KRd across both the weighted (HR) and unweighted comparisons (HR). It is worth noting that the ESS of the weighted BVd arm (126.42) was within the threshold (>60) for sufficient population overlap (126.42), and the superior OS outcomes for BVd after weighting were consistent with those from the

unweighted comparison versus KRd. An overview of the OS HRs for BVd versus KRd before and after population matching is presented in Table 7 and Figure 5.

Table 7. MAIC base-case results - OS

Treatment arm	Sample size	Median OS (months)	BVd versus KRd	
			HR	95% CI
Weighted BVd	126.42*	[redacted]	[redacted]	[redacted]
Unweighted BVd	243.00*	[redacted]	[redacted]	[redacted]
KRd	396.00*	48.3	N/A	

Abbreviations BVd, belamaf in combination with bortezomib and dexamethasone; CI, confidence interval; ESS, effective sample size; HR, hazard ratio; ITC: indirect treatment comparison; KRd, carfilzomib in combination with lenalidomide and dexamethasone; MAIC, matching-adjusted treatment comparison; OS, overall survival.
Note: *The weighted BVd sample size corresponds to the ESS after matching for the covariates adjusted in the base-case analysis (section 2.1.5.2). The sample size of the unweighted BVd arm and the KRd arm correspond to the ITT arm sample size.
Source: GSK data on file [19]

Figure 5. Comparison of OS for BVd vs. KRd

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; CI, confidence interval; KRd, carfilzomib in combination with lenalidomide and dexamethasone; OS, overall survival.
Source: GSK data on file [19]

The KRd OS KM curve as well as the weighted and unweighted BVd OS KM curves are shown in Figure 6. The weighted BVd OS KM curve is closely aligned to the unweighted BVd curve, with the unweighted curve falling below the weighted between 10 to 20 months. Importantly, both the weighted and unweighted BVd OS KM curves remained above the KRd KM curve after approximately 12 months, showcasing the improved OS outcomes associated with BVd compared to KRd. This is consistent with

the MAIC results yielding a statistically significant lower median HR for both the weighted and unweighted BVd arm versus KRd (Table 7). The KM observations underscoring the superior OS outcomes for BVd are also aligned with the median OS for both the weighted and unweighted BVd arms still not reached at a median follow-up of 39.4 months (IA2 DCO), whilst median OS for KRd was 48.3 months (Table 7).

Figure 6. OS KM curves, BVd (weighted and unweighted) vs KRd – base-case

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone; OS: overall survival; KM: Kaplan-Meier.
Note: The number of patients at risk at time zero for the weighted BVd KM curve differs from the ESS. This is due to the ESS being calculated as the sum of the square weights divided by the sum of the weights, whilst the number at risk is simply the sum of the weights.
Source: GSK data in file [19]

2.1.4.3.3. Overall survival compared with progression-free survival in the base-case

The PFS and OS outcomes for the weighted BVd population in the MAIC base-case were compared to check the clinical plausibility of the results following the population matching process. Figure 7 showcases that the weighted PFS and OS BVd KM curves are clinically plausible as OS remains higher than PFS throughout the study period, except for a very short interval at approximately two months where PFS>OS. This is due to a highly weighted patient which is censored for PFS but subsequently has an OS event, leading to OS falling below PFS.

Figure 7. Weighted OS and PFS KMs for BVd when matched to KRd – base-case

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; IRC: independent review committee; KRd, carfilzomib in combination with lenalidomide and dexamethasone; OS, overall survival; PFS, progression-free survival
Note: The number of patients at risk at time zero for the weighted BVd KM curve differs from the ESS. This is due to the ESS being calculated as the sum of the square weights divided by the sum of the weights, whilst the number at risk is simply the sum of the weights.
Source: GSK data on file [19]

2.1.5.4. Sensitivity analyses results

As outlined in section 2.1.4, sensitivity analyses were conducted to explore uncertainties caused by high variation between PFs and TEMs in the BVd arm of DREAMM-7 and the KRd arm of ASPIRE. An overview of the results for PFS and OS for each of the analyses is shown in Table 8. Additional MAIC outputs and results for each planned sensitivity analysis are presented in Appendix 1.4.

For all three sensitivity analyses, the direction of the effect for PFS was the same with the base case. For PFS, the HRs and corresponding 95% CI of all four sensitivity analyses were completely aligned with the MAIC base-case results (Table 8). Overall, the MAIC PFS HRs are considerably lower than the HR of the unweighted comparison against KRd and statistically significant in favour of BVd for all analyses conducted. Importantly, the reduction of the median PFS HR estimates across all MAIC analyses compared to the unweighted comparison further showcases the improved treatment effect versus KRd for all the matched BVd populations.

Similarly to PFS, all four sensitivity analyses for OS yielded results that corroborated the superior OS outcomes for BVd versus KRd, in line with the base-case. With the

exception of sensitivity analysis 2, both the weighted and unweighted comparisons yielded equal OS HR, demonstrating a statistically significant OS benefit for BVd versus KRd (Table 8). Even though the median HR estimate from sensitivity analysis 2 was higher compared to the rest of the analyses ([redacted] compared to [redacted], Table 8), the results were also directionally in favour of BVd.

Table 8. MAIC sensitivity analyses results vs base-case

Analysis	PFs and TEMs included in the matching process of the DREAMM-7 BVd arm	BVd arm sample size	BVd versus KRd	
			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: BVd, belamaf in combination with bortezomib and dexamethasone; CI, confidence interval; ESS, effective sample size; KRd, carfilzomib in combination with lenalidomide and dexamethasone; LoT, line of treatment; MAIC, matching-adjusted treatment comparison; OS, overall survival; PF, prognostic factor; PFS, progression-free survival; TEM, treatment effect modifier.
Note: *The BVd sample size corresponds to the ESS after matching for the covariates adjusted in each analysis. The sample size of the BVd arm in the unweighted comparison (N=243) and the KRd arm in all analyses (N=396) correspond to the ITT arm sample sizes.
Source: GSK data on file [19]

It should be noted that the results of sensitivity analysis 2, which included R-ISS in the matching process (Table 8) should be interpreted with caution, since they are unlikely to provide meaningful insights. R-ISS is an important prognostic factor for RRMM and patients with R-ISS stage III are expected to have poorer outcomes compared to patients with stages 1-2. As discussed in section 2.1.3.2, nearly one third of the ASPIRE trial patients (31%) had missing R-ISS data at baseline. Additionally, there were substantially more ASPIRE patients at baseline that were R-ISS stage III (9.3%) compared to the BVd arm of DREAMM-7 (3%). To account for the large proportion of missing R-ISS data from ASPIRE, the assumption was made that data was missing completely at random. Therefore, R-ISS was reweighted to 100%, leading to a proportion of R-ISS III patients of 14% for KRd. This resulted in the few R-ISS III patients in DREAMM-7 being assigned large weights, with an extremely high weight (>20) being assigned to a single BVd patient in sensitivity analysis 2 (see also Appendix 1.4.2) The resulting ESS (71.28) for this sensitivity analysis was slightly above the acceptable threshold (set at 60), implying increased bias and uncertainty.

This indicates that the matching exercise for this analysis was inadequate in resolving the large differences in the PFs and TEMs in the DREAMM-7 BVd arm and ASPIRE KRd arm, as evidenced by the large weights.

In addition, one of the reweighted R-ISS III DREAMM-7 patients was censored shortly after baseline for PFS, and subsequently died shortly afterwards. As a result, the OS KM curve dropped sharply and fell below the PFS KM curve, which did not have a corresponding drop as this patient had been censored. Importantly, the weighted OS KM curve in sensitivity analysis 2 remained below the PFS KM curve from approximately 1 to 10 months (see also Appendix 1.4.2.2). Taking all the above into account, the results of sensitivity analysis 2 lacked face validity since they produced clinically implausible outcomes as patients cannot progress after death.

Sensitivity Analysis 4, which includes β2-microglobulin in the matching process, helps reduce some of the uncertainty surrounding the MAIC analysis regarding exclusion of R-ISS. As discussed in Section 2.1.4, β2-microglobulin was identified by clinicians to be a viable proxy for R-ISS. The results of sensitivity analysis 4 show slightly less favourable HRs and KM curves for BVd, as expected, given the higher proportion of DREAMM-7 patients with lower β2-microglobulin levels, an indicator of better prognosis. Nevertheless, the results remain consistent with the base case, with HRs statistically significant at the 95% confidence level. Furthermore, a comparison of the PFS and OS KM (curves between the base case and sensitivity analysis 4 (Figure 8 and Figure 9) shows that the BVd-weighted curves have similar shapes and separation to the KRd curves from ASPIRE. Overall, the inclusion of β2-microglobulin in the matching process strengthens confidence in the relative treatment effect of BVd

versus KRd by better accounting for key prognostic factors, while still demonstrating statistically significant improvements in PFS and OS.

Figure 8: Comparison of base case and sensitivity analysis 4 weighted BVd PFS KM

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival.

Figure 9: Comparison of base case and sensitivity analysis 4 weighted BVd OS KM

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KM: Kaplan-Meier; MAIC, matching-adjusted indirect comparison; OS: overall survival.

2.1.6. Strengths and limitations

Unanchored MAICs were conducted to estimate the relative efficacy of BVd versus KRd in patients with 2L+ RRMM. This approach has been used in a number of NICE oncology health technology assessments, including the recent TA783 for RRMM, for which a MAIC was conducted on OS [27].

If baseline characteristics across studies are not comparable, the results of any unadjusted comparison performed may be biased. To this end, MAICs improve the comparability of populations and allow for the calculation of treatment effects associated with reduced bias. MAICs require the assumption that all TEMs and PFs are captured and controlled for in the analysis. PFs and TEMs for MM were identified and ranked through clinical validation based on their importance as potential sources of heterogeneity which could lead to bias in the MAIC. EMD was identified as an important TEM in MM but was not included in the matching exercise as it was not reported in the ASPIRE trial. This may incur a bias of unknown direction in the MAIC results and represents one of the limitations of this analysis.

After matching the DREAMM-7 BVd arm to the KRd arm of ASPIRE for the remaining PFs and TEMs identified, the resulting BVd ESS was assessed to understand the overlap of the patient populations. It is important that estimates resulting from the MAIC are based on as large a sample size as possible, to ensure robust and reliable

results. Thus, balancing the number of covariates being adjusted for against the ESS is a vital consideration for the analysis. The ESS when adjusting for all PFs and TEMs (71.2) was close to the threshold (60) for effective distribution of weights and management of uncertainty. This indicated a lack of sufficient overlap between the weighted BVd population and the KRd arm of the ASPIRE trial. Removal of R-ISS stage from the matching process, for which data were also missing for one third of the KRd arm, resulted in a substantially increased ESS (126.4). Matching for all PFs and TEMs except for R-ISS stage was subsequently chosen as the MAIC base-case. Exclusion of the remaining highest ranked PFs and TEMs, namely cytogenic risk and ≥4 prior LoTs, from the matching process in sensitivity analyses resulted in ESS similar to the base case.

Even though removal of R-ISS considerably increased ESS for the base-case analysis, R-ISS staging is a key TEM in MM. It is worth noting though that a large proportion of patients had unknown R-ISS stage in the KRd arm of ASPIRE (31.1%) [8, 9]. In addition, there were still relatively few patients that were R-ISS III in DREAMM-7 (3.3%) compared to the proportions in ASPIRE both before (9.3%) and after reweighting (13.6%). Since R-ISS stage III patients are expected to have poorer outcomes compared to those with stages 1-2, exclusion of R-ISS from the base-case matching maintains the imbalance in R-ISS observed between the studies. However, inclusion of R-ISS stage in the matching process for sensitivity analysis 2 resulted in a substantial reduction of ESS (71.2 versus 126.4 in the base-case) and an extremely high weight (>20) for a single BVd patient with R-ISS III. Considering all these, inclusion of R-ISS stage in the matching process was unlikely to provide clinically meaningful results. Therefore, exclusion of R-ISS in the base-case matching process was considered an acceptable limitation of the method.

In response to the limitations of the MAIC analysis which includes R-ISS in the matching process, a sensitivity analysis including serum β2 microglobin was conducted. Serum β2-microglobin is a key component of the R-ISS staging system [23] and is strongly correlated with disease burden and prognosis in multiple myeloma [24, 25]. Whilst serum β2 microglobin may not be a perfect proxy for R-ISS, experts considered it to be the most suitable substitute, as it reflects one of the main determinants of R-ISS staging and highlighted that it may help mitigate some of the limitations arising from the absence of complete R-ISS data. Importantly the results of the sensitivity analysis including serum β2 microglobin in the matching process were consistent with the base case, both in terms of HRs and the shape and separation of the BVd KM curves to the KRd curves.

The MAICs demonstrated that patients treated with BVd had statistically significant PFS and OS benefits compared with KRd across weighted and unweighted comparisons. For both PFS and OS outcomes, BVd consistently demonstrated superior results relative to KRd, across all MAIC base-case and sensitivity analyses, highlighting the robustness and reliability of the analyses. These findings indicate that BVd is more effective than KRd at slowing disease progression and mortality in RRMM patients. Taken together, the results from the IA2-updated trial evidence, the IA2 NMAs and the IA2-informed MAIC against KRd underscore the universal clinical Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

benefit from BVd for PFS and OS compared to the relevant 2L comparators in the NICE pathway. Importantly, the results further emphasize that BVd will have the greatest impact on the widest possible patient population in 2L, effectively covering all RRMM patients who have had only one previous treatment irrespective of prior exposure to lenalidomide.

3. Cost-effectiveness

As detailed in the CS, GSK developed a de novo CEM for the appraisal of BVd for the treatment of adult patients with RRMM who have had one prior LoT. The economic model submitted as part of the CS was used to estimate the total costs and quality-adjusted life years (QALYs) associated with BVd compared to relevant comparators that have the potential to be displaced with recommendation of BVd in 2L for patients for whom lenalidomide is unsuitable in England and Wales. Therefore, the initial version of the CEM compared BVd with treatments that were part of the decision problem addressed in the CS, namely DVd, hKd, and SVd.

The CEM has been subsequently updated to incorporate a comprehensive KRd analysis, which is the only remaining relevant comparator included in the NICE pathway at 2L that was within the scope issued for this appraisal. To incorporate KRd in the CEM, a functionality has been included to allow for the comparison of BVd versus KRd using results of the MAIC analysis. The comparison of BVd with DVd, hKd and SVd is still available in this version of the CEM, as well as the committee's preferred base-case of using the SACT data as a baseline curve for DVd.

Section 3.1 includes details for the patient population entering the model and the corresponding baseline characteristics, as well as the sources of inputs for BVd and KRd. The CEM clinical effectiveness parameters based on the IA2 results of the DREAMM-7 trial and the MAIC results of BVd versus KRd are described in section 3.2. Additional CEM inputs that incorporate the IA2-updated DREAMM-7 data and align with the EAG preferred base-case are detailed in sections 3.3 and 3.4.

3.1. Economic analysis

This section outlines the comparators considered for the lenalidomide-suitable population of the updated CEM, as well as details of the patient population entering the model and its corresponding baseline characteristics. The model structure and settings were kept consistent with those presented in sections B.3.2.3 and B.3.2.4, respectively in the CS.

3.1.1. Patient population

The population entering the model is aligned with the ASPIRE patient population, as the weighted BVd population from the MAIC analysis of DREAMM-7 is presented as the base-case analysis against KRd (N=126.4). Given the differences in outcomes between the weighted and unweighted BVd arms (Sections 2.1.4.3.1 and 2.1.4.3.2), it is important to capture the results of the MAIC in totality to be able to assess differences in treatment effect between KRd and BVd throughout the timeframe of the available data.

It should be noted that the weighted BVd data included is aligned to the ITT population of ASPIRE. While this population is broader than the proposed patient population, we

believe it to be the best approach to inform cost-effectiveness; given the higher patient numbers (required for a more robust MAIC analysis) and strong overlap between trials.

3.1.2. Baseline characteristics

Baseline characteristics for the modelled cohort are based on the weighted BVd mean age from the base case MAIC analysis comparing BVd to KRd and are presented in Table 9. See Section 2.1.5.2 for more details of the baseline characteristics following MAIC analysis.

Table 9. Patient baseline characteristics for the base-case economic analysis

Characteristic	ITT
Baseline age (years)	[redacted]
Baseline weight (kg)	[redacted]
Baseline BSA (m^2)	[redacted]
% of males	55%

Abbreviations: BSA, body surface area; ITT, intention-to-treat.
Source: DREAMM-7 [18]

Previously, the committee demonstrated preference for the population, including baseline age, to be aligned to that of the population in the NHS clinical practice. This was satisfied by the company providing DVd SACT for the baseline curve for DVd and applying the relative effects of outcomes from DREAMM-7 (BVd) and the NMA results (hKd, SVd). However, for comparisons between BVd and KRd, SACT or other RWE baseline data are unavailable (see section 2.1.2).

Advice from the EAG in the latest critique (post ACM1) is as follows;

"it is inconsistent to assume a starting age from a different source without considering the impact of age on mortality. The OS curves from DREAMM-7 reflect the all-cause mortality risks of a population with a baseline age of 64 years in the trial (as per the company's original base-case analysis). As mortality risk in the general population increases with age, using an older age than that reflected in the observed survival data risks introducing adjustments for the general population mortality at an earlier time point in the extrapolations for both DVd and BVd."

The company agree that misalignment of the starting age introduces bias into the analysis. Given this identified risk, the base-case age aligns with the baseline age from the MAIC, and the mean age of patients from SACT was ran as a scenario analysis. It should be noted this scenario only impacts the capping of mortality by the general population values, and disproportionately impacts BVd. At base-case settings, BVd mortality is capped at approximately 17 years, whereas for KRd; mortality is capped at approximately 30 years. For an unbiased analysis, differing age would impact both arms equally throughout the time period. However, this analysis cannot be pursued without comprehensive patient-level data from ASPIRE.

Overall, the difference in age between the MAIC (used in base-case) and UK patients is deemed to be a tolerable uncertainty in the analysis, as it is unlikely to significantly impact relative effectiveness between BVd and KRd, and therefore decision making.

3.1.3. Intervention technology and comparators

The intervention being considered in the CEM is BVd. Belamaf is available in 100mg and 70mg vials which are administered as an IV infusion. The dosage used in the CEM is 2.5mg/kg of belamaf Q3W, with dose reductions and delays as observed in the patient-level data from DREAMM-7 accounted in the model. Bortezomib is given in 1.3mg/m^2 doses administered through a SC injection, four times every three weeks. Dexamethasone is given as 20mg oral tablets (eight times every three weeks). This aligns with the DREAMM-7 CSR [18] and the draft summary of product characteristics (SmPC) [28].

For this report, the only comparator under consideration is KRd. It was incorporated in the model as per its marketing authorisation and was given according to its licensed dosing regimens. For details regarding the MAIC that was conducted to provide comparative efficacy results between BVd and KRd please refer to section 2.1 and Appendix 1.

3.2. Clinical parameters and variables

3.2.1. Data sources for survival endpoints

The key outcomes used in the economic model are PFS, OS and TTD. Clinical effectiveness data for both BVd and KRd (PFS and OS) was sourced from the MAIC (described in section 2.1). As part of the NICE HTA process (recent EAG critique), the EAG highlighted uncertainty on whether the proportional hazards (PH) assumption holds for the comparison with BVd, as formal diagnostic tests did not fully allow rejecting this assumption. To address this uncertainty the company have fitted independent parametric models to the survival Kaplan Meier (KM) data for both treatment arms, for both PFS and OS, instead of applying MAIC HRs to the unweighted BVd data. The fitting of independent parametric models is in line with the methods recommended by NICE DSU TSD 14.

Due to unavailability of published data to inform a MAIC for TTD, assumptions were made to fit plausible TTD estimations for KRd (see Table 10 and section 3.2.2).

Table 10 summarises the clinical efficacy input data used in the CEM.

Table 10. Clinical inputs for CEM

Endpoint	Source of clinical effectiveness	
	BVd	**KRd**
PFS/OS	Base-case: DREAMM-7 direct extrapolation of BVd arm (MAIC) weighted to match ASPIRE	Base-case: ASPIRE direct extrapolation of KRd arm (unweighted)
TTD	Base-case: DREAMM-7 direct extrapolation of BVd arm (aligned to the IPD dosage from the IA2 data)	Base-case: DVd HR between PFS and TTD (DREAMM-7) Scenarios: - TTD=PFS - ASPIRE median PFS to median TTD calculations (see section 3.2.2)

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; CEM, cost-effectiveness model; DREAMM, Driving Excellence in Approaches to Multiple Myeloma; HR, hazard ratio; IPD, individual patient data; KRd, carfilzomib in combination with lenalidomide, and dexamethasone; MAIC, matching adjusted indirect comparison; OS, overall survival; PFS: progression-free survival; TTD, time to treatment discontinuation.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) [29]

3.2.2. Parametric survival modelling for BVd

Parametric survival models were used to extrapolate the IA2-updated DREAMM-7 survival curves for PFS, OS and TTD in the ITT (MAIC weighted) BVd treatment arm of the DREAMM-7 trial over a lifetime horizon of the CEM, in line with the approach followed in the CS. These analyses have been carried out in line with the NICE TSD 14 [30].

It is worth noting that curve selections for PFS, OS and TTD data are consistent with the extrapolations considered appropriate by the EAG based on the ITT DREAMM-7 IA2 data and informed the EAG base-case analysis [31].

Previously, a simplified approach was provided. The MAIC HRs were applied to the extrapolated KM curves of the unweighted BVd arm to generate the corresponding KRd survival curves over a lifetime horizon in the CEM. Given the availability of the BVd weighted data in the CEM, and the survival analysis carried out for both weighted BVd and KRd outcomes, a full proportional hazard and curve choice assessment has been carried out to appropriately inform the correct choice for data extrapolation.

In light of the sensitivity analysis 4 results, the company did not conduct independent modelling given the consistency in the shape of the KM data compared to the base case, particularly with OS (Figure 8 and Figure 9), and therefore the results of the independent modelling of PFS and OS are highly likely to be consistent with the base-case results of the MAIC.

3.2.3. Progression free survival

Parametric models were fitted to the weighted BVd patient level data generated from the base case MAIC analysis comparing BVd to KRd, as discussed in Section 2.1 to provide long-term extrapolations for PFS. The base case MAIC analysis adjusted for all PFs and TEMs, except for R-ISS. Parametric models were also fitted to the unweighted KRd patient level data to provide long-term extrapolations of PFS.

3.2.3.1. Conclusions of the diagnostic plots

While the log-cumulative hazard plot (Figure 10) intersects (which suggest PH may be violated), the lines are also relatively parallel. It is not possible to conclusively determine whether the PH assumption holds. The Schoenfeld residual plot (Figure 11), and the quantile-quantile plot (Figure 12) suggests that the relative hazards are likely to vary over time, and as such that the PH assumption may not hold. The residual plot in Figure 11 has a zero-slope; however, there are some fluctuations, meaning this plot also suggests that the PH assumption may be violated. Figure 12 indicates that the quantiles do not lie in a straight line, suggesting that the constant accelerated factor (AF) assumption may be violated. Therefore, dependent models which assumed a proportional treatment effect may not be appropriate and hence independent models were selected for use in the base-case analyses.

Inspection of the hazard plot (Figure 13) show that the hazard rate for BVd and KRd are relatively constant for the duration of the time horizon where the bulk of the data lies. This means that simpler models with a constant hazard (exponential) may be appropriate for modelling the hazard rates.

Figure 10: Cumulative log-log plot for PFS

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KRd, carfilzomib in combination with lenalidomide, and dexamethasone; PFS, progression-free survival.

Figure 11: Schoenfeld residuals plot for PFS

Abbreviations: PFS, progression-free survival.

Figure 12: Quantile-quantile plot for PFS

Abbreviations: PFS, progression-free survival.

Figure 13: Hazard rate plots for PFS

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KRd, carfilzomib in combination with lenalidomide, and dexamethasone; PFS, progression-free survival.

3.2.3.2. Independent survival curves

Six standard parametric independent models were fitted to the unweighted KRd and weighted BVd arms; exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised Gamma.

A summary of the goodness-of-fit statistics for the PFS extrapolations is presented in Table 11. Table 12 outlines the landmark PFS rates for unweighted KRd and weighted BVd.

Table 11: AIC and BIC statistical goodness-of-fit data for PFS

Distribution	Weighted BVd		Unweighted KRd	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	2385.42	2389.40
Weibull	[redacted]	[redacted]	2387.31	2395.27
Gompertz	[redacted]	[redacted]	2386.33	2394.29
Log-logistic	[redacted]	[redacted]	2383.46	2391.43
Log-normal	[redacted]	[redacted]	2405.90	2413.86
Generalised Gamma	[redacted]	[redacted]	2387.53	2399.48

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; BVd, belamaf in combination with bortezomib, and dexamethasone; KRd, carfilzomib in combination with lenalidomide, and dexamethasone; PFS, progression-free survival

Table 12: Unweighted KRd and weighted BVd landmark survival rates (PFS)

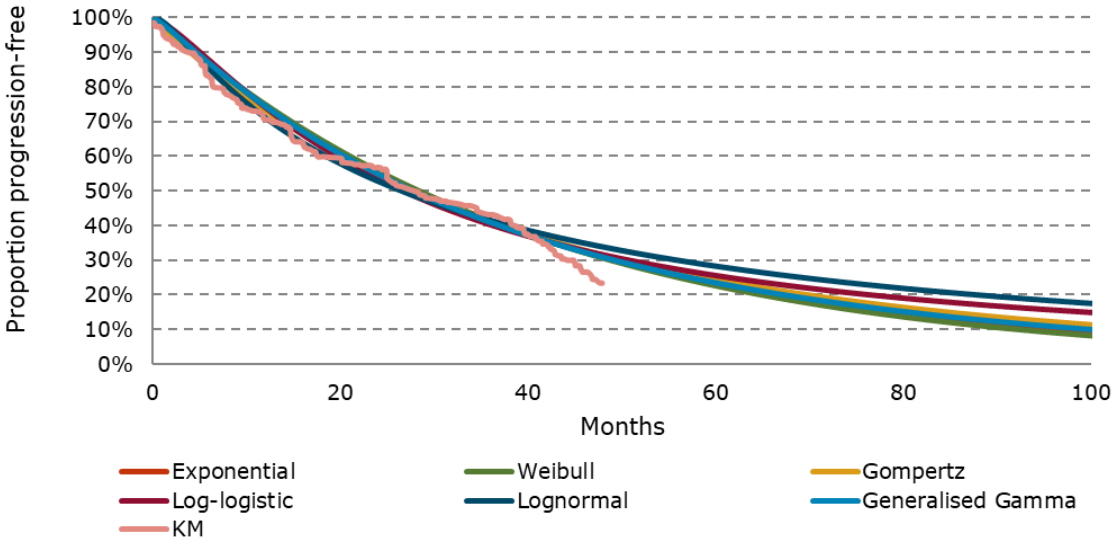
Distribution	Intervention	PFS (%) at landmark timepoints			
		Years			
		1	2	5	10
Exponential	Weighted BVd	[redacted]	[redacted]	[redacted]	[redacted]
	Unweighted KRd	75	56	23	5
Weibull	Weighted BVd	[redacted]	[redacted]	[redacted]	[redacted]
	Unweighted KRd	75	56	23	5
Gompertz	Weighted BVd	[redacted]	[redacted]	[redacted]	[redacted]
	Unweighted KRd	73	55	24	8
Log-logistic	Weighted BVd	[redacted]	[redacted]	[redacted]	[redacted]
	Unweighted KRd	74	54	26	12
Log-normal	Weighted BVd	[redacted]	[redacted]	[redacted]	[redacted]
	Unweighted KRd	71	53	28	14
Generalised Gamma	Weighted BVd	[redacted]	[redacted]	[redacted]	[redacted]
	Unweighted KRd	74	55	24	7

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KM, Kaplan-Meier; KRd, carfilzomib in combination with lenalidomide, and dexamethasone; PFS, progression-free survival

Figure 14: PFS independent curves for weighted BVd

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KM, Kaplan-Meier; PFS, progression-free survival
Note: The exponential and Weibull curves are overlapping in this figure.

Figure 15: PFS independent curves for unweighted KRd



Abbreviations: KM, Kaplan-Meier; KRd, carfilzomib in combination with lenalidomide, and dexamethasone; PFS, progression-free survival

3.2.3.3. Summary of base-case curve choice

The PH assessment between weighted BVd and unweighted KRd was inconclusive. According to the AIC and BIC, the exponential was the best fitting curve for weighted BVd, while the exponential was also among the best fitting curve for the unweighted KRd extrapolation (with the log-logistic curve also being considered a statistically similar fit given the closeness of the AIC and BIC). The hazard plot also indicated a simpler model (such as the exponential) could be an appropriate distribution. Together, these tests indicate the exponential to be a robust option and was therefore chosen for the base case. Additionally, the shape of this curve is aligned to the settings chosen by the EAG and committee across all comparators (BVd and DVd unweighted from DREAMM-7, and adjusted curves to incorporate the NMA) for the 2L population, when lenalidomide is unsuitable. There is therefore consistency across these two populations, and similar conclusions to the clinical plausibility which were incorporated within the original company submission.

3.2.4. Overall survival

In line with the methods for PFS, parametric models were fitted to the BVd patient level data generated from the MAIC analysis comparing BVd to KRd, as discussed in Section 2.1. Parametric models were also fitted to the unweighted KRd OS patient level data.

3.2.4.1. Conclusions of the diagnostic plots

Inspection of the log-cumulative hazards (Figure 16), Schoenfeld residual plot (Figure 17), and the quantile-quantile plot (Figure 18) suggest that the relative hazards are likely to vary of time, and as such it is concluded that the PH assumption does not hold. In Figure 16, the respective lines intersect, therefore the hypothesis that the PH assumption holds between BVd and KRd could be rejected. The residual plot in Figure 17 does not suggest a non-random pattern against time providing evidence that the PH assumption is violated; however, Figure 18 indicates that the quantiles lie in a straight line, suggesting that the constant AF assumption is not violated. Therefore, dependent models which assumed a proportional treatment effect may not be appropriate and hence independent models were selected for use in the base-case analyses.

Inspection of the hazard plot (Figure 19) show that the hazard rate for BVd and KRd are relatively constant for the bulk of the available data, with no clear turning point in the hazards, meaning that simpler models with a constant hazard (exponential) may be appropriate for modelling the hazard rates.

Figure 16: Cumulative log-log plot for OS

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KRd, carfilzomib in combination with lenalidomide, and dexamethasone; OS, overall survival.

Figure 17: Schoenfeld residuals plot for OS

Abbreviations: OS, overall survival.

Figure 18: Quantile-quantile plot for OS

Abbreviations: OS, overall survival.

Figure 19: Hazard rate plots for OS

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KRd, carfilzomib in combination with lenalidomide, and dexamethasone; OS, overall survival.

3.2.4.2. Independent survival curves

Six standard parametric independent models were fitted to the unweighted KRd and weighted BVd arms; exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised Gamma.

A summary of the goodness-of-fit statistics for the OS extrapolations is presented in Table 13. Table 14 outlines the landmark OS rates for unweighted KRd and weighted BVd.

Table 13: AIC and BIC statistical goodness-of-fit data for OS

Distribution	Weighted BVd		Unweighted KRd	
	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

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; BVd, belamaf in combination with bortezomib, and dexamethasone; KRd, carfilzomib in combination with lenalidomide, and dexamethasone; OS, overall survival

Table 14: Unweighted KRd and weighted BVd landmark survival rates (OS)

Distribution	Intervention	OS (%) at landmark timepoints					
		Years					
		1	2	5	10	15	20
Exponential	Weighted BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Unweighted KRd	84	70	41	17	7	3
Weibull	Weighted BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Unweighted KRd	87	73	40	13	4	1
Gompertz	Weighted BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Unweighted KRd	86	73	40	10	1	0
Log-logistic	Weighted BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Unweighted KRd	87	72	41	20	13	9
Log-normal	Weighted BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Unweighted KRd	84	69	42	24	16	11
Generalised Gamma	Weighted BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

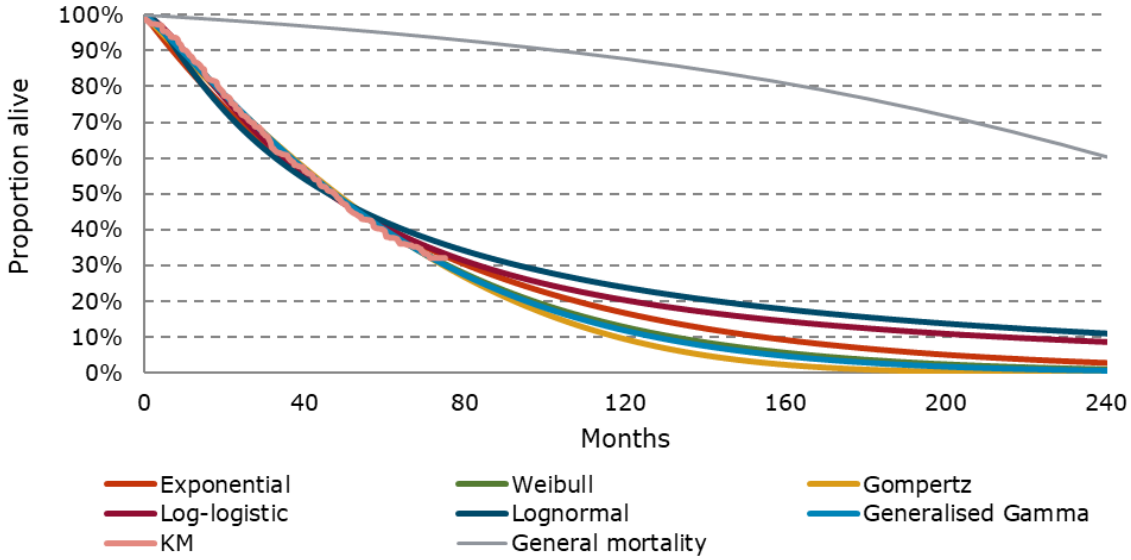
Distribution	Intervention	OS (%) at landmark timepoints					
		Years					
		1	2	5	10	15	20
	Unweighted KRd	87	73	40	12	3	1

Abbreviations: KM, Kaplan-Meier; OS, overall survival

Figure 20: OS independent curves for weighted BVd

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KM, Kaplan-Meier; OS, overall survival

Figure 21: OS independent curves for unweighted KRd



Abbreviations: KM, Kaplan-Meier; KRd, carfilzomib in combination with lenalidomide, and dexamethasone; OS, overall survival

3.2.4.3. Clinical validation (KRd)

The Company conducted five 1:1 interviews with UK clinical experts experienced in managing patients with RRMM. In each interview, clinicians were presented with landmark OS predictions for KRd from the ASPIRE trial at 5, 10, and 15 years [32]. Three out of five clinicians stated the more pessimistic KRd curves to be the most plausible (generalised gamma, Gompertz or Weibull). Two clinicians stated the exponential curve to be the most plausible; however, three out of five clinicians highlighted that for the exponential curve the 15-year tail of the curve (predicting 7% of patients alive) was considered clinically implausible.

3.2.4.4. Summary of base-case curve choice

In summary, the majority of the PH tests provided evidence to suggest the PH assumption was violated between KRd and weighted BVd OS. This would suggest that PH models (standard Weibull, exponential or Gompertz) would not be appropriate across both KRd and weighted BVd. These findings outline the key rationale for supporting independent modelling of the KRd and weighted BVd curves, given the previous hazard ratio approach submitted to NICE assumed proportional hazards.

Weighted BVd OS was similar to the unweighted data. Given advice from the committee and the EAG, more optimistic curves are likely to be implausible and so the exponential curve was chosen for the base-case. Weighted BVd OS outcomes are therefore well aligned to the 2L population for whom lenalidomide is unsuitable.

For KRd, AIC indicated the generalised gamma, Weibull or Gompertz to be the best statistical fit, while BIC indicates the Weibull, Gompertz or exponential to be the best fit. Given the implausibility of the exponential, Weibull or Gompertz distributions, due to likely PH violation, the generalised gamma was chosen for base-case given the strong alignment to the feedback elicited from the clinicians. Within the scenario analysis, the Weibull and exponential distributions were explored to test the impact on the results, given these are the second and third most suitable options chosen by clinicians.

3.2.2. BVd – Time to treatment discontinuation

The BVd TTD extrapolation is unchanged from the original submissions, aligned to the Weibull distribution. This was validated by both the EAG and the NICE committee as appropriate and is bound to the IPD belamaf dosing analysis which is also aligned to the committee and the EAG preferences.

3.2.3. KRd – Time to treatment discontinuation

Due to unavailability of publicised data to inform a MAIC for TTD, assumptions were made to fit plausible TTD estimations for KRd. As outlined in previous communications to NICE, using BVd as a baseline for TTD has a high likelihood of biasing the analysis by overestimating discontinuation for patients receiving KRd. In order to address this

issue, the following three approaches were therefore included to appropriately model TTD for KRd in the CEM and ensure consistency across the comparators evaluated previously:

Table 15: Methods of extrapolating TTD for KRd

Method	Description	Rationale
DVd HR (PFS and TTD) as a proxy	The first approach (applied as the base-case) uses the DREAMM-7 IA2 ITT data for DVd to estimate a hazard ratio between PFS and TTD. This was applied as a proxy to estimate the TTD for KRd.	While the most reasonable approach is to align assumptions used for other non-trial comparators (hKd and SVd), the MAIC was conducted to estimate treatment outcomes of KRd versus the BVd arm of DREAMM-7. DVd could therefore not be used directly to serve as a baseline. This approach replicates the method validated by the EAG as appropriate within the EAG report (using DVd as a baseline for TTD outcomes), by providing a consistent PFS-TTD profile between hKd, SVd and KRd. In addition, similar approaches were taken across recent appraisals TA897 (DVd 2L) and TA917 (DRd 1L) [33, 34].
ASPIRE median PFS to median treatment duration	A scenario analysis was conducted, using data from the ASPIRE trial (the source of efficacy included in the MAIC). Median PFS (26.1 months) and median treatment duration (85 weeks) was taken from the latest publication of the ASPIRE trial (Siegel et al. [35]). While the median duration for carfilzomib alone (KRd) was available, it was aligned to the stopping rule, and so cannot be used to inform the shape of the TTD curve). The median duration of lenalidomide alone was used as a proxy for all treatments within KRd. This was substantiated from the closeness of the separated TTD curves of lenalidomide and	While this approach was positively received in TA695, there is some uncertainty around the shape of the curve for carfilzomib discontinuation, given the shape of median duration is masked by the carfilzomib stopping rule. Comprehensive data informing the shape of TTD is unavailable from the ASPIRE ITT population, as TA695 only includes subgroup data. However, the available figures in TA695 indicate lenalidomide and carfilzomib are either closely aligned (Figure 10, clarification questions), or more patients discontinued lenalidomide than carfilzomib (Figure 23, TA695 [[36]]).

	carfilzomib, displayed in Figure 10 within the company response to clarification questions of TA695 ([36]). Replicating a similar method used in TA695; a hazard ratio was derived to adjust PFS of KRd to estimate TTD using a goalseek function to satisfy the following formula: $(median\ PFS\ in\ ASPIRE - median\ treatment\ duration\ in\ ASPIRE) = (median\ modelled\ PFS - median\ modelled\ TTD)$	Given the uncertainty in how these trends would carry over to the ITT analysis, this was deemed a conservative scenario analysis.
PFS=TTD	To address uncertainty in the TTD of KRd, an additional scenario analysis was included to set PFS to being equal to TTD.	This scenario aligns to the analysis requested by the EAG within TA695, as well as analyses included as part of the original company submission. However, this analysis was deemed as lacking clinical plausibility to be suitable as a base case, given a proportion of patients would discontinue treatment while remaining progression-free.

Abbreviations: DVd, Daratumumab in combination with bortezomib and dexamethasone; EAG, external assessment group; hKd, high-dose carfilzomib in combination with dexamethasone; SVd, Selinexor in combination with bortezomib and dexamethasone; KRd, Carfilzomib in combination with lenalidomide and dexamethasone; PFS, Progression-free survival; TTD, Time-to-treatment discontinuation; HR, Hazard ratio; IA2, Interim analysis 2; ITT, Intention-to-treat; DRd, Daratumumab in combination with lenalidomide and dexamethasone; MAIC, Matching-adjusted indirect comparison.

3.2.5. Summary of base case curve choices

The resulting base-case curves for the PFS weighted BVd and unweighted KRd are presented in Figure 22.

Figure 22: Base-case PFS extrapolated curves for weighted BVd and unweighted KRd (exponential)

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KM, Kaplan-Meier; KRd, carfilzomib in combination with lenalidomide; PFS, progression-free survival

The resulting base-case curves for the OS weighted BVd and unweighted KRd are presented in Figure 23.

Figure 23: Base-case OS extrapolated curves for weighted BVd (exponential) and unweighted KRd (generalised gamma)

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KM, Kaplan-Meier; KRd, carfilzomib in combination with lenalidomide, and dexamethasone; PFS, progression-free survival

Figure 24: Base-case TTD extrapolated curves for BVd (Weibull) and KRd (DVd HR as proxy)

3.2.6. Safety

The incidence of treatment-emergent AEs of Grade 3 or 4 occurring in ≥5% patients was considered for BVd and KRd in the economic analysis to derive disutilities and costs associated with AEs.

Safety data from the DREAMM-7 study was used to inform the AEs associated with BVd in the economic model (see Section B.2.10 of the CS). For KRd, the incidence of AEs were sourced from Siegel et al (2018) [35].

The AEs included in the base-case CEA for BVd and KRd are presented in Table 16.

Table 16. Incidence of Grade ≥3 adverse events reported in ≥5% of patients in the BVd arm from DREAMM-7 and the KRd arm from ASPIRE (31)

Adverse event	BVd	KRd
Neutropenia	[redacted]	0.31
Anaemia	[redacted]	0.19
Thrombocytopenia	[redacted]	0.17
Lymphopenia	[redacted]	0
Pneumonia	[redacted]	0.16
Peripheral neuropathy	[redacted]	0.03
Hypertension	[redacted]	0.06
Leukopenia	[redacted]	0
Nausea	[redacted]	0.01
Diarrhoea	[redacted]	0.05
Fatigue	[redacted]	0.08
Dyspnoea	[redacted]	0
Back pain	[redacted]	0.02
Hypokalaemia	[redacted]	0.11

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) [29]; Siegel et al. 2018 [35]

The sum product of these incidence rates and disutilities or costs associated with AEs, as described in section 3.4.4, was calculated to obtain the total AE disutility and total AE cost per treatment. Disutilities and unit costs associated with the AEs are assumed to be the same for BVd and KRd, therefore the difference in terms of total AE disutility and AE cost is driven by the AE incidence rates. The total AE disutility was attributed to the first four weeks of the model and AE cost applied as a one-off episode cost, under the assumption that AEs were likely to occur very soon after treatment and only require acute care. This approach to modelling a one-off AE cost is consistent with the approach used in NICE TA658 in MM [37].

In line with the preferences of the committee, additional AE disutilities for eye-related side effects were estimated based on data from the DREAMM-7 trial (median time to resolution of first event to baseline - Bilateral worsening of BCVA, 20/50 or worse) and

a proxy disutility from TA369 [dry eye] of -0.16. The overall impact of inclusion amounts to an insignificant QALY impact of -0.0087 to the BVd arm.

Given both clinical and patient experts stated that the EQ-5D-3L in the trial is likely to capture the impact of eye-related side effects [38], an additional scenario was ran to remove this disutility.

3.3. Measurement and valuation of health effects

In the base-case of the model, utility values for the progression-free (PFS) health states were derived from an analysis of EQ-5D-3L from DREAMM-7 that was presented in the CS. This approach was concluded as appropriate by the NICE committee and the EAG.

The Hatswell et al., 2019 [39] source was used to produce the decrement for the progressed disease (PD) state as a weighted average (rather than a simple average) across lines of subsequent treatment. This was based on information on rates of attrition across lines of treatment from Yong et al. and was concluded as the appropriate approach by the committee. This approach was therefore used for the base-case.

The rationale for diverging from the company BC (which assumed treatment-specific utility values for the PFS state) was due to the clinical implausibility of the PD utility being higher than PFS for comparators. The company has agreed that this lacks clinical plausibility, but it also should be noted that using the DREAMM-7 data without applying treatment specific values also rectifies this issue and allows for alignment between the utility and trial outcome data used to power the model results. A scenario was therefore run using DREAMM-7 data across PFS and PD, without accounting for treatment-specific effects.

The utility values used in the updated model are presented in Table 17.

Table 17. Progression-free and progressed disease treatment-specific health state utilities used in the model – Base-case

Treatment	Utility	Source
PFS (on-treatment/off-treatment)*		
BVd	[redacted]	DREAMM-7 [18]
KRd	[redacted]	DREAMM-7 [18]
PD		
All treatments	[redacted]	DREAMM-7 [18] and Hatswell et al. 2019 [41]

Note 1: *PFS off-treatment utility values are assumed to be the same as on-treatment.
Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DREAMM, DRiving Excellence in Approaches to Multiple Myeloma; DVd, daratumumab in combination with bortezomib, and dexamethasone; KRd, carfilzomib in combination with bortezomib and dexamethasone; PD, progressed disease; PFS, progression-free survival.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) [29]

3.4. Cost and healthcare resource use identification, measurement, and valuation

As described in the CS, the economic analysis was conducted from an NHS and personal social services (PSS) perspective and included treatments costs (including drug acquisition and administration) for both 2L and subsequent lines of treatment, disease management and monitoring costs, adverse event costs and terminal care costs.

Unit costs were obtained from routinely collected evidence sources, such as NHS reference costs 2021/22 [42], the British National Formulary (BNF) [45], and Personal Social Services Research Unit (PSSRU) 2023.

3.4.1. Drug acquisition and administration cost

3.4.1.1. Drug unit costs

Belamaf is available as 100mg and 70mg powder for concentration for solution for infusion at a list price of £16,848.00 and £11,784.00, respectively. For carfilzomib, the unit size, pack size and cost per pack are sourced from the BNF, while for bortezomib and lenalidomide they were sourced from eMIT in line with the EAG report.

Drug acquisition costs are applied in line with the treatment cycle length for each comparator as per the dosing schedule (section 3.4.1.2) until treatment discontinuation.

Unit costs applied for each drug are presented in Table 18.

Table 18. Drug acquisition costs (List)

Drug	Unit size (mg)	Pack size (number of units)	Cost per pack (£)	Unit cost (list price) (£)	Source
Belamaf (100mg vial)	100	1	16,848.00	16,848.00	DM+D [46]
Belamaf (70mg vial)	70	1	11,784.00	11,784.00	DM+D [47]
Bortezomib	3.5	1	66.29	66.29	eMIT*
Dexamethasone	20	10	20.00	2	BNF [43]
Carfilzomib	30	1	528.00	528.00	BNF [44]
Lenalidomide	25	21	28.27	1.35	eMIT**

Note: *The cost used in the model (i.e. £66.29 for Bortezomib 3.5mg powder for solution for injection vials / Packsize 1) is in line with the EAG report and was sourced from the eMIT version published on 5 April 2024.
**The cost used in the model (£28.27 per pack) is in line with the EAG critique, sourced from eMIT
Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; GSK, GlaxoSmithKline.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) [29]

3.4.1.2. Dosing

Belamaf dosing for BVd in the CEM base-case is based on IPD from the DREAMM-7 trial, an approach which was considered appropriated by both the EAG and NICE Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

committee [38]. For carfilzomib and lenalidomide in the case of the KRd comparator, the RDI was high (Table 20), closely aligning to the SmPC dosage. Therefore, dosing for KRd, is based on SmPC label, with RDI applied to account for dose reductions or delays. Again, this methodology aligns with committee and EAG advice on other comparators to BVd. The model also includes functionality to include or exclude wastage for BVd and KRd, defining the proportion of administrations with wastage. When wastage is assumed, method of moments (MoM) calculations derives the number of vials needed per cycle based on weight or body surface area (BSA).

For the base-case, the following settings are applied:

- Belamaf dosing using IPD as per the actual dose received.
- All other treatments within the combinations (BVd and KRd) use RDI
- Wastage calculations applied to 100% of administrations.

SmPC aligned dosing for each drug included in the drug acquisition costs are presented Table 19.

Table 19. Details of treatment administration of BVd and KRd, based on the Summary of product characteristics (SmPC)

Regimen	Drug	Treatment cycle	Dose
BVd	Belamaf	All treatment cycles (day 1 only)	2.5mg/kg
	Bortezomib	Treatment cycles 1-8 (days 1, 4, 8 and 11)	1.3mg/m^2
	Dexamethasone	Treatment cycles 1 - 8 (days 1, 2, 4, 5, 8, 9, 11 and 12)	20mg
KRd	Carfilzomib	Treatment cycle 1 (days 1 and 2)	20mg/m^2
		Treatment cycle 1 (days 8, 9, 15 and 16)	27mg/m^2
		Treatment cycle 2-12 (days 1, 2, 8, 9, 15 and 16)	27mg/m^2
		Treatment cycle 13-18 (days 1, 2, 15, and 16)	27mg/m^2
	Lenalidomide	All treatment cycles (days 1-21)	25mg/m^2
	Dexamethasone	All treatment cycles (1, 8, 15 and 22)	40mg/m^2

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone; m, metre; mg, milligram; SmPC, Summary of product characteristics
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) [29]

Dose delays and reductions are key modifications in clinical practice to manage toxicity and tolerability of active MM therapies. For KRd, a constant RDI was used to capture the impact of dose alterations in the model and align treatment costs to actual doses received by patients. The RDI for KRd was sourced from the ASPIRE trial [35]. For BVd, IPD was used to track the doses received by patients over time (see Section 3.4.1 and response to clarification question B13). The RDI values used in the model are presented in Table 20.

Table 20. Relative dose intensity

Drug	RDI	Source
Belamaf (100mg vial)	[redacted]	DREAMM-7 CSR [18]
Belamaf (70mg vial)	[redacted]	
Bortezomib	[redacted]	
Dexamethasone	[redacted]	
Carfilzomib	94%	TA695 [48], ASPIRE
Lenalidomide	80%	

Abbreviations: CSR, Clinical study report; mg, milligram; RDI, Relative dose intensity
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) [29]

3.4.1.2.1. Wastage

Wastage was incorporated using the same approach (MoM calculations) as described in section B.3.5.1.2.2 of the CS. For all interventions and comparators, the model includes functionality to include or exclude wastage, defining the proportion of administrations with wastage. When wastage is assumed, MoM calculations derive the number of vials needed per cycle based on weight or BSA. Wastage is included in the model base-case. In the base-case, wastage is applied to 100% of administrations. Given the potential for vial sharing within NHS practice to reduce wastage; a scenario analysis was also included which assumes no wastage occurs.

The acquisition costs, including wastage using the MoM calculations is described in section B.3.5.1.2.2 of the CS.

3.4.1.3. Drug administration costs

For oral treatments, no treatment administration costs are assumed. Unit costs of administration for drugs that are administered intravenously or subcutaneously were based on the NHS reference costs 2021/2022 [42], as described in section B.3.5.1.3 of the CS.

Administration schedules are sourced from the DREAMM-7 CSR for BVd and ASPIRE trial for KRd. The administration schedules for BVd and KRd are presented in Table 21.

In alignment with the EAG and committee preferred base-case, a stopping rule of 18 cycles has been implemented in the CEM base-case to reflect the stopping rule in the ASPIRE trial and in UK clinical practice (through the blueteq criteria), with administration of carfilzomib assumed to stop after treatment cycle 18.

According to the SmPC, treatment with KRd can continue beyond 18 cycles based on individual benefit/risk assessment, allowing patients to continue receiving KRd treatment until disease progression or until unacceptable toxicity occurs [49]. Recognising the possibility for future changes to blueteq criteria, the CEM includes a scenario to enable KRd patients to remain on carfilzomib treatment beyond cycle 18, following the same dosing schedule as in treatment cycles 13-18 (Table 19).

Table 21. Administration schedules

Regimen	Drug	Treatment cycle	Treatment cycle duration (days)	Dose	Administration method	Admins per treatment cycle
BVd	Belamaf	All treatment cycles (day 1 only)	21	2.5mg/kg	IV-simple	1
	Bortezomib	Treatment cycles 1-8 (days 1, 4, 8 and 11)	21	1.3mg/m^2	SC	4
	Dexamethasone	Treatment cycles 1 - 8 (days 1, 2, 4, 5, 8, 9, 11 and 12)	21	20mg	Oral	8
KRd	Carfilzomib	Treatment cycle 1 (days 1 and 2)	28	20mg/m^2	IV-simple	2
		Treatment cycle 1 (days 8, 9, 15 and 16)	28	27mg/m^2		4
		Treatment cycle 2-12 (days 1, 2, 8, 9, 15 and 16)	28	27mg/m^2		6
		Treatment cycle 13-18 (days 1, 2, 15, and 16)	28	27mg/m^2		4
	Lenalidomide	All treatment cycles (days 1-21)	28	25mg/m^2	Oral	21
	Dexamethasone	All treatment cycles (1, 8, 15 and 22)	28	40mg/m^2	Oral	4

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone; IV, Intravenous; kg, kilogram; m, meter; mg, milligram; SC, subcutaneous
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) [29]

3.4.1.4. Drug acquisition and administration summary

The acquisition and administration costs for BVd are based on the IPD dosing (based on MoM approach). Also, for cycles 2+, BVd acquisition and administration costs are dependent on dose delays and reductions in the IPD. Hence, acquisition and administration costs per cycle are not reported for BVd as they vary over time. A summary of the total acquisition and administration costs for KRd is included in Table 22.

Table 22. Summary of acquisition and administration costs

Intervention	Treatment cycle	Acquisition cost per cycle (£)	Administration cost per cycle (£)	Total cost per cycle (£)
KRd	1	[redacted]	[redacted]	[redacted]
	2-12	[redacted]	[redacted]	[redacted]
	13-18	[redacted]	[redacted]	[redacted]

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone.
Note: Additional scenarios have been included in the CEM to account for proportions of patients continuing carfilzomib treatment for cycles 19+ (see Appendix 4.3.8).
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) [29]

3.4.2. Subsequent treatments

Given that patients with MM receive multiple LoTs, and prior therapies received have an impact on the future treatment pathway, subsequent treatments are an important aspect to capture in cost-effectiveness assessments. This dependency creates a challenge, as given the global scope of the trial, subsequent treatments are based on differing MM treatment pathways.

For the base-case, the following settings are applied in line with the committee's preferences:

- Teclistamab included as a subsequent treatment option
- Expert 2 to inform subsequent treatment distribution, aligned to original submission
- Subsequent treatment costs applied upon progression
- Raab et al. 2019 to inform percentage of patients continuing to subsequent treatment lines

Cost of subsequent treatments were captured for up to two lines of subsequent treatment, as described in section B.3.5.2 of the CS.

3.4.2.1. First subsequent treatment

The distribution of first subsequent treatment across comparators was updated from the approach followed in the CS, to align with the EAG base-case [31]. In the EAG base-case, the distribution of subsequent treatments was assumed to be the same

with BVd for all comparators included in the model. The same distribution of first subsequent treatments was therefore used in the model for BVd and KRd, as outlined in Table 23 below.

In response to the committee's request, teclistamab monotherapy has been incorporated as a subsequent treatment option in the CEM base-case. To account for the line-of-treatment skipping occurring between 3L and 4L which was highlighted by clinicians, teclistamab has been included among the first subsequent treatment option. This has been implemented in the CEM as a toggle for its inclusion or exclusion as a treatment option. The company anticipates teclistamab to become the new standard of care in 3L, assuming a 40% market share and displacing all other subsequent treatment options, which are reweighted accordingly. The EAG has acknowledged that the market share of teclistamab is likely to have a minor impact on the estimates of cost-effectiveness. Additionally, a scenario is also explored where teclistamab monotherapy is excluded as an option for subsequent treatment, where isatuximab in combination with pomalidomide and dexamethasone (IPd) is assumed to be standard of care.

Table 23. Distribution of first subsequent treatments across treatment arms, as included in the base-case of the cost-effectiveness model

Subsequent treatment	Any treatment arm (BVd or KRd)
Dara	[redacted]
IxaRd	[redacted]
Pd	[redacted]
IPd	[redacted]
PanoVd	[redacted]
Palliative chemotherapy	[redacted]
Kd	[redacted]
Rd	[redacted]
Teclistamab monotherapy	[redacted]

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; Dara, daratumumab; IPd, isatuximab in combination with pomalidomide, and dexamethasone; IxaRd, ixazomib in combination with lenalidomide, and dexamethasone; Kd, carfilzomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone; PanoVd, panobinostat in combination with bortezomib and dexamethasone; Pd, pomalidomide and dexamethasone; Rd, lenalidomide and dexamethasone
Source: Porteous et al. (2023)

3.4.2.2. Second subsequent treatment

For the second line of subsequent treatment, experts' responses provided as part of the UK clinical validation interviews (see Appendix M of the CS) were averaged and normalised for BVd based on the first line of subsequent treatment received in the model. The same distribution of subsequent treatments was subsequently used for KRd in the CEM. The distribution of second subsequent treatments for both comparators are presented in Table 24.

Table 24. Distribution of second subsequent treatments across treatment arms, as included in the base-case of the cost-effectiveness model

Subsequent treatment	Any treatment arm (BVd or KRd)
Dara	[redacted]
IxaRd	[redacted]
Pd	[redacted]
IPd	[redacted]
PanoVd	[redacted]
Palliative chemotherapy	[redacted]
Kd	[redacted]
Rd	[redacted]

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; Dara, daratumumab; IPd, isatuximab in combination with pomalidomide, and dexamethasone; IxaRd, ixazomib in combination with lenalidomide, and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone; PanoVd, panobinostat in combination with bortezomib and dexamethasone; Pd, pomalidomide and dexamethasone; Rd, lenalidomide and dexamethasone
Source: Porteous et al. (2023)

For both BVd and KRd treatment arms, £[redacted] and £[redacted] are applied as the first and second subsequent treatment costs, respectively, in the model [29].

3.4.3. Disease management costs

Patients receiving RRMM treatments require symptom management and frequent monitoring, including outpatient visits, imaging procedures, and diagnostic procedures. For the DREAMM-7 clinical validation, the clinical experts stated that monitoring aligned to the treatment administration scheduling [51]. Treatment-specific symptom management and monitoring resource use for BVd is informed based on EE opinion for the frequency of follow-up care for progression-free patients (on and off treatment) and post-progression, as described in section B.3.5.3 of the CS. Given the similarities of treatment administration scheduling between KRd and hKd, it was assumed that disease management frequencies of hKd would be suitable for KRd in the model.

Table 25 below summarises the health-state-specific disease management costs per cycle applied in each model cycle for each treatment arm.

Table 25. Costs associated with routine monitoring and management of MM

Healthcare resource	Unit cost (£)	Health state	Resource use per model cycle		Unit cost Source
			BVd	KRd	
Haematologist visit	209.41	PFS (on-tx)	[redacted]	[redacted]	NHS code WF01A [42]
		PFS (off-tx)	[redacted]	[redacted]	
		PD	[redacted]	[redacted]	
Full blood count	2.96	PFS (on-tx)	[redacted]	[redacted]	
		PFS (off-tx)	[redacted]	[redacted]	

Healthcare resource	Unit cost (£)	Health state	Resource use per model cycle		Unit cost Source
			BVd	KRd	
		PD	[redacted]	[redacted]	NHS code DAPS05 [42]
Biochemistry	1.55	PFS (on-tx)	[redacted]	[redacted]	NHS code DAPS04 [42]
		PFS (off-tx)	[redacted]	[redacted]	
		PD	[redacted]	[redacted]	
Protein electrophoresis	1.55	PFS (on-tx)	[redacted]	[redacted]	NHS code DAPS04 [42]
		PFS (off-tx)	[redacted]	[redacted]	
		PD	[redacted]	[redacted]	
Immunoglobin	1.55	PFS (on-tx)	[redacted]	[redacted]	NHS code DAPS04 [42]
		PFS (off-tx)	[redacted]	[redacted]	
		PD	[redacted]	[redacted]	
Serum-free light chain	1.55	PFS (on-tx)	[redacted]	[redacted]	NHS code DAPS04 [42]
		PFS (off-tx)	[redacted]	[redacted]	
		PD	[redacted]	[redacted]	
Ophthalmologist	143.93	PFS (on-tx)	[redacted]	[redacted]	WF01A [42]
		PFS (off-tx)	[redacted]	[redacted]	
		PD	[redacted]	[redacted]	
Total health state cost per model cycle (£)		PFS (on-tx)	[redacted]	[redacted]	
		PFS (off-tx)	[redacted]	[redacted]	
		PD	[redacted]	[redacted]	

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab; hKd, high-dose carfilzomib and dexamethasone; MM, Multiple myeloma; NHS, National Health Services; PD, Progressed disease; PFS, Progression-free survival; SVd, Selinexor in combination with bortezomib, and dexamethasone; tx, treatment.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) [29]

3.4.4. Adverse events

The model considers how treatment-related AEs impact the costs and QoL of patients receiving all relevant comparators. In line with existing CEAs in MM (for example, NICE TA897, the CEM considered Grade ≥3 AEs only [52]. AE incidence data for BVd and KRd are sourced from DREAMM-7 [18] and ASPIRE [35], respectively. AE incidence data used in the CEM for BVd and KRd are presented in Table 16 Section 3.2.6.

As AEs have a minor impact on the cost-effectiveness results, a simple naive comparison of AEs was conducted. Treatment-related AEs (Grade≥3) are incorporated as one-off events and the impact is attributed to the first cycle of treatment for patients entering the model, under the assumption that AEs are likely to occur very soon after treatment initiation and only require acute care. The unit costs for Grade ≥3 AEs were sourced from the NHS reference costs 2021/2022 [42] and are presented in Table 26.

Table 26. Grade ≥3 AE unit costs

Adverse event	Unit cost (£)
Neutropenia	1,772.97
Anaemia	1,439.66
Thrombocytopenia	2,163.16
Lymphopenia	1,772.97
Pneumonia	2,505.31
Peripheral neuropathy	1,342.94
Hypertension	781.13
Leukopenia	1,772.97
Nausea	824.90
Diarrhoea	1,446.84
Fatigue	824.90
Dyspnoea	241.01
Back pain	1,118.92
Hypokalaemia	2,639.41

Abbreviations: AE, Adverse event.
Source: NHS reference costs [42]

Grade ≥3 eye-related side effects are also included; however, given the specificity of corneal events to belamaf, these AEs are applied only to the BVd arm as a one-off cost. The model applies the probability of experiencing an ocular event in the BVd arm only in the first cycle. The unit cost of blurred vision and dry eyes is assumed equal to a keratopathy AE. In line with the company's response to the EAG question B10 during the clarification stage, the unit cost of a keratopathy AE has been updated from the CS. As outlined in the company's response, the keratopathy costs were updated to reflect the overall resource use for ophthalmology visits and artificial tear eye drops. The frequency of use for both these resources was adapted based on the severity of the ocular AE (mild, moderate or severe), in line with the rationale presented in the appraisal for belamaf [ID2701] [53].

Based on this update, patients with mild or moderate keratopathy are assumed to visit an ophthalmologist (including an ophthalmic examination with a visual acuity and slit lamp examination) every 3 weeks during an event. In contrast, patients with more severe keratopathy are expected to visit an ophthalmologist every week until resolution of the event (assumed to take up to 5 weeks). In addition, mild and moderate keratopathy were assumed to need 1 pack of 10 ml eye drops whereas severe keratopathy was assumed to need 5 packs of 10 ml eye drops. Based on these, the company used the average cost of moderate and severe AEs to approximate Grade ≥3 AE unit costs (£505.87), closely aligning with the cost indicated in the EAG's clarification question (£397.18).

The resulting updated unit costs associated with Grade ≥3 AEs, and the total ocular-based AE cost applied as a one-off cost for Grade ≥3 AEs occurring for keratopathy, blurred vision and dry eyes are presented in Table 27 and Table 28, respectively.

Table 27. Eye-related side effects unit costs

Eye-related adverse event	Grade ≥3-unit cost (£)	Source
Keratopathy	505.87	NHS code WF01B [42]
Blurred vision	505.87	Assumed same as keratopathy
Dry eyes	505.87	Assumed same as keratopathy

Abbreviations: AE, adverse event; NHS, National Health Services

A summary of AE costs is presented in the Table 28 below.

Table 28. Summary of total AE costs

Total AE costs	BVd	KRd
AE (non-ocular) - One-off costs (£)	[redacted]	[redacted]
AE (ocular) one-off cost (£)	[redacted]	-

Abbreviations: AE, Adverse event; BVd, belamaf in combination with bortezomib, and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone

3.4.5. End-of life costs

In line with the approach followed in the CS, terminal care costs are applied as a one-off cost of £12,397.00 to all patients who transition to the death health state [54].

3.5. Summary of base-case analysis variables and assumptions

3.5.1. Summary of base-case analysis inputs

A summary of variables applied in the economic analysis is presented in Table 29.

Table 29. Summary of variables applied in the base-case economic analysis

Parameter	Mean Value	SE	Lower bound	Upper bound	PSA distribution
Model settings					
Cohort size	1	-	-	-	-
Time horizon (years)	37	-	-	-	-
Age (years)	[redacted]	-	-	-	-
Discount rate costs (%)	3.5	-	-	-	-
Discount rate outcomes (%)	3.5	-	-	-	-
Survival inputs					
BVd PFS (weighted through the MAIC analysis)	Exponential				
BVd OS (weighted through the MAIC analysis)	Exponential				
BVd TTD (unweighted)	Weibull				
KRd TTD (DVd PFS vs. TTD [DREAMM-7])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition costs					
BVd Bortezomib RDI (%)	[redacted]	[redacted]	[redacted]	[redacted]	BETA
BVd Dexamethasone RDI (%)	[redacted]	[redacted]	[redacted]	[redacted]	BETA
KRd cost per treatment cycle 1 (£)	[redacted]	-	-	-	-
KRd cost per treatment cycle 2-12 (£)	[redacted]	-	-	-	-
KRd cost per treatment cycle 13-18 (£)	[redacted]	-	-	-	-
KRd carfilzomib RDI	91%	-	-	-	-
KRd lenalidomide RDI	80%	-	-	-	-
KRd dexamethasone RDI	82%	-	-	-	-
Drug administration costs					
Administration cost per treatment cycle with BVd treatment cycle 1-8 (£)	[redacted]	[redacted]	[redacted]	[redacted]	GAMMA
Administration cost per treatment cycle with BVd treatment cycle 9+ (£)	[redacted]	[redacted]	[redacted]	[redacted]	GAMMA
Administration cost per treatment cycle with KRd treatment cycle 1 (£)	[redacted]	[redacted]	[redacted]	[redacted]	GAMMA
Administration cost per treatment cycle with KRd treatment cycle 2-12 (£)	[redacted]	[redacted]	[redacted]	[redacted]	GAMMA
Administration cost per treatment cycle with KRd treatment cycle 13-18 (£)	[redacted]	[redacted]	[redacted]	[redacted]	GAMMA
Subsequent treatments					
BVd one-off subsequent treatment cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	GAMMA
KRd one-off first subsequent treatment cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	GAMMA
BVd one-off second subsequent treatment cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	GAMMA
KRd one-off second subsequent treatment cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	GAMMA
BVd first subsequent treatment, % patients	81%	0.16	40%	100%	BETA
KRd first subsequent treatment, % patients	81%	0.16	40%	100%	BETA
Second subsequent treatment, % patients	34%	0.07	22%	48%	BETA
Disease management costs					
BVd PFS on tx disease management total cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	GAMMA
BVd PFS off tx disease management total cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	GAMMA
BVd PD disease management total cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	GAMMA

BVd PFS on tx disease management - ophthalmologist cost	[redacted]	[redacted]	[redacted]	[redacted]	GAMMA
KRd PFS on tx disease management total cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	GAMMA
KRd PFS off tx disease management total cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	GAMMA
KRd PD disease management total cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	GAMMA
End of life costs					
End of life cost (£)	12,397.00	2,479.40	8,022.68	17,707.92	GAMMA
Adverse event costs					
BVd adverse event total cost	[redacted]	[redacted]	[redacted]	[redacted]	GAMMA
KRd adverse event total cost	2,108.25	421.65	1,364.35	3,011.43	GAMMA
Quality of life					
Utility: PFS on-tx	[redacted]	[redacted]	[redacted]	[redacted]	BETA
Utility: PFS off tx	[redacted]	[redacted]	[redacted]	[redacted]	BETA
Utility: PD	[redacted]	[redacted]	[redacted]	[redacted]	BETA
BVd adverse event total disutility	0.28	0.06	0.18	0.39	BETA
KRd adverse event total disutility	0.22	0.04	0.14	0.32	BETA

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone; PD, progressed disease; PFS, progression-free survival; PSA, probability sensitivity analysis; RDI, relative dose reduction; OWSA, one-way sensitivity analysis; SE, standard error; tx, treatment

3.5.2. Assumptions

A summary of modelling assumptions is provided, divided by aspect of the cost-effectiveness model, in Table 30.

Table 30. List of assumptions for the base-case cost-effectiveness analysis

Category	Assumption	Justification
Population and comparators	The DREAMM-7 trial is representative of patients with RRMM in the 2L setting in the UK	The clinical trial population for DREAMM-7 assessed belamaf in patients with RRMM, with several clinical trials sites located in the UK.
Comparators	Making BVd available to the widest possible patient group in second line (2L)	KRd is the only clinically relevant comparator for BVd for 2L patients for whom lenalidomide is a suitable option. While Rd is available at 2L, it is not a relevant comparator given extremely low usage. This was substantiated by the clinical expert validation sessions in support of the CS (see also Appendix M of the CS), during which only one out of three clinical experts suggested Rd would have any usage at 2L, and only in 1% patients [6, 7] Additionally, the published Draft Guidance for ID6212 identified KRd as the most relevant comparator for the lenalidomide suitable population at 2L, based on the EAG's own clinical advice. [1]
Model structure and settings	The key costs and outcomes associated with RRMM are captured using a PSM model structure.	A PSM considers estimates for each clinical endpoint separately (i.e. PFS, OS and TTD are modelled independently) and, as such, maintains consistency between the endpoints used in the cost-effectiveness analysis and the published clinical data. Additionally, the use of a PSM structure is widely accepted in oncology by HTA bodies across the globe and the application is well understood by clinician experts and health economists alike [55].
	The key costs and outcomes associated with RRMM are captured by PF and PD and death health states.	The choice of modelling PF and PD health states is intended to capture important differences in costs and quality of life within RRMM in a similar fashion to other models in MM. PF captures the costs and consequences of active treatments, monitoring, and treatment-related AEs, whilst PD captures the costs and outcomes of subsequent treatment and monitoring, while death captures end-of-life care.
	The progression-free health state was divided into on- and off-treatment in order to differentiate costs based on treatment status. Drug acquisition and admin costs are only included in PF on-tx	The PF on- and off-treatment split was chosen based on the observation that in MM some patients withdraw from active treatment before disease progression, which was also aligned with previous NICE TAs [56], and this has an impact to treatment and monitoring costs.

Category	Assumption	Justification
	Lifetime horizon of 37 years	The mean age of the population is 63 years (based on the mean age of the weighted BVd arm in the MAIC base-case) therefore a 37-year time horizon was considered long enough to capture the clinical and economic impacts of RRMM in a 2L setting.
	Discount rate of 3.5%	This is in line with the NICE reference case.
	No half cycle correction applied	The one-week cycle length was assumed to be sufficiently short to capture model transitions.
	The model looks at the perspective of the NHS & PSS	This is in line with the NICE reference case [55].
	KRd TTD extrapolation uses DVd PFS vs. TTD from DREAMM-7	Aligned to the method agreed with by the EAG and committee for SVd and hKd.
Clinical effectiveness	Grade 3+ AE incidences occurring with <5% in either the BVd or KRd arms of DREAMM-7 and ASPIRE, respectively, are not included	Grade 3+ AEs occurring in small amounts of patients are not likely to impact cost-effectiveness since with <5% incidence in both arms, small incremental difference is seen between the BVd and KRd.
Cost and resource use inputs	Belamaf dosing is informed by the actual DREAMM-7 dose received.	Dose delays / interruptions were frequent, as a consequence of managing eye-related side effects. To model the relationship more accurately between time on treatment and dose intensity, an individual patient level analysis of dose intensity was conducted (embedded in the model). This methodology accurately depicts the dosing and management of eye-related side effects with BVd treatment that is expected to be reflective in clinical practice and aligns with advice from the EAG and NICE committee.
	RDI is assumed to be constant throughout treatment for KRd.	Dose delays and reductions for all other comparators to BVd in the model were limited (all treatments included in combinations with large cost impact were estimated to have >90% RDI). Paucity of IPD dosage data for the non-trial comparator KRd means constant RDI assumptions were necessary.
	Wastage is assumed on 100% of administrations. For IV and SC administrations, dosing is calculated using method of moments.	Although vial sharing is practiced, it is uncertain what is the proportion of administrations to which vial sharing is practiced. Hence, the analysis follows a conservative approach, assuming that wastage is applied to 100% of administrations. The impact of this assumption on the ICER is explored in scenario analysis where no wastage is applied.
	No administration costs for oral first-line or subsequent treatments.	Oral treatments can be taken at home without assistance from a health care professional.
	Disease management costs for KRd assumed same as hKd	For the DREAMM-7 clinical validation, the clinical experts stated that monitoring aligned to the treatment administration scheduling [51]. Given the similarities of treatment administration scheduling between KRd and hKd, it was assumed that disease management frequencies of hKd would be suitable for KRd in the model.

Category	Assumption	Justification
	TRAEs (Grade ≥3) are incorporated as one-off events and the impact is attributed to the first cycle of treatment for patients entering the model.	AEs are likely to occur very soon after treatment initiation and only require acute care.
	Unit costs associated with treatment of different types of eye-related side effects are assumed to be the same.	Non-admitted face to face outpatient service with a Consultant has been assumed for the treatment of eye-related AEs.
	The proportion of patients receiving subsequent treatment is informed by the literature.	DREAMM-7 was not considered an appropriate source to inform the proportion of patients who continued to subsequent treatment therapy due to immaturity of patients entering subsequent treatment. Hence, the proportion of patients who received a first and second line of subsequent treatment was informed by Raab (2019) [57] in the base-case, while a scenario was conducted using estimates from Yong (2016) .
	The distribution of patients in each subsequent treatment is informed by clinical expert opinion, and teclistamab was included; aligned with NICE committee preference.	Expert opinion was selected as the preferred approach to inform the number of patients who continued to subsequent treatment for the BVd arm. Given the three scenarios provided by clinicians, GSK have included the subsequent treatments estimations from EE2 in the cost-effectiveness model base case, as these values closely align with the NICE HTA guidance of centring the evidence on current clinical practice [30]. The same distribution of subsequent treatments with BVd has been assumed for KRd. In addition, teclistamab is assumed to be included for first-subsequent treatment, in line with preferences by the NICE committee.
	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 up to two 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 treatment, upon disease progression. The rationale for this assumption was based on the structural limitations of PSMs and the limitation in available evidence to map the timing of subsequent treatments across two subsequent treatment lines for all included comparators. Hence, a simplified approach was taken to assume that costs associated with second line of subsequent treatment incur at the same time as costs of first line of subsequent treatment.
	End-of-life care costs is applied as a one-off cost in the cycle in which patients die.	Patients will accrue end-of-life care costs before they die and therefore, they are applied within the cycle of death.

Category	Assumption	Justification
Health-related quality of life	EQ-5D utility scores from DREAMM-7, plus the Hatswell utility decrement, are sufficiently robust to inform HRQoL of patients with RRMM whether PF or with PD.	In line with the NICE and ICER reference cases by using data directly from the DREAMM-7 clinical trial. For progressed disease, a decrement calculated from Hatswell et al. was used, in line with preferences of the NICE committee.
	Eye-related side effects QALYs	A disutility associated with eye-related side effects was included, in line with preferences by the NICE committee.
	Age-related utility decrements are applied in every cycle.	Age-related utility decrements are applied in the model to incorporate the natural decline in HRQoL associated with increasing age and to ensure the utility of 2L MM patients does not exceed that of the general population.

Abbreviations: AE, Adverse event; BVd, belamaf in combination with bortezomib, and dexamethasone; HR, Hazard ratio; HRQoL, Health-Related Quality of Life; HTA, Health Technology Assessment; ICER, Incremental Cost-Effectiveness ratio; IV, Intravenous; KRd, carfilzomib in combination with lenalidomide and dexamethasone; MM, Multiple Myeloma; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PD, progressed disease; PF, Progression-free; QALY, Quality adjusted life year; RDI, relative dose intensity; SC, Subcutaneous; TDD, time to treatment discontinuation; TTRAE, Treatment-related adverse event; 2L, second line

3.6. Base case results

3.6.1. Base-case cost-effectiveness analysis results

Total costs, life years, QALYs, and incremental cost per QALY gained for BVd versus KRd are presented in

Table 31

Table 31. In the base-case analysis, BVd generates [redacted] incremental LYs, [redacted] incremental QALYs and £[redacted] incremental costs over a lifetime horizon compared with KRd, resulting in an ICER of £165 per QALY gained.

Table 31. Fully incremental analysis (PAS vs list, deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	INHB at £20,000	INHB at £30,000
KRd	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	165	3.94	3.11

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; ICER, incremental cost-effectiveness ratio; KRd, carfilzomib in combination with lenalidomide and dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years
Note: Incremental results are presented versus non-dominated options

3.7. Exploring uncertainty

3.7.1. Probabilistic sensitivity analysis

The PSA was ran for 1000 iterations in order to obtain an estimate of the variability of the results and the probability of cost-effectiveness. The results were closely aligned with the company base-case, indicating that the findings were robust when probabilistic distributions were applied to the model inputs. The results of the PSA (CEAC) indicate a 99.3% chance of cost-effectiveness of BVd against all comparators (list price) at a £30,000 QALY threshold.

Table 32. Probabilistic fully incremental analysis (PAS vs list)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	INHB at £20,000	INHB at £30,000
KRd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BVd	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; ICER, incremental cost-effectiveness ratio; KRd, carfilzomib in combination with lenalidomide and dexamethasone; LYG, life years gained; QALYs, quality-adjusted life years
Note: Incremental results are presented versus non-dominated options

Figure 25. Incremental cost-effectiveness plane

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone; PSA, probabilistic sensitivity analysis; WTP, willingness to pay

3.7.2. Deterministic sensitivity analysis

Figure 26. OWSA tornado diagram (BVd vs. KRd)

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; ICER, incremental cost effectiveness ratio; kg, kilogram; KRd, carfilzomib in combination with lenalidomide and dexamethasone; PD, progressed; PFS, progression free survival; OS, overall survival; tx, treatment; SVd, Selinexor in combination with bortezomib, and dexamethasone

Table 35. OWSA results of the top 10 most sensitive parameters only

Parameter	Lower bound (£)	Upper bound (£)	Difference (£)
B-Vd one-off subsequent treatment cost	[redacted]	[redacted]	[redacted]
Utility: PD	[redacted]	[redacted]	[redacted]
B-Vd first subsequent treatment, % patients	[redacted]	[redacted]	[redacted]
KRd one-off subsequent treatment cost	[redacted]	[redacted]	[redacted]
KRd first subsequent treatment, % patients	[redacted]	[redacted]	[redacted]
Administration cost per treatment cycle with KRd treatment cycle 2-12 (£)	[redacted]	[redacted]	[redacted]
B-Vd one-off second subsequent treatment cost	[redacted]	[redacted]	[redacted]
B-Vd PD disease management total cost	[redacted]	[redacted]	[redacted]

B-Vd PFS on tx disease management total cost	[redacted]	[redacted]	[redacted]
TTD HR - KRd TTD vs. KRd PFS	[redacted]	[redacted]	[redacted]

Abbreviations: PFS, progression-free survival; PD, progressed disease; BVd, belamaf in combination with bortezomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone

3.7.3. Scenario analysis

A number of scenario analyses was conducted to estimate the impact of structural and model input model assumptions on the cost-effectiveness of BVd. The list of scenarios explored in the model, and the corresponding rationale are presented in Table 33. The inputs used for each scenario are presented in Appendix 4.

Table 33. Scenario analyses explored in the model

Model setting	Base-case	Scenario analysis	Rationale
Age	DREAMM-7 weighted (through MAIC): 64	SACT data: 70	Using starting age from a different source to the MAIC could introduce bias into the analysis. To mitigate this, the weighted BVd mean age from the base case MAIC comparing BVd to KRd has been selected. A scenario analysis is conducted using the mean age of patients from the SACT dataset.
Time horizon	37 years	30 years	37 years represents lifetime horizon. Scenarios are explored to test the impact of shorter time horizons.
		20 years	
Discount rates for costs and outcomes	3.5%	0%	3.5% as per NICE reference case. Values of 0% and 6% are tested to explore the impact of discounting.
		6%	
Parametric survival modelling for OS and PFS	BVd PFS using direct extrapolation from parametric model. KRd PFS modelled by applying MAIC base-case HR to BVd PFS curve	BVd PFS using direct extrapolation from parametric model. KRd PFS modelled by applying MAIC sensitivity analyses HR to BVd PFS curve	In the base-case, PFS was modelled independently for the BVd arm. The KRd PFS curve was modelled by applying the MAIC base-case HR to BVd PFS curve. Four scenario analyses were conducted by applying the unweighted and sensitivity analyses HRs from the MAIC to the BVd PFS curve.
	OS curves using direct extrapolation from parametric model; BVd as baseline	OS extrapolated using PFS:OS surrogacy (BVd baseline curve)	In the base-case, OS was modelled using direct extrapolation in OS from DREAMM-7 trial. However, alternative approaches have been explored in scenario analysis. A scenario analysis was conducted in which OS was extrapolated assuming a surrogacy between PFS and OS outcomes (Appendix 4.2, [58]). In this scenarios HRs for KRd are applied to the baseline BVd PFS curve to estimate OS for each comparator.

Model setting	Base-case	Scenario analysis	Rationale
	PFS - BVd (weighted) - Exponential	PFS - BVd (weighted) - using the curve with best statistical fit, generalised Gamma	This scenario was included to test the impact of using alternative extrapolations based on statistical fit.
		PFS - BVd (weighted) - using the curve with 3rd best statistical fit, Gompertz	
	PFS - KRd (unweighted) Exponential	PFS - KRd (unweighted) - using the curve with best statistical fit, log-logistic	This scenario was included to test the impact of using alternative extrapolations based on statistical fit.
	OS - BVd (weighted) - Exponential	OS - BVd (weighted) - Weibull	This scenario was included as the next most plausible option for weighted BVd OS.
	OS - KRd (unweighted) – Generalised Gamma	OS - KRd (unweighted) - using curve with next best statistical fit, Weibull	The Weibull and exponential distributions were explored to test the impact on the results, given these are the second and third most suitable options chosen by clinicians.
		OS - KRd (unweighted), Exponential	
Modelling of TTD	DVd PFS-TTD HR	PFS = TTD	This scenario aligns to the analysis requested by the EAG within TA695.
		ASPIRE median PFS vs median duration of treatment	This was included as a conservative scenario analysis, utilizing the extent of treatment duration data available from publications.
Wastage	Wastage included	No wastage costs included	In the base-case, no vial sharing is assumed. However, as some treatments included in the model may allow for vial sharing to be implemented in practice, a scenario has been conducted to assess the impact of assuming no wastage on the results.

Model setting	Base-case	Scenario analysis	Rationale
Dosing	IPD off-label dosing: Per actual dose received in DREAMM-7	IPD off-label dosing: Per SmPC dose	In the base-case belamaf dosing in BVd is based on individual patient data (IPD) from the DREAMM-7 trial. The use of IPD-based dosing as per actual dose received in DREAMM-7 was implemented to reflect the time-variable trend identified for the RDI of belamaf, which is expected to be seen in clinical practice. A scenario analysis is conducted using the SmPC doses instead of the actual dose received in DREAMM-7, while still accounting for the time-variable trend in RDI observed in DREAMM-7. In this scenario, the belamaf acquisition cost for each dose is as per the closest labelled doses from the belamaf SmPC of 1.9 mg/kg and 2.5 mg/kg. Costing as per the SmPC assumes actual doses of 1.7-2.1 mg/kg and 2.2-2.7 mg/kg incur the acquisition cost of 1.9 mg/kg and 2.5 mg/kg doses, respectively.
Drug administration costs	KRd stopping rule is applied at cycle 18	KRd treatment is allowed to continue for a proportion of patients from cycle 19 onwards	Administration of carfilzomib in the model base-case is assumed to stop after treatment cycle 18, in line with the carfilzomib SmPC. Additional information from the carfilzomib SmPC indicates that dosing may be continued beyond treatment cycle 18 based on an individual risk/benefit assessment until disease progression or unacceptable toxicity occurs. A scenario has been included in the CEM to account for patients in the KRd arm continuing carfilzomib treatment for cycles 19+, following the same dosing schedule as in treatment cycles 13-18. (see Appendix 4.3.8).
Health care resource use	Clinical expert opinion	Sourced from TA897	Clinical expert opinion was used in the base-case to inform the frequency of use of various monitoring and disease management costs in different model health states for BVd and all other comparators included in the CS (including hKd). Considering the similar administration schedule for the shared carfilzomib and dexamethasone treatment components between KRd and hKd, healthcare resource use for KRd for treatment-specific symptom management and disease monitoring was assumed to be aligned to hKd. In a scenario analysis the impact of informing health care resource use based on TA897 [52] was explored. An assumption was made that frequency of use was equal among both treatment arms. Inputs for this scenario are presented in Appendix 4.3.1.
Subsequent treatment	Subsequent Tx distribution: clinical expert 2 (Current practice)	Subsequent Tx distribution: clinical expert 1 (MAIA pathway aligned)	Clinical expert opinion was used in the base-case analysis to inform the distribution of subsequent treatments for BVd (Appendix M of the CS). EE2 opinion was used in the base-case as their feedback was aligned with the NICE HTA guidance of centering the evidence on current clinical practice [30].
		Subsequent Tx distribution: clinical	

Model setting	Base-case	Scenario analysis	Rationale
		expert 3 (NICE treatment pathway aligned)	Three scenario analyses were conducted to explore the impact on the ICERs when using different sources to inform the distribution of subsequent treatment: - Scenario using EE1 opinion (aligned to the future pathway with DRd approval) - Scenario using EE 3 opinion (aligned to the exact NICE pathway) - Estimates were informed based on Porteous et al. 2023 using inputs from TA897 [52]. Inputs for these three scenarios can be found in Appendix 4.3.2, Appendix 4.3.3 and Appendix 4.3.4. In all these scenarios, the same distribution of subsequent treatments with BVd has been assumed for KRd.
		Subsequent Tx distribution: TA897	
	Subsequent Tx distribution: clinical expert 2 (Current practice) Health care resource use: Clinical expert opinion	Subsequent Tx distribution: TA897 Health care resource use: TA897	This scenario was conducted to reflect the joint impact of the assumptions described in the two scenarios above, when using inputs from TA897 [52] to inform the distribution of subsequent lines of treatment, and healthcare resource utilisation.
	Application of subsequent Tx costs: Upon progression	Application of subsequent Tx costs: First cycle	In the base-case it is assumed that the costs of subsequent treatment lines are applied as one-off costs upon disease progression. The percentage of patients who received subsequent treatment lines is sourced from Raab (2019) [57], which provides estimates of patients on the proportion of patients receiving active treatment, by line of treatment. There is some uncertainty as to what proportion of patients would go on to receive subsequent treatment at any given time point. Hence, a scenario analysis was conducted, simplifying this calculation and assuming that subsequent treatment costs are applied as a one-off cost in the first cycle of the model.
	Source for % of patients continuing to subsequent Tx Lines: Raab et al. 2019	Source for % of patients continuing to subsequent Tx Lines: Yong et al. 2016	In the base-case evidence, Raab (2019) [57] was used to inform the percentage of patients receiving subsequent lines of treatment. The proportion of patients who received a first and second line of subsequent treatment was assumed to be the same across all comparators in the model. To reflect the uncertainty in these model input parameters, a scenario analysis is conducted where the percentage of patients receiving subsequent lines of treatment is informed by Yong (2016) (see Appendix 4.3.5).
	Teclistamab included as a subsequent treatment option	Teclistamab not included	Teclistamab monotherapy was not included among the comparators identified during the scoping phase of this evaluation. In this scenario, teclistamab is not included as

Model setting	Base-case	Scenario analysis	Rationale
			a subsequent treatment option and IPd remains the standard of care in 3L, aligned with the original company submission.
Utilities	PD health state utility sourced from Hatswell et al. weighted (treatment non-specific)	PD health state utility sourced from DREAMM-7	A scenario is conducted using DREAMM-7 data across PFS and PD states, without applying treatment specific utilities, for alignment between utility and trial outcome data used in the model.
	AE disutilities included	AE disutilities not included	In the base-case, AE disutilities were informed by TA695 and TA897. However, considering that the impact of AE may be already captured by the DREAMM-7 EQ-5D-3L data, a scenario is conducted assuming no additional impact of AE on health state utilities.
	Source of AE disutilities: TA695 & TA897	Source of AE disutilities: TA695	In the base-case TA897 and TA695 were used to inform disutilities associated with AEs. To assess the impact of using AE inputs, a scenario was conducted where AE disutilities reported only TA695 was used (see Appendix 4.3.7).
	Eye-related disutilities included	Eye-related disutilities excluded	The impact of eye-related side effects is likely captured within the EQ-5D-3L, as highlighted by both patient groups and clinicians (see section 3.2.6). A scenario was therefore conducted without the inclusion of additional eye-related disutilities.

Abbreviations: AE, adverse event; BVd, belamaf in combination with bortezomib, and dexamethasone; DVd, daratumumab in combination with bortezomib, and dexamethasone; hKd, high-dose carfilzomib and dexamethasone; HR, hazard ratio; HTA, Health Technology Assessment; IPD, individual patient data; OS, overall survival; PH, proportional hazards; PFS, progression-free survival; TA, technology appraisal; TTD, time to treatment discontinuation; Tx, treatment; SmPC, Summary of Product Characteristics; SVd, Selinexor in combination with bortezomib, and dexamethasone

3.7.3.1. Scenario results: BVd vs. KRd

The results of the scenario analyses with BVd discounted price for BVd vs. KRd are presented in Table 37.

Table 37. Scenario analyses: ICERs for BVd vs. KRd (BVd discounted price, deterministic analysis results)

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	Change relative to base-case ICER
Base-case	[redacted]	[redacted]	**165**	**-**
Age using SACT data source	[redacted]	[redacted]	**Dominating**	**-**
30 years	[redacted]	[redacted]	Dominating	-
20 years	[redacted]	[redacted]	Dominating	-
Discount (costs and benefits) 0%	[redacted]	[redacted]	5,144	+4,979
Discount (costs and benefits) 6%	[redacted]	[redacted]	Dominating	-
PFS - BVd (weighted) – generalised Gamma	[redacted]	[redacted]	4,347	+4,182
PFS - BVd (weighted) – Gompertz	[redacted]	[redacted]	4,425	+4,260
PFS - KRd (unweighted) – log-logistic	[redacted]	[redacted]	2,051	+1,886
OS - BVd (weighted) - Weibull	[redacted]	[redacted]	3,743	+3,578
OS - KRd (unweighted) - Weibull	[redacted]	[redacted]	Dominating	-
OS - KRd (unweighted) - Exponential	[redacted]	[redacted]	Dominating	-
TTD – KRd, PFS = TTD	[redacted]	[redacted]	Dominating	-
TTD – KRd, ASPIRE median PFS vs. median duration of treatment	[redacted]	[redacted]	Dominating	-
No wastage costs included	[redacted]	[redacted]	Dominating	-
IPD off-label dosing: Per SmPC dose	[redacted]	[redacted]	379	+214
Health care resource use sourced from TA897	[redacted]	[redacted]	Dominating	-

Subsequent Tx distribution: clinical expert 1 (Future treatment pathway)	[redacted]	[redacted]	Dominating	-
Subsequent Tx distribution: clinical expert 3 (NICE treatment pathway aligned)	[redacted]	[redacted]	Dominating	-
Subsequent Tx distribution: TA897	[redacted]	[redacted]	Dominating	-
Subsequent Tx distribution: TA897 Health care resource use: TA897	[redacted]	[redacted]	Dominating	-
Application of subsequent Tx costs: First cycle	[redacted]	[redacted]	Dominating	-
Source for % of patients continuing to subsequent Tx Lines: Yong et al. 2016	[redacted]	[redacted]	Dominating	-
PD health state utility sourced from DREAMM-7	[redacted]	[redacted]	164	-1
AE disutilities not included	[redacted]	[redacted]	165	0
Source of AE disutilities: TA695	[redacted]	[redacted]	165	0
Eye-related disutilities excluded	[redacted]	[redacted]	165	0

Abbreviations: AE, adverse event; BVd, belamaf in combination with bortezomib, and dexamethasone; HR, hazard ratio; ICER, Incremental Cost-Effectiveness Ratio; IPD, individual patient data; KRd, carfilzomib in combination with lenalidomide and dexamethasone; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TA, technology appraisal; TTD, time to treatment discontinuation; Tx, treatment; SmPC, Summary of Product Characteristics

3.8. Benefits not captured in the QALY calculation

3.9. Validation

3.9.1. Model technical quality control

An internal validity check was performed by the model developers using a quality control process. This involved testing the selection and results of different modelling options, calculation spot checks, validation against source data and extreme value testing to assess whether the model responded logically to the tests.

The quality check explored the following general aspects of the model:

- Top-down tests, involving systematic variation of the model input parameters to establish whether changes in inputs results in expected changes in the model outputs.
- Model internal functionality involving testing all key model parameters, and extreme value testing in key sections of the model.
- Accuracy of input data involving a cross-checking of the model inputs in Excel against the corresponding data sources.

Overall, the validation identified no issues with the computational accuracy of the model.

3.10. Interpretation and conclusions of economic evidence

The analysis provided supports a strong case for reimbursement for all patients at 2L, irrespective of prior lenalidomide exposure. These results were robust against key sensitivity analyses and scenario analyses. In addition, there is a clear benefit to cost-effectiveness from appropriately modelling the extrapolation of both KRd and weighted BVd and undertaking a more comprehensive analysis of KRd TTD.

The key conclusions of the analysis are the following:

- The results of the model demonstrate a large benefit to patient outcomes from treating with BVd compared to KRd for patients suitable for treatment with lenalidomide in 2L therapy ([redacted] LYG, and [redacted] QALY gain).
- The cost-effectiveness analyses in this report has been strengthened following the previous analyses submitted to NICE post ACM1 regarding 2L patients who are suitable for lenalidomide treatment. The previous analyses submitted post ACM1 overestimated KRd discontinuation and underestimated the predicted incremental health benefits of treating with BVd. Rectifying both issues strengthens the cost-effectiveness outcomes of BVd versus KRd and reduces the uncertainty within the analysis.

Overall, the analysis incorporates a carefully considered approach designed to utilise the best available evidence to power cost-effectiveness analysis of BVd versus KRd. In doing so, the results demonstrate that broadening access to all 2L patients is an efficient use of NHS resources.

Recommending BVd for all 2L patients would ensure equitable access for the small and transient population of individuals who are lenalidomide naïve at first relapse. The expansion of the 2L population has already received public support from Myeloma UK and the clinical community.[3]

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Appendix 1 Additional supportive evidence for the MAIC

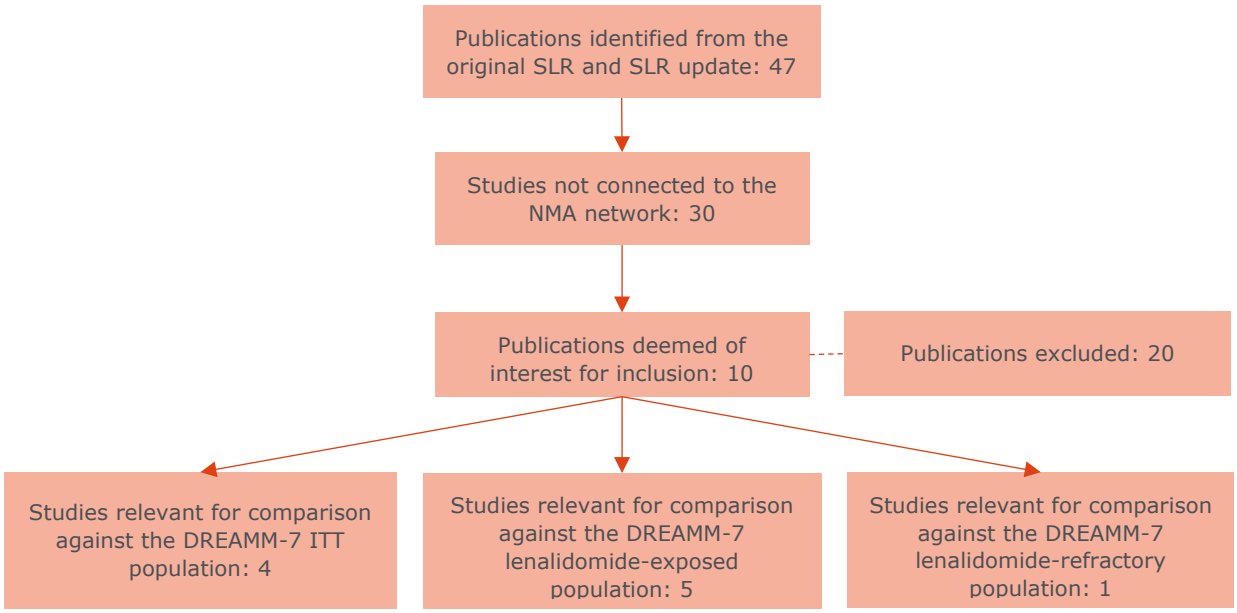
Appendix 1.1 MAIC feasibility assessment for the comparison of BVd against KRd

Underlying all indirect comparisons are two main assumptions:

- Transitivity: Trials of different treatment comparisons included in the evidence base have a sufficiently similar distribution of potential effect modifiers
- Consistency: The direct and indirect evidence are in agreement, allowing synthesis of both types of evidence in the same analytic framework

Of the 47 studies identified in the SLR, 30 studies did not form a connected network of evidence and, of these, ten comparator studies were considered relevant for a unanchored ITC (Figure 27).

Figure 27. Identification of relevant studies by the SLR considered in the feasibility assessment of an unanchored ITC



Abbreviations: ITT, intention-to-treat; NMA, network meta-analysis; SLR, systematic literature review
Source: GSK data on file [19]

Of the ten relevant comparator studies, four were relevant for comparison against the DREAMM-7 ITT population, five were relevant for comparison against the lenalidomide-exposed population, and one was relevant for comparison against the lenalidomide refractory population (Table 34).

Table 34. Intervention arms of studies considered relevant for inclusion in the MAIC

Study	Intervention	Comparator	Population
DREAMM-7 *[18]*	**BVd**	**DVd**	ITT*
APOLLO *[59]*	**DPd**	**Pd**	Lenalidomide-exposed
ASPIRE *[8, 9]*	**KRd**	**Rd**	ITT*
CARTITUDE-4 *[60]*	**Cilta-cel**	**SoC**, including: **DPd**: 87% **PVd**: 13%	Lenalidomide-refractory
ELOQUENT-2 *[61]*	**ERd**	**Rd**	ITT*
ELOQUENT-3 *[62]*	**EPd**	**Pd**	Lenalidomide-exposed
ICARIA-MM *[63]*	**IsaPd**	**Pd**	Lenalidomide-exposed
KarMMa-3 *[64]*	**Ide-cel**	**SoC**	ITT*
NIMBUS *[65]*	**Pd**	**d**	Lenalidomide-exposed
POLLUX *[66]*	**DRd**	**Rd**	ITT*
TOURMALINE *[67]*	**IxaRd**	**Rd**	ITT*

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; Cilta-cel, ciltacabtagene autoleucel; d, dexamethasone; DPd, daratumumab in combination with pomalidomide, and dexamethasone; DRd, daratumumab in combination with lenalidomide, and dexamethasone; EPd, elotuzumab in combination with pomalidomide, and dexamethasone; ERd, elotuzumab in combination with lenalidomide, and dexamethasone; Ide-cel, idecabtagene vicleucel; IsaPd, isatuximab in combination with pomalidomide, and dexamethasone; ITC, indirect treatment comparison; ITT, intention-to-treat; IxaRd, ixazomib in combination with lenalidomide, and dexamethasone; KRd, carfilzomib in combination with lenalidomide, and dexamethasone; NMA, network meta-analysis; Pd, pomalidomide and dexamethasone; Rd, lenalidomide and dexamethasone; SoC, Standard of care.
Note: *The ITT population represents the ITT population of the DREAMM-7 trial
Source: GSK data on file [19]

As there is no common treatment arm between DREAMM-7 and ASPIRE an unanchored approach was required. For an unanchored population-adjusted ITC to be feasible, there must be adequate data and overlap of relevant prognostic factors and TEMs in both the intervention and comparator studies. A feasibility assessment was conducted to determine whether MAICs between DREAMM-7 and ASPIRE was feasible. The following study characteristics were assessed:

- **The quality and methods of the trials** (study phase, design, cross-over, blinding, inclusion/exclusion criteria).
- **Study treatment arm** (treatment exposure, dose, duration, timing).
- **Outcomes** (definitions of outcomes, availability of data).
- **PFs and TEMs** (see Appendix 1.2).

MAICs were deemed feasible between the DREAMM-7 BVd arm and the ASPIRE KRd arm for PFS and OS.

Appendix 1.2 Prognostic factors and treatment effect modifiers

TEMs and prognostic factors were sourced from the literature and validated by a clinical expert then ranked in order of importance for inclusion in the MAIC. A list of potential prognostic factors and TEMs are presented in presented in Table 35. These were identified based on those baseline characteristics presented during clinical validation, from known TEM and prognostic factors sourced from a targeted literature review of previous health technology appraisals in RRMM, from a previous NMA conducted by Dimopoulos et al. 2018 [68], and a systematic literature review conducted by Rose et al. 2022 [69].

Table 35. Baseline characteristics and covariates

Covariate	**Highlighted by the clinician as important to consider in the MAIC**	**Dimopoulos et al. (2018) *[68]***	**Rose et al. 2022 *[69]****	**Belamaf MAIC 5L+ TCR****	**TA695*****	**TA657**
Age (median)	✓			✓	✓	
Gender (% male)	✓					
Ethnicity (race)	✓					
ECOG PS (PS >=2 %)	✓				✓	✓
ISS stage (% stage I, II, III, unknown)	✓				✓	✓
R-ISS stage (% stage I, II, III, unknown)						
Cytogenetic risk profile	✓					
EMD (%)	✓			✓		
Prior lines of treatment (1, 2, 3, and ≥4)	✓	✓	✓	✓	✓	
Prior bortezomib exposure					✓	✓
Prior IMiD exposure			✓			
Prior lenalidomide exposure					✓	✓
Prior thalidomide exposure						

Prior daratumumab exposure						
Refractory status	✓		✓		✓	✓
LDH						
Prior SCT	✓					✓
Creatinine clearance (< 50, 50–80, ≥ 80mL/min)	✓					✓
Time from initial diagnosis	✓				✓	✓
β2-microglobulin (< 3.5 vs ≥ 3.5 mg/L)						✓

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; EMD, extramedullary disease; IMiD, Immunomodulatory imide drug; ISS, International Staging System; LDH, lactate dehydrogenase; MAIC, matching adjusted indirect comparison; mg/L, milligram per litre; mL/min, millilitre per minute; rISS, Revised International Staging System; SCT, stem cell transplant; TCR, triple class refractory.
Note 1: *Systematic review and meta-analysis of the evidence for effect modification of HRs for OS and PFS with respect to refractory status and number of treatment lines. No other modifiers were considered.
Note 2: **MAIC developed for NICE submission for belamaf in a later line of MM (5L+ TCR); publication expected 2023.
Note 3: ***Recommendation based on previous line of treatment including included bortezomib.
Note 4: IMiDs include lenalidomide, thalidomide and pomalidomide.

Clinical validation of the list of potential TEM and prognostic factors in Table 35 was carried out to establish which were important to include in the MAIC and in what order of priority. Given that an unanchored ITC was required the TEM and prognostic factors were assessed in the intervention arm only. Of those that were highlighted during the clinical validation, gender and ethnicity were not included in the final list of covariates of prognostic factors and TEM as the clinician deemed them of lower importance to those factors ranked in the list below. Prior SCT was also not included in the final list of prognostic factors and TEMs as DREAMM-7 excluded patients with prior allogeneic SCT, but the clinician did not specify prior autologous SCT as a prognostic factor or TEM. The final list of prognostic factors and TEMs to include, in order of priority is reported below:

1. Prior lines of treatment (1 prior line, 2 prior lines, 3 prior lines, and ≥4 prior lines)
2. Refractory status to the specific agent(s) being used in the trial
3. ISS stage (% stage I, II, III, unknown)
4. Cytogenetic risk profile
5. Extramedullary disease (EMD)
6. Creatinine clearance

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

7. Time from initial diagnosis
8. Age
9. ECOG PS

The top eight ranked prognostic factors and TEMs were considered and are assessed in Table 36. Gender, prior stem cell transplant and ethnicity were identified as possible prognostic factors and TEMs but were outside of this ranking.

Table 36. Consideration and assessment of the top eight ranked prognostic factors and TEMs

Order of priority	TEM	Comparison within the ITT population of ASPIRE and DREAMM-7
1	Prior lines of treatment (1 prior line, 2 prior lines, 3 prior lines, and ≥4 prior lines)	• Comparisons to ASPIRE required recoding of DREAMM-7 data as ASPIRE groups lines 2-3. This lost information on a key prognostic factor and is a potential limitation of a MAIC. • DREAMM-7 had 30 patients with ≥4 prior LoTs, whilst ASPIRE only had one. This resulted in a large reduction the ESS.
2	Refractory status to the specific agent(s) being used in the trial	• ASPIRE, which reported refractory status to both LoT and IMiDs, reported values that were sufficiently different to DREAMM-7 such that adjustment was required.
3	ISS/R-ISS stage (% stage I, II, III, unknown)	• Comparison with ASPIRE was feasible as R-ISS is reported to align with DREAMM-7. • R-ISS stages I, II and III in DREAMM-7 differed from the equivalent ISS stages in ASPIRE, such that adjustment was required. • Categories were recoded to I-II and III based on advice received by a clinician expert.
4	Cytogenetic risk profile (standard, high)	• There was a large proportion of missing data for cytogenetic risk in ASPIRE, which was a limitation of adjusting for this characteristic. • A sensitivity analysis was conducted excluding cytogenic risk from the matching exercise. This scenario did not yield a significantly higher ESS relative to the base-case.
5	Extramedullary disease (yes/no)	• Adjustment was infeasible as ASPIRE did not report EMD.
6	Creatinine clearance (eGFR)	• Both studies reported creatinine clearance, however, ASPIRE used an eGFR threshold of <50ml compared <60ml used in DREAMM-7. • DREAMM-7 was recategorised to align with ASPIRE, however, creatinine clearance levels were not comparable across the trials.
7	Age (median years)	• Age was similar across ASPIRE and DREAMM-7.
8	ECOG PS (0, 1, 2, >2)	• There was good overlap between ASPIRE and DREAMM-7, however, differences in reporting meant that categories were recoded for comparisons to ASPIRE.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; EMD, extramedullary disease; ESS, effective sample size; IMiD: immunomodulatory imide drug; ISS, International Staging System; LoT, line of treatment; MAIC, matching-adjusted indirect comparison; PS, performance status; R-ISS, revised International Staging System; TEM, treatment effect modifier.
Note 1: *Gender and ethnicity were not included as the clinician deemed them of lower importance to those factors ranked in the list below. Prior SCT was not included as DREAMM-7 excluded patients with prior allogeneic SCT and the clinician did not specify prior autologous SCT as a prognostic factor or TEM.
Note 2: IMiDs include lenalidomide, thalidomide and pomalidomide.
Source: GSK data on file [19]

Appendix 1.3 Statistical methods

Appendix 1.3.1 Background

In the absence of head-to-head trials, indirect comparison studies permit the comparison of two or more technologies. Various statistical frameworks for adjusted indirect comparisons are considered acceptable by HTA bodies for the elicitation of comparative evidence. MAIC is a non-parametric likelihood reweighting method proposed by NICE TSD 18 that compares treatment effects, while minimising bias arising from imbalanced prognostic or effect-modifying baseline characteristics across trial populations [20].

This section describes the statistical analysis plan for the MAIC that was developed to assess the comparative efficacy of BVd vs KRd for PFS and OS using the DREAMM-7 IA2 data cut. Based on the considerations outlined in section 2.1.2, an unanchored MAIC was deemed feasible between the DREAMM-7 BVd arm and the ASPIRE KRd arm for the endpoints of interest that would be used to inform the company's CEA, namely PFS and OS (see section 3).

Appendix 1.3.2 Details of analyses

A pairwise MAIC was conducted to estimate the comparative efficacy of BVd versus KRd in the ITT population. For further description of the methodology underpinning the MAIC, please refer to section 2.1.

Appendix 1.3.2.1 Base-case analysis: adjusting for all feasible PFs and TEMs except R-ISS

The analysis adjusting for all feasible PFs and TEMs except R-ISS was selected as the base-case analysis as it was the only analysis to produce plausible results. R-ISS was excluded from the base-case analysis as the difference in the distribution of data was noted as being likely to lead to unstable estimates since relatively few patients were R-ISS III in DREAMM-7 (3.7%) compared to the reweighted proportion for KRd (9.3%). For further details regarding the base-case analysis, please refer to section 2.1.

Appendix 1.3.2.2 Sensitivity analyses

The following sensitivity analyses were conducted to explore uncertainties caused by high variation in certain PFs and TEMs between DREAMM-7 and ASPIRE:

- Sensitivity analysis 1: Exclusion of cytogenetic risk profile in the matching process
- Sensitivity analysis 2: Adjusting for all feasible TEMs and PFs, including R-ISS

- Sensitivity analysis 3: Truncated population, excluding ≥4 prior LoT in the matching process

For further details of each sensitivity analysis, please refer to section 2.1.4 and Appendix 1.4.

Appendix 1.3.2.3 Statistical model

Statistical modelling was based on IPD from the ITT population of BVd patients in DREAMM-7 and aggregate data and digitised IPD of KRd from the ASPIRE study (3, 4). The analysis can be summarised in the following steps, as per NICE TSD 18 [20]:

- A logistic propensity score model was created (using IPD from DREAMM-7 BVd arm) which included the TEMs and PFs.
- Weights were estimated using the method of moments to set the weights so that that covariate distributions were balanced across the DREAMM-7 and ASPIRE trial populations.
    - Histograms of the generated weights were presented to assess the distribution of the weights and the presence of extremely high or variable weights.
- The propensity score model was used to weight the treated population from DREAMM-7 to match the baseline characteristics of treated patients in ASPIRE in order to predict outcomes for BVd in a population corresponding to those evaluated in ASPIRE.
- Indirect comparisons for BVd versus the KRd arm of ASPIRE were performed
    - PFS and OS were compared using the Cox regression model and SEs were calculated using a robust estimator.
- Two measures of treatment effect were considered:
        - HRs
        - KM plots

Appendix 1.3.2.4 Software

The MAIC analyses were conducted in the freely available software package R using code modified from the NICE TSD 18, which is based on the following R packages: dplyr, tidyr, wakefield, writexl, ggplot2, sandwich, survey, readxl, tidyverse, xlsx, survival, survminer, flextable, officer, devtools, MAIC, muhaz, vctrs, Hmisc, rms, felxsurv, plyr, dplyr, rstudioapi, naniar [20].

Appendix 1.4 Additional MAIC results

Appendix 1.4.1 Sensitivity analysis 1: Exclusion of cytogenetic risk profile in the matching process

Appendix 1.4.1.1 PFs and TEMs before and after weighting the BVd arm

The baseline characteristics for the DREAMM-7 BVd arm before and after weighting for the first sensitivity analysis (i.e. exclusion of cytogenetic risk profile in the matching process) are presented in Table 37. The TEMs and PFs of the DREAMM-7 BVd arm were closely aligned to the KRd arm from the ASPIRE trial after weighting.

Table 37. BVd baseline characteristics before and after weighting vs KRd – Sensitivity analysis 1

TEM or PF	DREAMM-7 BVd (%) at baseline		ASPIRE KRd (%) at baseline[2, 3]
	Before weighting	After weighting	
Mean age (years)	64.5	[redacted]	63.3
1 prior LoT	51%	[redacted]	46%
2-3 prior LoT	37%	[redacted]	53%
≥*4* prior LoT	12%	[redacted]	0.3%
Refractory to IMiD	39%	[redacted]	21%
Refractory to lenalidomide	33%	[redacted]	7%
R-ISS 1/2*	96%	[redacted]	86%
R-ISS 3*	4%	[redacted]	14%
Standard cytogenetic risk profile	72%	[redacted]	75%
High cytogenetic risk profile	28%	[redacted]	25%
ECOG PS 0/1	96%	[redacted]	90%
ECOG PS 2	4%	[redacted]	10%
Creatinine clear <50 mL/min	16%	[redacted]	6%

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance score; IMiD: Immunomodulatory imide drug; LoT, line of treatment; KRd, carfilzomib in combination with lenalidomide and dexamethasone; MAIC, matching-adjusted indirect comparison; min, minute; mL, millilitre; PF, prognostic factor; R-ISS, revised International Staging System; TEM, treatment effect modifier.
Note: IMiDs include lenalidomide, thalidomide and pomalidomide.
Source: GSK data on file [19]

Rescaled weights are presented in Figure 28 for BVd matched to KRd. All patients in the BVd arm were assigned weights below six, indicating relatively stable weightings and good overlap between the two trial populations. The rescaled weights indicate that approximately 20% of patients were assigned a weighting that was close to zero, indicating that they may have been excluded from the analysis. However, over a third

(approximately 33%) were assigned a weight close to one suggesting an overlap and similarities between the trial populations.

The analysis yielded an ESS of 126.44 (BVd arm ITT; N = 243), resulting in a reduction of 48% of the ITT arm sample size. However, the ESS is acceptable according to the pre-specified threshold of 60 (section 2.1.5.1 and Appendix 1.3). Therefore, the analysis was considered to be sufficiently robust to generate meaningful outcomes.

Figure 28. Rescaled weights for BVd in sensitivity analysis 1

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone.
Source: GSK data on file [19]

Appendix 1.4.1.2 PFS and OS results – sensitivity analysis 1

Figure 29 and Figure 30 present the weighted and unweighted KM curves for BVd versus the KRd curve for OS and PFS, respectively when cytogenetic risk was excluded from matching.

The weighted BVd OS KM curve is closely aligned to the unweighted BVd curve, with the unweighted curve falling below the weighted between 10 to 33 months (Figure 29). Importantly, both the weighted and unweighted BVd OS KM curves remained above the KRd KM curve after approximately 15 months, highlighting the improved OS outcomes associated with BVd compared to KRd. This aligns with the MAIC sensitivity analysis results yielding a statistically significant lower median HR for both the weighted and unweighted BVd arm versus KRd (Table 8).

Figure 29. OS KM curves, BVd (weighted and unweighted) vs KRd – sensitivity analysis 1

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KM, Kaplan-Meier; KRd, carfilzomib in combination with lenalidomide and dexamethasone; OS, overall survival.
Source: GSK data on file [19]

The KRd PFS KM curve, as well as the weighted and unweighted BVd PFS KM curves are shown in Figure 30. Both the weighted and unweighted BVd curves remained above the KRd curve after approximately eight months, further underscoring the superior PFS outcomes associated with BVd. This is aligned with the MAIC sensitivity analysis results yielding a statistically significant lower median HR for the weighted BVd (Table 8).

Figure 30. PFS KM curves, BVd (weighted and unweighted) vs KRd – sensitivity analysis 1

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KM, Kaplan-Meier; KRd, carfilzomib in combination with lenalidomide and dexamethasone; PFS, progression-free survival.
Source: GSK data on file [19]

The weighted PFS and OS BVd KM curves in Figure 31 demonstrate clinical plausibility as the OS curve remained above the PFS curve throughout the study period. Although there was a transient period at approximately two months where this was not the case, this resolved during the remainder of the study period.

Figure 31. Weighted OS and PFS KMs for BVd when matched to KRd – sensitivity analysis 1

Abbreviations: IRC: IRC: independent review committee; OS: overall survival; PFS, progression-free survival.
Source: GSK data on file [19]

Appendix 1.4.2 Sensitivity analysis 2: Adjusting for all feasible TEMs and PFs, including R-ISS

Appendix 1.4.2.1 PFs and TEMs before and after weighting the BVd arm

The baseline characteristics for the DREAMM-7 BVd arm before and after weighting for the second sensitivity analysis (i.e. adjusting for all feasible TEMs and PFs, including R-ISS) are presented in Table 38. The TEMs and PFs of the DREAMM-7 BVd arm were closely aligned to the KRd arm from the ASPIRE trial after weighting.

Table 38. BVd baseline characteristics before and after weighting vs KRd – Sensitivity analysis 2

TEM or PF	DREAMM-7 BVd (%) at baseline		ASPIRE KRd (%) at baseline[2, 3]
	Before weighting	After weighting	
Mean age (years)	64.5	[redacted]	63.3
1 prior LoT	51%	[redacted]	46%
2-3 prior LoT	37%	[redacted]	53%
≥4 prior LoT	12.30%	[redacted]	0.30%
Refractory to imide	39%	[redacted]	21%
Refractory to lenalidomide	33%	[redacted]	7%
R-ISS 1/2*	96%	[redacted]	86%

R-ISS 3*	4%	[redacted]	14%
Standard cytogenetic risk profile	72%	[redacted]	75%
High cytogenetic risk profile	28%	[redacted]	25%
ECOG PS 0/1	96%	[redacted]	90%
ECOG PS 2	4%	[redacted]	10%
Creatinine clear <50 mL/min	16%	[redacted]	6%

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance score; IMiD: Immunomodulatory imide drugs; LoT, line of treatment; KRd, carfilzomib in combination with lenalidomide and dexamethasone; MAIC, matching-adjusted indirect comparison; min, minute; mL, millilitre; PF, prognostic factor; R-ISS, revised International Staging System; TEM, treatment effect modifier.
Note: IMiDs include lenalidomide, thalidomide and pomalidomide.
Source: GSK data on file [19]

Rescaled weights are presented in Figure 32 for BVd matched to KRd. This analysis is unlikely to provide meaningful results as it was heavily influenced by two patients, who were assigned weights of approximately 9 and 20 accounting for approximately 12% of the reweighted sample.

Figure 32. Rescaled weights for BVd in sensitivity analysis 2

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone.
Source: GSK data on file [19]

Appendix 1.4.2.2 PFS and OS results – sensitivity analysis 2

Figure 33 demonstrates a lower OS for patients treated with BVd compared to KRd until approximately 20 months for the weighted comparison (approximately 14 months

in the unweighted analysis), after which BVd is associated with greater OS than KRd. The weighted analysis shows a sharp drop in OS at one month due to a highly weighted patient that died at this time point. The same drop is not observed in Figure 33 for PFS as the patient died and was censored prior to progression.

Figure 33 and The KRd PFS KM curve, as well as the weighted and unweighted BVd PFS KM curves are shown in Figure 34. Both the weighted and unweighted BVd curves were closely aligned to the PFS KRd until approximately ten months, after which BVd was associated with a higher PFS.

Figure 34 present the weighted and unweighted BVd KM curves versus the KRd curve, for OS and PFS, respectively, when all PFs and TEMs (including R-ISS) were adjusted for in the MAIC.

Figure 33 demonstrates a lower OS for patients treated with BVd compared to KRd until approximately 20 months for the weighted comparison (approximately 14 months in the unweighted analysis), after which BVd is associated with greater OS than KRd. The weighted analysis shows a sharp drop in OS at one month due to a highly weighted patient that died at this time point. The same drop is not observed in Figure 33 for PFS as the patient died and was censored prior to progression.

Figure 33. OS KM curves, BVd (weighted and unweighted) vs KRd – sensitivity analysis 2

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KM, Kaplan-Meier; KRd, carfilzomib in combination with lenalidomide and dexamethasone; PF: prognostic factor; PFS, progression-free survival; TEM: treatment effect modifier.
Source: GSK data on file [19]

The KRd PFS KM curve, as well as the weighted and unweighted BVd PFS KM curves are shown in Figure 34. Both the weighted and unweighted BVd curves were closely

aligned to the PFS KRd until approximately ten months, after which BVd was associated with a higher PFS.

Figure 34. PFS KM curves, BVd (weighted and unweighted) vs KRd – sensitivity analysis 2

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KM: Kaplan-meier; KRd, carfilzomib in combination with lenalidomide and dexamethasone; PFS, progression-free survival.
Source: GSK data on file [19]

The weighted PFS and OS BVd KM curves demonstrate that the results of the MAIC (adjusting for all PFs and TEMs) lacked face validity and were clinically implausible as the weighted OS curve fell below the PFS curve at approximately 1 to 10 months. (Figure 35). This highlights an issue with the matching exercise for this analysis due to the large differences in the PFs and TEMs in the DREAMM-7 BVd arm and ASPIRE KRd arm, which resulted in large unstable weights.

Figure 35. Weighted OS and PFS KMs, adjusted for all feasible TEMs and PFs, including R-ISS – BVd when vs KRd

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KM: Kaplan-meier; KRd, carfilzomib in combination with lenalidomide and dexamethasone; OS: overall survival; PF: prognostic factor; PFS, progression-free survival; TEM: treatment effect modifier.
Source: GSK data on file [19]

Appendix 1.4.3 Sensitivity analysis 3: Truncated population, excluding ≥4 prior LoT in the matching process

Appendix 1.4.3.1 PFs and TEMs before and after weighting the BVd arm

The baseline characteristics for the DREAMM-7 BVd arm before and after weighting for the third sensitivity analysis (i.e. truncated population excluding ≥4 prior LoT in the matching process) are presented in Table **39**. The TEMs and PFs of the DREAMM-7 BVd arm were closely aligned to the KRd arm from the ASPIRE trial after weighting.

Table 39. BVd baseline characteristics before and after weighting vs KRd – Sensitivity analysis 3

TEM or PF	DREAMM-7 BVd (%) at baseline		ASPIRE KRd (%) at baseline[2, 3]
	Before weighting	After weighting	
Mean age (years)	64.7	[redacted]	63.3
1 prior LoT	58%	[redacted]	46%
2-3 prior LoT	42%	[redacted]	53%
≥4 prior LoT	0.00%	[redacted]	0.30%
Refractory to imide	33%	[redacted]	21%

Refractory to lenalidomide	28%	[redacted]	7%
R-ISS 1/2*	98%	[redacted]	86%
R-ISS 3*	2%	[redacted]	14%
Standard cytogenetic risk profile	75%	[redacted]	75%
High cytogenetic risk profile	25%	[redacted]	25%
ECOG PS 0/1	96%	[redacted]	90%
ECOG PS 2	4%	[redacted]	10%
Creatinine clear <50 mL/min	15%	[redacted]	6%

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance score; IMiD: Immunomodulatory imide drug; LoT, line of treatment; KRd, carfilzomib in combination with lenalidomide and dexamethasone; MAIC, matching-adjusted indirect comparison; min, minute; mL, millilitre; PF, prognostic factor; R-ISS, revised International Staging System; TEM, treatment effect modifier.
Note: IMiDs include lenalidomide, thalidomide and pomalidomide.
Source: GSK data on file [19]

Rescaled weights are presented in Figure 36 for BVd matched to KRd. Although approximately 28% of patients were assigned a weighting that was close to zero, over a third (approximately 35%) were assigned a weight close to 1. This indicating similarities between the trial populations, in line with the base-case. No patients were assigned relatively large weights, with all weights being below 5 suggesting that the MAIC is stable and there is good overlap between the two trial populations.

Figure 36. Rescaled weights for BVd in sensitivity analysis 3

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone; LoT, line of treatment.
Source: GSK data on file (10)

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

Appendix 1.4.3.2 PFS and OS results – Sensitivity analysis 3

Figure 37 and Figure 38 present the weighted and unweighted OS and PFS KMs for BVd compared to KRd, respectively, when excluding ≥4 prior LoTs.

The weighted BVd OS KM curve is closely aligned to the unweighted BVd curve, with the unweighted curve falling below the weighted between approximately 8 and 23 months (Figure 37). Importantly, both the weighted OS KM curve remained above the KRd KM curve after approximately 12 months (14 months in the unweighted analysis), highlighting the improved OS outcomes associated with BVd compared to KRd. This aligns with the MAIC sensitivity analysis results yielding a statistically significant lower median HR for both the weighted and unweighted BVd arm versus KRd (Table 8).

Figure 37. OS KM curves, BVd (weighted and unweighted) vs KRd – sensitivity analysis 3

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KM, Kaplan-Meier; KRd, carfilzomib in combination with lenalidomide and dexamethasone; LoT, line of treatment; OS, overall survival.
Source: GSK data on file [19]

The KRd PFS KM curve, as well as the weighted and unweighted BVd PFS KM curves are shown in Figure 38. The weighted and unweighted BVd curves were closely aligned and remained above the KRd curve after approximately eight months, further underscoring the superior PFS outcomes associated with BVd. This aligns with the MAIC sensitivity analysis results yielding a statistically significant lower median HR for the weighted BVd (Table 8).

Figure 38. PFS KM curves, BVd (weighted and unweighted) vs KRd – sensitivity analysis 3

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KM: Kaplan-meier; KRd, carfilzomib in combination with lenalidomide and dexamethasone; LoT, line of treatment; PFS, progression-free survival.
Source: GSK data on file [19]

Figure 39 presents weighted PFS and OS BVd KM curves and demonstrates their clinically plausibility as OS remained larger than PFS throughout the study period. Of note, there was a transient period at ~two months where PFS and OS were approximately equal, however this was corrected during the remainder of the period.

Figure 39. Weighted OS and PFS KMs for BVd when matched to KRd – sensitivity analysis 3

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KM: Kaplan-meier; KRd, carfilzomib in combination with lenalidomide and dexamethasone; LoT, line of treatment; PFS, progression-free survival.
Source: GSK data on file [19]

Appendix 1.4.4 Sensitivity analysis 4: Inclusion serum β2-microglobulin profile in the matching process

Appendix 1.4.4.1 PFs and TEMs before and after weighting the BVd arm

The baseline characteristics for the DREAMM-7 BVd arm before and after weighting for the first sensitivity analysis (i.e. inclusion β2 microglobin in the matching process) are presented in Table 40. The TEMs and PFs of the DREAMM-7 BVd arm were closely aligned to the KRd arm from the ASPIRE trial after weighting.

Table 40. BVd baseline characteristics before and after weighting vs KRd – Sensitivity analysis 4

TEM or PF	DREAMM-7 BVd (%) at baseline		ASPIRE KRd (%) at baseline[2, 3]
	Before weighting	After weighting	
Mean age (years)	64.5	[redacted]	63.3
1 prior LoT	51%	[redacted]	46%
2-3 prior LoT	37%	[redacted]	53%
≥*4* prior LoT	12%	[redacted]	0.3%

Refractory to IMiD	39%	[redacted]	21%
Refractory to lenalidomide	33%	[redacted]	7%
R-ISS 1/2	96%	[redacted]	86%
R-ISS 3	4%	[redacted]	14%
Standard cytogenetic risk profile	72%	[redacted]	75%
High cytogenetic risk profile	28%	[redacted]	25%
ECOG PS 0/1	96%	[redacted]	90%
ECOG PS 2	4%	[redacted]	10%
Creatinine clear <50 mL/min	16%	[redacted]	6%

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance score; IMiD: Immunomodulatory imide drug; LoT, line of treatment; KRd, carfilzomib in combination with lenalidomide and dexamethasone; MAIC, matching-adjusted indirect comparison; min, minute; mL, millilitre; PF, prognostic factor; R-ISS, revised International Staging System; TEM, treatment effect modifier.
Note: IMiDs include lenalidomide, thalidomide and pomalidomide.
Source: GSK data on file [19]

Rescaled weights are presented in Figure 40 for BVd matched to KRd. All patients in the BVd arm were assigned weights below eight, indicating relatively stable weightings and good overlap between the two trial populations. The rescaled weights indicate that approximately 41% of patients were assigned a weighting that was close to zero, indicating that they may have been excluded from the analysis. However, over a third (approximately 36%) were assigned a weight close to one suggesting an overlap and similarities between the trial populations.

The analysis yielded an ESS of 109.73 (BVd arm ITT; N = 243), resulting in a reduction of 45% of the ITT arm sample size. However, the ESS is acceptable according to the pre-specified threshold of 60 (section 2.1.5.1 and Appendix 1.3). Therefore, the analysis was considered to be sufficiently robust to generate meaningful outcomes.

Figure 40. Rescaled weights for BVd in sensitivity analysis 4

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone.

Source: GSK data on file [19]

Appendix 1.4.1.3 PFS and OS results – sensitivity analysis 4

Figure 29 and Figure 30 present the weighted and unweighted KM curves for BVd versus the KRd curve for OS and PFS, respectively when the B2 microglobin profile was included in the matching process.

The weighted BVd OS KM curve is closely aligned to the unweighted BVd curve; both curves remained above the KRd KM curve after approximately 15 months, highlighting the improved OS outcomes associated with BVd compared to KRd. This aligns with the MAIC sensitivity analysis results yielding a statistically significant lower median HR for both the weighted and unweighted BVd arm versus KRd (Table 8).

Figure 41. OS KM curves, BVd (weighted and unweighted) vs KRd – sensitivity analysis 4

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KM, Kaplan-Meier; KRd, carfilzomib in combination with lenalidomide and dexamethasone; OS, overall survival.
Source: GSK data on file [19]

The KRd PFS KM curve, as well as the weighted and unweighted BVd PFS KM curves are shown in Figure 42. Both the weighted and unweighted BVd curves remained above the KRd curve after approximately eight months, further underscoring the superior PFS outcomes associated with BVd. This is aligned with the MAIC sensitivity analysis results yielding a statistically significant lower median HR for the weighted BVd (Table 8).

Figure 42. PFS KM curves, BVd (weighted and unweighted) vs KRd – sensitivity analysis 4

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KM, Kaplan-Meier; KRd, carfilzomib in combination with lenalidomide and dexamethasone; PFS, progression-free survival.
Source: GSK data on file [19]

The weighted PFS and OS BVd KM curves in Figure 43 demonstrate clinical plausibility as the OS curve remained above the PFS curve throughout the study period. Although there was a transient period at approximately two months where this was not the case, this resolved during the remainder of the study period.

Figure 43. Weighted OS and PFS KMs for BVd when matched to KRd – sensitivity analysis 4

Abbreviations: IRC: IRC: independent review committee; OS: overall survival; PFS, progression-free survival.
Source: GSK data on file [19]

Appendix 2 Clinical results and disaggregated results from the model

Appendix 2.1 Clinical outcomes from the model

Table 41 demonstrates the progression-free survival for the full intention to treat (ITT) population over the lifetime time horizon.

Table 41. Progression-free survival for ITT population over the lifetime time horizon

PFS		Mean	Median	Landmark year												
		(Months)	(Months)	0	1	2	3	4	5	10	15	20	25	30	35	40
BVd (weighted)	KM	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-	-	-
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KRd (unweighted)	KM	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ITT, intention-to-treat; PFS, progression-free survival; KM, Kaplan-Meier; BVd, belamaf in combination with bortezomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone

Table 42 demonstrates the overall survival for the ITT population over the lifetime time horizon.

Table 42. Overall survival for ITT population over the lifetime time horizon

OS		Mean	Median	Landmark year												
		(Months)	(Months)	0	1	2	3	4	5	10	15	20	25	30	35	40
BVd (weighted)	KM	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-	-	-
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KRd (unweighted)	KM	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ITT, intention-to-treat; OS, overall survival; KM, Kaplan-Meier; BVd, belamaf in combination with bortezomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone

Appendix 2.2 Disaggregated results of the base-case deterministic incremental cost-effectiveness analysis

A summary of quality-adjusted life years (QALYs) gained by health state is presented in Table 43 (overall) and Table 44 (disaggregated).

Table 43. QALYs per treatment per health state (overall)

Item	BVd	KRd
PFS on treatment	[redacted]	[redacted]
PFS off treatment	[redacted]	[redacted]
PD	[redacted]	[redacted]
Total	[redacted]	[redacted]

Abbreviations: PFS, progression-free survival; PD, progressed disease; QALY, quality-adjusted life year; BVd, belamaf in combination with bortezomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone

Table 44. QALYs per treatment per health state (disaggregated)

BVd vs. KRd					
Health state	QALY BVd	QALY KRd	Increment	Absolute increment	% absolute increment
PFS on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS off treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS, progression-free survival; PD, progressed disease; QALY, quality-adjusted life year; BVd, belamaf in combination with bortezomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone

A summary of life years (LYs) gained by health state is presented in Table 45.

Table 45. LYs per treatment per health state

BVd vs. KRd					
Health state	LY BVd	LY KRd	Increment	Absolute increment	% absolute increment
PFS on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS off treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS, progression-free survival; PD, progressed disease; LY, life year; BVd, belamaf in combination with bortezomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone

A summary of costs per treatment per cost category is presented in

Table 46 (overall) and Table 47 (disaggregated), with costs estimated based on a list price for all treatments and the confidential simple PAS price for belamaf.

Table 46. Costs per treatment per cost category (overall)

Item	BVd	KRd
Treatment cost (£)	[redacted]	[redacted]
Health state cost (£)	[redacted]	[redacted]
Subsequent treatment cost (£)	[redacted]	[redacted]
Adverse event cost (£)	[redacted]	[redacted]
Total cost (£)	[redacted]	[redacted]

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone

Table 47. Costs per treatment per cost category (disaggregated)

BVd vs. KRd					
Health state	**Cost BVd**	**Cost KRd**	**Increment**	**Absolute increment**	**% absolute increment**
Treatment cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state cost (£)					
Subsequent treatment cost (£)					
Adverse event cost (£)					
Total cost (£)					

Abbreviations: BVd, belamaf in combination with bortezomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone

A summary of costs by health state is presented in Table 48Table 48, with costs estimated based on a list price for all treatments and the confidential simple PAS price for belamaf.

Table 48. Costs per treatment per health state

BVd vs. KRd					
Health state	**Costs BVd**	**Costs KRd**	**Increment**	**Absolute increment**	**% absolute increment**
PFS on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS off treatment					
PD					
Total					

Abbreviations: PFS, progression-free survival; PD, progressed disease; BVd, belamaf in combination with bortezomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone

Appendix 3 Additional supportive evidence for cost-effectiveness assessment

Appendix 3.1 Scenario inputs for cost-effectiveness analysis

Appendix 4.3.1 Scenario inputs: Health care resource use sourced from TA897

The monitoring and management costs associated with multiple myeloma (MM) are assumed to be equivalent between the two comparators based on TA897 (Table 49).

Table 49. Costs associated with routine monitoring and management of MM

Healthcare resource	Unit cost (£)	Health state	Resource use per model cycle		Unit cost source
			BVd	KRd	
Haematologist visit	209.41	PFS (on-tx)	0.23	0.23	NHS code WF01A [70]
		PFS (off-tx)	0.23	0.23	
		PD	0.08	0.08	
Full blood count	2.96	PFS (on-tx)	0.21	0.21	NHS code DAPS05 [70]
		PFS (off-tx)	0.21	0.21	
		PD	0.39	0.39	
Biochemistry	1.55	PFS (on-tx)	0.19	0.19	NHS code DAPS04 [70]
		PFS (off-tx)	0.19	0.19	
		PD	0.33	0.33	
Protein electrophoresis	1.55	PFS (on-tx)	0.13	0.13	NHS code DAPS04 [70]
		PFS (off-tx)	0.13	0.13	
		PD	0.18	0.18	
Immunoglobin	1.55	PFS (on-tx)	0.12	0.12	NHS code DAPS04 [70]
		PFS (off-tx)	0.12	0.12	
		PD	0.19	0.19	
Serum-free light chain	1.55	PFS (on-tx)	0.05	0.05	NHS code DAPS04 [70]
		PFS (off-tx)	0.05	0.05	
		PD	0.09	0.09	
		PFS (off-tx)	0.00	0.00	
		PD	0.00	0.00	

Healthcare resource	Unit cost (£)	Health state	Resource use per model cycle		Unit cost source
			BVd	KRd	
Opthalmologist (Belamaf only - 4 Tx cycles)	143.93	PFS (on-tx)	0.33	0.00	WF01A [70]
Total health state cost per model cycle (£)		PFS (on-tx)	49.54	49.54	
		PFS (off-tx)	49.54	49.54	
		PD	19.13	19.13	

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone; MM, Multiple myeloma; NHS, National Health Services; PD, Progressed disease; PFS, Progression-free survival; tx, treatment
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) [29]

Appendix 4.3.2 Scenario inputs: Subsequent Tx distribution: clinical expert 1 (MAIA aligned)

The distribution of first and second subsequent treatments across various treatment arms according to clinical expert 1 is provided in Table 50 and Table 51, respectively. The costs associated with first and second subsequent treatments are presented in Table 52. Noting these values are reweighted to include teclistamab as subsequent treatment, aligned to the base-case.

Table 50. Distribution of first subsequent treatments across treatment arms

Subsequent treatment	Treatment arm	
	BVd	KRd
D	[redacted]	[redacted]
IxaRd	[redacted]	[redacted]
Pd	[redacted]	[redacted]
IPd	[redacted]	[redacted]
PanoVd	[redacted]	[redacted]
Palliative chemotherapy	[redacted]	[redacted]
Kd	[redacted]	[redacted]
Rd	[redacted]	[redacted]

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; D, Daratumumab; IPd, Isatuximab in combination with pomalidomide and dexamethasone; IxaRd, Ixazomab in combination with lenalidomide and dexamethasone; Kd, carfilzomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone; PanoVd, panobinostat in combination with bortezomib and dexamethasone; Pd, pomalidomide in combination with dexamethasone; Rd, lenalidomide in combination with dexamethasone
Source: Porteous et al. (2023)

Table 51. Distribution of second subsequent treatments across treatment arms

Subsequent treatment	Treatment arm	
	BVd	KRd
D	[redacted]	[redacted]
IxaRd	[redacted]	[redacted]
Pd	[redacted]	[redacted]
IPd	[redacted]	[redacted]
PanoVd	[redacted]	[redacted]
Palliative chemotherapy	[redacted]	[redacted]
Kd	[redacted]	[redacted]
Rd	[redacted]	[redacted]

Abbreviations BVd, belamaf in combination with bortezomib, and dexamethasone; D, Daratumumab; IPd, Isatuximab in combination with pomalidomide and dexamethasone; IxaRd, Ixazomab in combination with lenalidomide and dexamethasone; Kd, carfilzomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone; PanoVd, panobinostat in combination with bortezomib and dexamethasone; Pd, pomalidomide in combination with dexamethasone; Rd, lenalidomide in combination with dexamethasone
Source: Porteous et al. (2023)

Table 52. Summary of subsequent treatment costs

Treatment arm	First subsequent treatment cost (£)	Second subsequent treatment cost (£)
BVd	[redacted]	[redacted]
KRd	[redacted]	[redacted]

Abbreviations: BVd, Belamaf in combination with bortezomib and dexamethasone; dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone.

Appendix 4.3.3 Scenario inputs: Subsequent Tx distribution: clinical expert 3 (NICE treatment pathway aligned)

The distribution of first and second subsequent treatments across various treatment arms according to clinical expert 3 is provided in Table 53 and Table 54, respectively. The costs associated with first and second subsequent treatments are presented in Table 55.

Table 53: Distribution of first subsequent treatments across treatment arms

Subsequent treatment	Treatment arm	
	BVd	KRd
D	[redacted]	[redacted]
IxaRd	[redacted]	[redacted]
Pd	[redacted]	[redacted]
IPd	[redacted]	[redacted]
PanoVd	[redacted]	[redacted]
Palliative chemotherapy	[redacted]	[redacted]
Kd	[redacted]	[redacted]
Rd	[redacted]	[redacted]

Abbreviations BVd, belamaf in combination with bortezomib, and dexamethasone; D, Daratumumab; IPd, Isatuximab in combination with pomalidomide and dexamethasone; IxaRd, Ixazomab in combination with lenalidomide and dexamethasone; Kd, carfilzomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone; PanoVd, panobinostat in combination with bortezomib and dexamethasone; Pd, pomalidomide in combination with dexamethasone; Rd, lenalidomide in combination with dexamethasone

Table 54. Distribution of second subsequent treatments across treatment arms

Subsequent treatment	Treatment arm	
	BVd	KRd
D	[redacted]	[redacted]
IxaRd	[redacted]	[redacted]
Pd	[redacted]	[redacted]
IPd	[redacted]	[redacted]
PanoVd	[redacted]	[redacted]
Palliative chemotherapy	[redacted]	[redacted]
Kd	[redacted]	[redacted]
Rd	[redacted]	[redacted]

Abbreviations BVd, belamaf in combination with bortezomib, and dexamethasone; D, Daratumumab; IPd, Isatuximab in combination with pomalidomide and dexamethasone; IxaRd, Ixazomab in combination with lenalidomide and dexamethasone; Kd, carfilzomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and

dexamethasone; PanoVd, panobinostat in combination with bortezomib and dexamethasone; Pd, pomalidomide in combination with dexamethasone; Rd, lenalidomide in combination with dexamethasone

Table 55. Summary of subsequent treatment costs

Treatment arm	First subsequent treatment cost (£)	Second subsequent treatment cost (£)
BVd	[redacted]	[redacted]
KRd	[redacted]	[redacted]

Abbreviations: BVd, Belamaf in combination with bortezomib and dexamethasone; dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone.

Appendix 4.3.4 Scenario inputs: Subsequent Tx distribution: TA897

The distribution of first and second subsequent treatments across various treatment arms according to TA897 is provided in Table 56 and Table 57 respectively. The costs associated with first and second subsequent treatments are presented in Table 58.

Table 56. Distribution of first subsequent treatments across treatment arms

Subsequent treatment	Treatment arm	
	BVd	KRd
D	56%	56%
IxaRd	22%	22%
Pd	12%	12%
IPd	0%	0%
PanoVd	0%	0%
Palliative chemotherapy	0%	0%
Kd	0%	0%
Rd	10%	10%

Abbreviations D, Daratumumab; IPd, Isatuximab in combination with pomalidomide and dexamethasone; IxaRd, Ixazomab in combination with lenalidomide and dexamethasone; Kd, carfilzomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone; PanoVd, panobinostat in combination with bortezomib and dexamethasone; Pd, pomalidomide in combination with dexamethasone; Rd, lenalidomide in combination with dexamethasone
Source: Porteous et al. (2023)

Table 57. Distribution of second subsequent treatments across treatment arms

Subsequent treatment	Treatment arm	
	BVd	KRd
D	56%	56%
IxaRd	22%	22%
Pd	12%	12%
IPd	0%	0%
PanoVd	0%	0%
Palliative chemotherapy	0%	0%
Kd	0%	0%
Rd	10%	10%

Abbreviations BVd, belamaf in combination with bortezomib, and dexamethasone; D, Daratumumab; IPd, Isatuximab in combination with pomalidomide and dexamethasone; IxaRd, Ixazomab in combination with lenalidomide and dexamethasone; Kd, carfilzomib and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone; PanoVd, panobinostat in combination with bortezomib and dexamethasone; Pd, pomalidomide in combination with dexamethasone; Rd, lenalidomide in combination with dexamethasone
Source: Porteous et al. (2023)

Table 58. Summary of subsequent treatment costs

Treatment arm	First subsequent treatment cost (£)	Second subsequent treatment cost (£)
BVd	[redacted]	[redacted]
KRd	[redacted]	[redacted]

Abbreviations: BVd, Belamaf in combination with bortezomib and dexamethasone; dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone.

Appendix 4.3.5 Scenario inputs: Source for percentage of patients continuing to subsequent treatment lines: Yong et al. 2016

The percentage of patients requiring subsequent treatment(s) are presented in Table 59.

Table 59. Proportion of patients who require subsequent treatment

Treatment arm	Proportion of patients (first subsequent treatment)	Proportion of patients (second subsequent treatment)
BVd	62%	25%
KRd	62%	

Abbreviations: BVd, Belamaf in combination with bortezomib and dexamethasone; dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone.
Source: Yong (2016)

Appendix 4.3.6 Scenario inputs: Health state utility sourced from DREAMM-7

The utility values used in the model are presented in Table 60.

Table 60. Model health state utility values

Source	Utility		
Data Source	**DREAMM-7**	**TA897**	**TA695**
PFS, on treatment	[redacted]	0.74	0.75
PFS, off treatment	[redacted]	0.74	0.75
PD	[redacted]	0.67	0.70
Death	[redacted]	0.00	0.00

Abbreviations: AE, adverse event; DVd, daratumumab in combination with bortezomib, and dexamethasone; EAG, external assessment group; PD, progressed disease; PFS, progression-free survival.

Appendix 4.3.7 Scenario inputs: Source of adverse event disutilities: TA695

The disutilities associated with the adverse events used in the model are presented in Table 61.

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

Table 61. Adverse events disutilities

Adverse event	Disutility	Source
Neutropenia	0.15	TA695 [36]
Anaemia	0.31	TA695 [36]
Thrombocytopenia	0.31	TA695 [36]
Lymphopenia	0.00	TA695 [36]
Pneumonia	0.19	TA695 [36]
Peripheral neuropathy	0.00	TA695 [36]
Hypertension	0.00	TA695 [36]
Leukopenia	0.00	Unavailable
Nausea	0.00	Unavailable
Diarrhoea	0.00	Unavailable
Fatigue	0.12	TA695 [36]
Dyspnoea	0.00	Unavailable
Back pain	0.00	Unavailable
Hypokalaemia	0.20	TA695 [36]

Abbreviations: TA, Technology appraisal

Appendix 4.3.8 Scenario inputs: Continuation of carfilzomib treatment after cycle 18

The base case of the model assumed a stopping rule for carfilzomib at the end of cycle 18. A scenario was explored, allowing treatment to continue beyond cycle 18. The inputs for administration schedules and summary of administration and acquisition costs for the scenario considering continuation of carfilzomib treatment during cycle 19+ are presented in Table 62 and Table 63 respectively. Additionally, the model implements a toggle feature to allow for the inclusion or exclusion of the carfilzomib stopping rule, given the potential for patients to remain on treatment after cycle 18.

Table 62. Administration schedules

Regimen	Drug	Treatment cycle	Treatment cycle duration (days)	Dose	Administration method	Admins per treatment cycle
KRd	Carfilzomib	Treatment cycle 1 (days 1 and 2)	28	20mg/m^2	IV-simple	2
		Treatment cycle 1 (days 8, 9, 15 and 16)	28	27mg/m^2		4
		Treatment cycle 2-12 (days 1, 2, 8, 9, 15 and 16)	28	27mg/m^2		6
		Treatment cycle 13-18 (days 1, 2, 15, and 16)	28	27mg/m^2		4
		Treatment cycle 19+ (days 1, 2, 15, and 16)	28	27mg/m^2		4
	Lenalidomide	All treatment cycles (days 1-21)	28	25mg/m^2	Oral	21
	Dexamethasone	All treatment cycles (1, 8, 15 and 22)	28	40mg/m^2	Oral	4

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone; IV, Intravenous; kg, kilogram; m, meter; mg, milligram; SC, subcutaneous
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) [29]

Table 63. Summary of acquisition and administration costs

Intervention	Treatment cycle	Acquisition cost per cycle (£)	Administration cost per cycle (£)	Total cost per cycle (£)
KRd	1	[redacted]	[redacted]	[redacted]
	2-12	[redacted]	[redacted]	[redacted]
	13-18	[redacted]	[redacted]	[redacted]
	19+	[redacted]	[redacted]	[redacted]

Abbreviations: BVd, belamaf in combination with bortezomib, and dexamethasone; KRd, carfilzomib in combination with lenalidomide and dexamethasone.
Source: Cost-effectiveness model for BVd in a population of 2L+ multiple myeloma (DREAMM-7) [29]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Myeloma UK

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Disclosure
Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.]
Please state:

- the name of the company
- the amount
- the purpose of funding including whether it related to a product mentioned in the stakeholder list
- whether it is ongoing or has ceased.

The table below shows the 2024 income from the relevant manufacturers. Funding is received for a range of purposes and activities namely core grants, project specific work, honoraria, or sponsorship events.

	Core grant	Research / Project	Consultancy/ Honoraria	Events	Total
Akt Health Communications Ltd			240		240
Alexion Pharma UK Ltd		10000			10000
The Binding Site Ltd	25000				25000
Bristol-Myers Squibb Pharmaceuticals Ltd	10000				10,000
Gilead Sciences		19000			19,000
GlaxoSmithKline UK Limited			700		700
ITECHO Health Ltd		1500			6600
Johnson & Johnson / Janssen-Cilag Ltd	19400		200	13990	33590
Kyowa Kirin Ltd		5000			5000
Menarini Stemline UK Limited			1844	3423	5267
Merck Sharp and Dohme		15000			15000
Pfizer Limited		9391			9391
Oxford Biomedica UK Limited	5000				5000
Sebia				11192	11,192
Sanofi			720	33,990	34710
Takeda	20000		880	15389	36269
Totals	79400	59891	4584	77984	221,859

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None

Name of commentator person completing form:

[redacted]

Comment number	Comments
	Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**We are disappointed that the guidance restricts this treatment to patients whose condition is refractory to lenalidomide or cannot tolerate lenalidomide. This means patients at 2nd line who have not had lenalidomide are missing out on this effective treatment.** The guidance excludes people at second line for whom the treatment would be beneficial but who have not had lenalidomide at first line. The treatment is clinically effective, demonstrating statistically significant improvement in overall survival and progression free survival in patients who have not received lenalidomide (as demonstrated in the DREAMM-7 evidence submission). We recommend that the guidance includes this sub population of patients who are lenalidomide naïve. ***Whilst treatment with Belantamab has caused me some problems, I'm acutely aware that without access to this novel drug, I simply wouldn't be here! Despite my difficulties, I remain very active and walk 4 miles a day, 5 days a week. I'm doing everything I can, to stay alive and in good shape. There are no guarantees in life, but I hope to continue beating the odds and living the fullest life that I can, for as long as possible.*** *– myeloma patient who received belantamab mafadotin at 4th line on a clinical trial.* ***I started taking Belantamab in mid-August 2021 and so far it has been totally effective in controlling my myeloma. I'm in remission thanks to this treatment. It's a huge relief to see that it is working and it has given me a new lease of life. I was on my way to a hospice before belantamab.*** *– myeloma patient who received belantamab mafadotin at 5th line on a clinical trial.* Our patient community very much welcomed NICE's positive recommendation for BVd, via the draft guidance announcement. However, we received many contacts from patients expressing their frustration that that the draft guidance restricts treatment to those that are refractory or intolerant to lenalidomide. The myeloma treatment pathway is rapidly evolving, at pace, and the consequence is that there are populations of people who have not had a sequential treatment experience in line with the NICE myeloma pathway. These patients, who have not had a previous treatment with lenalidomide are facing an inequality of treatment choices at second line. We know through our interviews and focus groups, conducted with patients and clinicians, that access to treatments with proven safety and efficacy data is of the upmost importance in the clinical management of a heterogenous patient population. The consequence of the lenalidomide recommendation, in combination with the restriction of the recommendation to 2nd line only further exacerbates the lack of belantamab treatment options for those who have not received lenalidomide. If patients who are lenalidomide naïve at first line, receive it at second line, there is no option to receive belantamab at 3rd line.

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2	**We are concerned that patients who have not received lenalidomide at 1st line because it was not available, are now missing out a second time on a clinically effective treatment.** Our patient community experience of treatment includes one of disadvantage dependant on their diagnosis date. At the time of diagnosis, clinicians and patients are restricted to options available at that timepoint. We are concerned that patients, who were successfully treated with regimens that did not contain lenalidomide, for example, did not have the option of lenalidomide maintenance, are now being doubly disadvantaged by not having belantamab mafadotin with bortezomib and dexamethasone as a treatment option at 2nd line. A further inequality arises, in context of transplant eligible and ineligible patients. Those who are ineligible, are typically older and may not have been treated with lenalidomide regimens or lenalidomide maintenance at diagnosis. We ask that the committee consider the negative impact on patients who will be denied access to belantamab, as a consequence of their treatment options that were available at their time of diagnosis, decision factors which may also be attributed to age and eligibility for stem cell transplants. To ensure equitable access to belantamab and to enable clinician and patients to choose the most effective regimen for individual patients we ask that the lenalidomide restriction be removed. ***"The current treatments are OK if everything goes to plan. I don't understand why treatments can only be given in certain combos at this line. Why can't you try different things when you need them."*** ***"Honestly, it was heartbreaking. When someone you love is going through something like myeloma, you want to believe you're doing everything you can for them. But we were left feeling helpless—like we were always playing catch-up. That feeling of "what if" doesn't go away. It really undermines your trust in the system when access seems to depend more on timing or postcode than on what's best for the patient."***
3	**We are concerned that the guidance restricts this treatment to patients at 2nd line only.** Belantamab mafodotin plus bortezomib and dexamethasone is licensed for use at second line and beyond. We believe that patients at 3rd line should benefit from this treatment as demonstrated by the DREAMM7 clinical data. We urge GSK, NICE and NHSE to consider the clinical data and the need for treatment options, with new mechanisms of action which can effectively treat myeloma patients who have relapsed at first and second line. The announcement by NHSE of a worlds-first approval of belantamab was a pivotal milestone in the treatment of myeloma. The recommended restriction to 2nd line only, compounded by the requirement to be refractory or intolerant to lenalidomide poses significant inequality of health outcomes for those patients who are lenalidomide naïve or at 3rd line of their treatment journey.

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	We welcome consideration and a commercial agreement between GSK and NHSE to make belantamab available to those patients who may benefit from 2nd line onwards. ***'It's the best response I've had in all my years of treatment. It really is.'*** *– myeloma patient who received belantamab mafadotin at 4th line on a clinical trial.* ***'Since having Belantamab the impact on my quality of life has been much less. It's a good drug for me, especially over the past year - this is my 5th line of treatment. In the past I've had it really rough where I've been sleeping for 18 hours a day, I've been sore and swollen with sore feet and sore hands. However, since I've been on Belantamab there's been none of that. I've had very little peripheral neuropathy. I do still sleep a lot, I sleep 10 hours or so but that's not 18 hours like I was before. I am so much better compared to a few years ago before the Belantamab. I don't think about myeloma now I just get on with things.'*** *– myeloma patient who received belantamab mafadotin at 5th line on a clinical trial.*
4	
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Insert extra rows as needed

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- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	The UK Myeloma Society

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are pleased that this draft guidance will provide access to Bel-Bor-Dex in England for patients with relapsed multiple myeloma who have had one prior treatment and are exposed or intolerant to lenalidomide.
2	We notice that the restriction of prior lenalidomide exposure or intolerance was not an entry requirement for the DREAMM-7 trial and have some concern that lenalidomide naive patients are

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	currently not eligible. In addition, the published median PFS data for lenalidomide refractory patients is shorter than for the ITT population at 25.0 months and it could be argued that the population selected has excluded some patients who may benefit more (len-naive).
3	We notice that 125/243 (51%) of patients receiving Bel-Bor-Dex in DREAMM-7 had only had 1 prior line of therapy, the rest were more heavily pre-treated. This suggests that the excellent median PFS in the ITT population (36.6 months) would also include some patients who had received two or three lines of treatment. The UK NICE treatment algorithm currently includes a significant gap in effective therapies with a new mechanism of action at third line. Ideally patients would also be able to access Bel-Bor-Dex at 3rd line to fill this gap.
4	As the DG has limited access to 2nd line patients who are lenalidomide refractory or intolerant, for this population Car-Len-Dex is not a relevant comparator as this group would be unlikely to be offered lenalidomide based treatment again.
5	
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- Do not include medical information about yourself or another person from which you or the person could be identified.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Johnson & Johnson

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The Committee's preferred assumptions include teclistamab as fourth-line treatment. Within the Draft Guidance, it is noted that concerns were raised on the potential "*a loss of benefit with teclistamab at fourth line because it works in a similar way to belantamab. It noted there was a lack of evidence on the impact of belantamab treatment at second line on effectiveness of teclistamab fourth line*".

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	We would like to bring the Committee's attention to reassuring results from Touzeau et *al* (2024) on the MajesTEC-1 trial cohort C - a cohort of patients who had prior BCMA-targeted therapy (antibody-drug conjugate [ADC] or chimeric antigen receptor T-cell [CAR-T] therapy. Findings suggested that baseline BCMA expression and immune characteristics were unaffected by prior anti-BCMA treatment. Teclistamab provided clinically meaningful responses and favourable safety profile in patients with heavily pretreated R/RMM and prior anti-BCMA treatment. Prior BCMA-ADC exposure is not reported to affect survival outcomes with teclistamab at fourth-line and currently, the Blueteq approval criteria for teclistamab include prior exposure to BCMA-targeted ADC such as belantamab mafodotin (criteria 11). Based on the Committee's preferred assumptions to add teclistamab as a subsequent treatment and findings from Touzeau et al. (2024), we assume the eligibility criteria for teclistamab would remain unchanged once this appraisal is complete. Source: • Touzeau C et al. Efficacy and safety of teclistamab in patients with relapsed/refractory multiple myeloma after BCMA-targeting therapies. *Blood*. 2024;144(23):2375-88 • NHS England. National Cancer Drugs Fund List. V1.366. Updated 12 June 2025. Available at: https://www.england.nhs.uk/wp-content/uploads/2017/04/NationalCDF-list-ver1.366-120625-MASTER.pdf [last accessed: 19/06/2025]

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- Do not use abbreviations.
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Consultation on the draft guidance document – deadline for comments 5pm on Thursday 3 July. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Menarini Stemline

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 3 July. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the final draft guidance in section 3.20 does not make clear why sel-bor-dex and car-len-dex are not considered relevant comparators given that bel-bor-dex is not cost-effective against either comparator. The car-len-dex regimen can be assumed not to be a

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NICE National Institute for Health and Care Excellence

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	comparator given that it contains lenalidomide, and the recommendation for bel-bor-dex is for lenalidomide unsuitable. However, it is not clear why sel-bor-dex is not a comparator, given that the current recommendation for bel-bor-dex does not exclude lenalidomide and daratumumab refractory patients, the population where sel-bor-dex is currently recommended in the 2L (TA974). Given that this may cause confusion for this and future myeloma appraisals we ask that it is clarified in the final guidance why sel-bor-dex is not a relevant comparator.
2	
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The

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Single Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	
Other role	
Organisation	Royal College of Ophthalmologists
Location	
Conflict	
Notes	

Comments on the DG:

Has all of the relevant evidence been taken into account?

It appears that input is being sought from 'clinical experts', but it is not specified whether these are haematologists or ophthalmologists. Given the nature of the ocular adverse events and the proposed recommendation for ophthalmic surveillance, it is surprising that the Royal College of Ophthalmologists (RCOphth) was not invited to be a stakeholder, nor was an ophthalmologist included in the clinical expert panel. There is also a reference to the potential burden this recommendation may place on NHS ophthalmology departments, which are already under significant pressure with long waiting lists. However, the proposed pathway for implementing this surveillance remains unclear.

Are the recommendations sound and a suitable basis for guidance to the NHS?

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Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

"We have I have identified some relevant excerpts (pasted below) concerning ocular adverse events, the recommendation for ophthalmology surveillance for toxicity, and references to 'existing pathways' between oncology centres and ophthalmology services.

"Corneal adverse events relating to study treatment were more common with BelBor-Dex than Dar-Bor-Dex (the data was considered confidential by the company so cannot be reported here). The model included treatment specific ocular adverse events of grade 3 and above, including keratopathy, blurred vision and dry eyes. These adverse events were only applied to the Bel-Bor-Dex arm. The EAG noted that the incidence of keratopathy applied in the model was much lower than the incidence in DREAMM-7. In addition, the adverse events were applied as a one-off quality-of-life decrement to the first cycle in the model, using disutilities sourced from NICE's technology appraisal guidance on ciclosporin for treating dry eye disease that has not improved despite treatment with artificial tears. The EAG said that applying the adverse events as a one off may not be appropriate to capture adverse events that occur later or are experienced for a longer length of time. It also noted that time to onset and duration of events of grade 3 and above were not reported. The committee discussed whether EQ-5D-3L was sensitive enough to capture the impact on quality of life of ocular side effects and visual impairment with Bel-Bor-Dex. The clinical experts, along with the patient and expert submissions, advised that belantamab mafodotin is well tolerated, and that people are prepared to tolerate the ocular side effects. The clinical experts at committee thought that EQ-5D-3L is a reasonable tool to capture the impact of ocular side effects on quality of life. In addition, the committee noted that patient experts said that the EQ-5D-3L in the trial would have likely captured the impact of ocular adverse events on health-related quality of life, given the frequency of assessments. The committee noted that although EQ-5D-3L is not disease-specific, it allows for consistent evaluations across disease areas and the concern about sensitivity could apply to many conditions. But it acknowledged that the extent to which EQ-5D-3L captures the impact of vision loss on quality of life is uncertain. So, the committee concluded that a disutility for ocular adverse events should be included in the base case with scenarios exploring the impact of excluding a disutility for ocular adverse events"

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"The Cancer Drugs Fund lead explained that the ophthalmic monitoring needed for belantamab mafodotin would likely be burdensome for ophthalmology departments in the NHS, which has long waiting lists. They explained that delays in implementation would be likely. They highlighted that everyone must have an ophthalmic eye exam before each of the first 4 doses of belantamab mafodotin, and subsequent monitoring in the event of ocular adverse events. They explained that the mechanism of delivery of this monitoring service and the method of communication between ophthalmology departments or community services and oncologists was unclear. The clinical experts highlighted that about 30 to 40 hospitals took part in the compassionate-use scheme for belantamab mafodotin, and so hospitals have a pathway in place for eye examinations. The company explained that between 2018 and 2024, over 100 NHS sites administered belantamab mafodotin in different settings. It explained that the company is exploring the option of supporting people through access to communitybased ophthalmology at the point of recommendation. The committee recalled that the incidence and costs of ocular adverse events were applied as a one-off in the model, and the incidence of keratopathy applied in the model was lower than observed in DREAMM-7 (see section 3.11). It also recalled that time to onset and duration of adverse events of grade 3 and above was not reported. The committee said that there was uncertainty as to whether the cost of ocular adverse events had been adequately accounted for in the model. It said that this was because the model had not included continued monitoring until resolution of ocular adverse events. So, the cost of monitoring with belantamab mafodotin was likely to have been underestimated. It concluded that the base case should include the cost of monitoring ocular adverse events using hospital-based ophthalmology services, with a scenario analysis provided using the community-based ophthalmology services proposed by the company.""

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the DG:

This suggests that the patient has received lenalidomide on line 1 and has not progressed to line 2. This is extremely limiting. In my case I started line 1 treatment in January 2018 on VMP when I believe lenalidomide was not available for line 1. Hence I would not be eligible, nor would any of my contemporaries who started treatment at around the same time.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the DG:

This is unfair if a patient wasn't offered lenalidomide at first line treatment.

This fundamentally unfair to patients not offered lenalidomide at first line treatment. My husband was only offered dar-bor-dex which did not work. Thalidomide was not offered because of the peripheral neuropathy side effects. My husband already has significant peripheral neuropathy due to previous R-CHOP chemotherapy for MALT Non-Hodgkins Lymphoma. If thalidomide was not given because he could not tolerate it obviously he would not be able to tolerate lenalidomide, a more potent analog of thalidomide. But because he was not treated with lenalidomide and has never been offered lenalidomide as a treatment because it is not suitable for him why should this mean he is excluded from treatment with blenrep-bor-dex!?

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the DG:

My name is [redacted]. I have MM. My issue with the draft guidance is that it does not cover instances where a patient has been treated with chemotherapy for another condition before 1L for MM.
Such situations can affect the suitability of certain treatment options and at the same time make Blenrep the most appropriate 2L treatment.
In my own case, I was treated for low grade non-hodgkin's lymphoma in 2020 receiving 6 rounds of R-CHoP. A relapse was detected in 2023, for which I received R-BENDA. During the R-BENDA the genetic results of a liver biopsy became available. These showed that I had myeloma not lymphoma. From this point my 'myeloma journey' started. The generic point here is that my immune system was compromised by 6-rounds of R-CHoP and 3 rounds of R-BENDA. Hence, it could have been predicted that immunotherapy-based treatments of MM would have limited efficacy. I received 16 rounds of DVD. I was never offered lenalidomide. The DVD gave partial remission, which lasted for around 1 month after cessation of treatment. So now what are the options at 2L? The ideal option would be Blenrep, because it does not rely on an immune response. BUT the current guidance would exclude me (or anyone else in a similar situation) leaving immunotherapy as the sole 'option'. In conclusion, those having a compromised immune system due to previous chemo should have the option of Blenrep in 2L.
For your information, my MM is oligo-secretory and osteo-sclerotic, without POEMs. Maybe there is scientific benefit in having Blenrep-response data in such a case (which is rare, apparently). I am under the care of [redacted] at [redacted].
Thank you for considering my comment.

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Single Technology Appraisal (STA)
EXTERNAL ASSESSMENT GROUP REPORT
Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212]

Post-ACM1 EAG critique of additional evidence for BVd versus KRd for the lenalidomide-suitable 2L population

Produced by
York Technology Assessment Group, University of York, Heslington, York, YO10 5DD

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Declared competing interests of the authors

None.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CON) data have been [redacted].

Copyright statement

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1 OVERVIEW

This document presents the External Assessment Group's (EAG) critique of further evidence and additional analyses provided by the company after the first appraisal committee meeting (ACM1), which was received by the EAG on the 18th of July 2025.[1] It follows an earlier EAG review of additional evidence submitted by the company in February 2025 to respond to the committee's preferred assumptions after ACM1,[2] which was presented as an addendum to the EAG report on the 13th of May 2025.[3]

Within the short timelines provided to review the company documents, the EAG is unable to provide a detailed critique of the company's response (a document consisting of 122 pages detailing the further evidence and analyses since the previous EAG critique of evidence following ACM1, in addition to an updated company model with new cost-effectiveness results). The EAG has focused its critique on the key differences between the company's position regarding the comparison of belantamab mafodotin in combination with bortezomib and dexamethasone (BVd) and carfilzomib, lenalidomide, and dexamethasone (KRd) in the lenalidomide eligible population. This critique specifically examines how the company's position, including implementation of evidence in the cost-effectiveness analysis, has changed between the additional analyses presented after ACM1 (before draft guidance was issued) and that presented in this new submission (after draft guidance was issued).

The company has presented additional evidence on the cost-effectiveness of BVd for second line (2L) lenalidomide-suitable patients with relapsed or refractory multiple myeloma (RRMM). The treatment effectiveness in the company's updated cost-effectiveness analysis for this comparison is informed by the same unanchored matching-adjusted indirect comparison (MAIC) presented in the previous 'additional evidence' submission (dated February 2025).[2] This MAIC compared data for the 2L+ DREAMM-7 population (interim analysis 2 (IA2) data cut) with data on patients who received KRd from the ASPIRE trial.[2] However, in their latest evidence submission, the outputs of the MAIC are utilised differently in the company's updated base-case analysis.[1]

Section 2 makes reference to the EAG addendum of May 2025, where the clinical evidence and MAIC for this population have previously been critiqued by the EAG.[3] In Section 3.1, the updated cost-effectiveness analysis is critiqued, while additional EAG analyses are presented in Section 3.2. All cost-effectiveness results presented in this document are inclusive of the most recent Patient Access Scheme (PAS) discount on the list price of belantamab mafodotin. The corresponding results for analyses including confidential commercial arrangements for other drugs in the model are presented in a separate confidential appendix.

2 CLINICAL EFFECTIVENESS

2.1 Identification of studies

The DREAMM-7 and ASPIRE trials were previously identified through a systematic review, which was critiqued in the original EAG report.

In response to the previous company submission of additional evidence post-ACM1 in February 2025,[2] the EAG questioned whether non-randomised evidence of KRd was available to conduct an indirect comparison with BVd. The company indicated that they performed a targeted literature review to identify non-randomised evidence, but no suitable evidence was found. No further information has been presented regarding this literature review. However, the EAG believes the company's efforts to identify further evidence were reasonable.

2.2 Matching-adjusted indirect comparison (MAIC)

The unanchored MAIC comparing BVd (DREAMM-7 ITT population, updated IA2 data cut) and KRd (ASPIRE, final OS analysis, April 2017 data cut) was critiqued by the EAG in May 2025.[3] A brief overview is provided in this section. For further details please refer to the earlier critique.

2.2.1 ASPIRE trial population

The ITT population of ASPIRE differs from patients who are likely to be eligible to receive KRd in the NHS because ASPIRE participants were younger on average and the trial treatment was provided at 3L+ for 53.5% of patients. In addition, patients who previously received lenalidomide (19.8% in ASPIRE) and patients who had not received bortezomib in a previous line (34.1% ASPIRE) would not currently be eligible to receive KRd in the NHS. It is unclear what proportion of the ASPIRE ITT population would be eligible to receive KRd in NHS practice.[3]

2.2.2 Methods

The unanchored MAIC has several important limitations, which have been acknowledged by the company. The fact that it is an unanchored comparison, combined with the fact that weighting did not fully balance important covariates between the BVd and KRd arms, leads to considerable uncertainty in the estimates produced. Matching for R-ISS could not be achieved, potentially introducing bias favouring BVd, as the ASPIRE trial included a higher proportion of stage III R-ISS patients.[3]

2.2.3 Results

2.2.3.1 Covariates

Adjustments for differences in baseline characteristics between DREAMM-7 and ASPIRE through weighting are shown in Table 5 of the July 2025 additional evidence submission (p. 17).[1] The

weighting, among other changes, [redacted] the proportion of participants refractory to lenalidomide (32.5% unweighted sample, [redacted] weighted sample).

2.2.3.2 Progression-Free Survival (PFS)

The MAIC base-case results demonstrate longer PFS for BVd compared to KRd (additional evidence July 2025, section 2.1.4.3.1, p.19).[1] Weighting of data in the BVd arm [redacted]. The hazard ratio (HR) [redacted] for the weighted BVd versus KRd (additional evidence July 2025, table 6, p. 19).[1]

2.2.3.3 Overall Survival (OS)

The OS data from DREAMM-7 remains immature. Median OS is still not reached in the new data-cut. Participants were followed up for a median of [redacted] months in the BVd arm of DREAMM-7 and [redacted] months in the KRd arm of ASPIRE. In the base-case, OS is higher for BVd than KRd (Additional evidence July 2025, Section 2.1.4.3.2, pp. 20-21).[1] Applying the MAIC weights does not significantly alter results for the BVd arm, as illustrated by the overlapping unweighted and weighted Kaplan-Meier (KM) curves in Figure 6 (Additional evidence July 2025, Section 2.1.4.3.2, p. 22).[1] However, it is unclear how the failure to match R-ISS, and subsequent exclusion of this variable from the matching process, has affected the results based on the weighted OS curve, which may be biased in favour of BVd.

3 COST EFFECTIVENESS

3.1 Company's preferred assumptions after draft guidance

The company's updated cost effectiveness analysis for the BVd vs. KRd comparison at 2L in the lenalidomide-suitable population includes the following key elements:

- Updated electronic version of the cost-effectiveness model with functionality to:
    - Extrapolate the KRd PFS and OS KM curves from the ASPIRE trial (ITT population) with independently fitted parametric functions;
    - Extrapolate the BVd PFS and OS KM curves from the DREAMM-7 IA2 (ITT population) trial weighted via the unanchored MAIC to match the ASPIRE trial population with independently fitted parametric functions;
    - Model the KRd time to treatment discontinuation (TTD) curve using alternative approaches, namely:
        - By applying the HR between PFS and TTD for daratumumab, bortezomib and dexamethasone (DVd) to the KRd PFS extrapolated curve;

        - By deriving the HR between PFS and TTD for KRd from the ASPIRE trial data and applying this HR to the KRd PFS extrapolated curve;
        - By assuming that the KRd TTD curve equals the corresponding PFS curve.
- Updated cost-effectiveness analyses for the KRd vs. BVd comparison, including:
    - Revised base-case results (probabilistic and deterministic), which differ from the corresponding base-case analysis presented by the company in February 2025; the key differences in assumptions and data sources between analyses are illustrated in Table 1.
    - Uncertainty analyses including probabilistic, one-way deterministic sensitivity and extensive scenario analyses.
    - Internal validation of the updated model.

Table 1 Key differences between the company's previous (February 2025) and updated base-case (July 2025) parametrisation for the comparison of BVd vs. KRd

–	February 2025[2]	July 2025
Starting age	70 years – source: SACT	[redacted] years – source: DREAM-7 ITT MAIC weighted
PFS	KRd survival modelled by applying the estimated treatment effect from the unanchored MAIC (i.e., HR) for KRd vs. BVd to the unweighted BVd extrapolated survival curve (DREAMM-7 IA2 ITT). The HRs for KRd vs. BVd were estimated by comparing the KRd ASPIRE ITT KM curve to the unanchored MAIC weighted BVd KM curve (DREAMM-7 IA2 ITT)	KRd survival modelled by independently fitting extrapolation curves to: • BVd KM curve (DREAMM-7 IA2 ITT) weighted by the unanchored MAIC to reflect the ASPIRE ITT population • KRd KM curve (ASPIRE ITT)
OS		
TTD for KRd	The PFS HR for KRd vs. BVd ([redacted]) from the unanchored MAIC was used as a proxy for the TTD HR for KRd and applied to the BVd TTD extrapolation curve.	The TTD curve for KRd was derived by applying the HR for TTD vs. PFS ([redacted]) for DVd* to the extrapolated PFS KRd curve (informed by ASPIRE ITT)
KRd stopping rule	None	Maximum of 18 cycles for carfilzomib
Lenalidomide unit cost	£4230 per 21 capsules - source: BNF	£28.27 per 21 capsules - source: eMIT

*Using DREAMM-7 IA2 ITT data

Abbreviations: HR, hazard ratio; IA2, second interim analysis; ITT, intention to treat; PFS, Progression Free Survival; OS, Overall survival; TTD, Time to treatment discontinuation.

Points for Critique

The EAG considers that the company's documentation provides a comprehensive overview of the economic evidence available to inform the cost-effectiveness of BVd compared to KRd for the 2L treatment of RRMM in individuals who are eligible for lenalidomide. Whilst the EAG was not able to

review the model in depth given the short timelines, the EAG considers that the updated model remains suitable to inform decision making.

We note that the clinical evidence available to inform the population considered in the company's new submission is affected by additional uncertainty relative to the population for whom the draft guidance recommended BVd. This additional uncertainty is introduced by i) the use of an unanchored MAIC to compare the effectiveness of BVd vs. KRd (see Section 2.2.2) and ii) the use of evidence from the ITT population of ASPIRE to inform the MAIC (see Section 2.2.1). The EAG considers this uncertainty unavoidable but emphasises that it constitutes an evidentiary limitation that must be considered when evaluating the cost-effectiveness evidence.

The EAG broadly agrees that the company's approach to assess the cost-effectiveness of BVd vs. KRd in the lenalidomide-suitable population is appropriate, with the exception of the approach used to model the treatment effect for BVd vs. KRd on survival outcomes, particularly on: i) OS and ii) time to treatment discontinuation (TTD) of KRd. These two elements are critiqued in the next sections and EAG additional analyses combining the impact of alternative approaches to model OS and TTD for KRd are presented in Section 3.2.

3.1.1 Progression-free and overall survival

The company has updated their approach to modelling the treatment effectiveness of BVd vs. KRd on OS and PFS, by independently fitting parametric models to the survival KM data for both treatment arms, instead of applying MAIC HRs to the unweighted BVd data. The company justifies its updated approach based on uncertainties regarding whether the proportional hazards (PH) assumption holds for these survival data. The company presents a number of diagnostic plots (see Figures 10 to 13 and 16 to 19 of the company's additional evidence document, July 2025) to justify its updated approach on the basis of the PH assumption being violated.

Six standard parametric independent models were fitted to the unweighted KRd and MAIC weighted BVd arms (exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised Gamma) and measures of statistical goodness-of-fit, as well as landmark survival rates and survival plots for each parametric model are reported. These were considered when selecting the company's base case extrapolation models for PFS and OS, alongside clinical opinion on the plausibility of the long-term extrapolations.

The company's preferred extrapolations for BVd were the exponential distribution for both PFS and OS; this was in line with the committee and EAG's preference for the unweighted BVd data in the lenalidomide-unsuitable population.

For KRd, PFS was also extrapolated using an exponential distribution in the base-case analysis, while OS was extrapolated using a generalised gamma. The company justified its preference for the generalised gamma model to extrapolate OS, despite other models having better statistical fit (namely the Weibull on the basis of the Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC), and the Exponential and Gompertz on the basis of BIC) due to likely PH violation and alignment with clinical opinion. Scenario analyses were presented for the KRd OS extrapolation using the Weibull and exponential distributions, given these were the second and third most suitable options chosen by clinicians. The results of the company's base-case analysis are presented in Table 2, alongside those of the KRd OS extrapolation scenarios.

Table 2 Deterministic results of the company's base-case analysis and KRd OS scenarios

Option	Costs	LYs	QALYs	Inc. Costs	Inc. LYs	Inc. QALYs	ICER, /QALY
Company's base-case analysis							
KRd	[redacted]	[redacted]					
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£165
Company's scenario: KRd OS extrapolation with Weibull							
KRd	[redacted]	[redacted]					
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
Company's scenario: KRd OS extrapolation with Exponential							
KRd	[redacted]	[redacted]					
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

Abbreviations: BVd, belantamab mafodotin with bortezomib and dexamethasone; KRd, carfilzomib plus lenalidomide and dexamethasone.

Points for critique

The EAG is concerned that the company's approach to modelling OS for KRd may not appropriately capture the uncertainty in the treatment effect of BVd vs. KRd for the following reasons. First, while the EAG agrees with the company that the PH assumption may not hold, particularly for OS, it is still relevant to consider analyses assuming PH holds as it cannot be ruled out. Therefore, it is important to consider analyses where the HRs derived for the unanchored MAIC are utilised to derive the PFS and OS curves for KRd.

Second, the company does not present cost-effectiveness analyses applying alternative weightings to BVd despite the MAIC sensitivity analysis suggesting that the OS HR for BVd vs. KRd are sensitive to the inclusion of R-ISS in the set of variables for matching (see Table 8 of the company's additional evidence document, July 2025[1]) The EAG considers that excluding R-ISS from the matching process may be appropriate given the level of missingness on the R-ISS variable in the ASPIRE trial, but notes that the existence of an imbalance in the proportion of patients with R-ISS 3 in the BVd

DREAMM-7 arm before and after the company's base-case weighting compared to the KRd ASPIRE arm (see Table 5 of the company's additional evidence document, July 2025[1]) It is, therefore, important to consider the impact of weighting BVd according to alternative covariates (i.e., with and without R-ISS) in the updated cost-effectiveness analysis, as the potential imbalance in R-ISS distribution between BVd and KRd (higher proportion of R-ISS III in KRd vs. BVd) may favour the survival outcomes for BVd. The use of these alternative HRs provides a way to explore uncertainty on whether the MAIC has successfully adjusted for all relevant covariates (as the company only provides alternative extrapolation curves fitted to BVd weighted by all relevant covariates except R-ISS).

Thus, in Section 3.2 additional analyses are presented where PFS and OS for KRd are modelled assuming PH (i.e., using the HRs from the unanchored MAIC to derive the KRd survival) and using MAIC HRs from analysis adjusting for all relevant covariates, with and without R-ISS.

Finally, even if PH does not hold for OS, the EAG is not satisfied that the generalised gamma distribution provides the most appropriate OS extrapolation for KRd. The Weibull and the exponential distributions appear to have similar statistical fits to the data (with the Weibull showing a better fit than the generalised gamma in AIC and BIC), and the Weibull was considered plausible by three of the company's five clinical experts.

The EAG considers that the assessment of the implied HRs between BVd and KRd over time for different extrapolation assumptions is informative when assessing the clinical plausibility of the long-term OS projections. The EAG plotted the implied HRs over time for BVd vs KRd when KRd OS is extrapolated with the exponential, Weibull and generalised gamma distributions; these are shown in Figure 1. The graph also shows the HRs for BVd vs. the MAIC HRs from analysis adjusting for all relevant covariates, with and without R-ISS (which are used in the EAG PH scenarios). Please note that for the purposes of illustrating treatment effect over time, the underlying hazard rates were not constrained by the general population mortality hazards (but this constraint is applied in the model).

Figure 1 Implied OS HRs over time for the different survival modelling approaches

Figure 1 suggests that:

- Analyses assuming PH are supportive of a smaller treatment effect for BVd vs. KRd for the majority of the time horizon.
- When KRd OS is extrapolated with an independently fitted exponential distribution, the implied treatment effect implicitly reflects PH (as BVd is also modelled with an independent exponential distribution), but this treatment effect is greater than the effect implied by the unanchored MAIC HRs.
- KRd OS extrapolations with both the Weibull and generalised gamma distributions suggest a trend in HR variation over time consistent with the empirical hazard plots for the weighted DREAMM-7 BVd and ASPIRE KRd KM curves (i.e., [redacted]; see Figure 19 of the company's additional evidence document, July 2025[1]) and that the treatment effect [redacted]. The EAG, notes however, that the empiric hazard behaviour at the end of observed follow-up is more uncertain, particularly for the weighted BVd curve, which is more immature than KRd [redacted](see Figure 6, of the company's additional evidence document, July 2025[1]).

- The company's preferred extrapolation approach for KRd OS (i.e., generalised gamma) results in a greater treatment effect than using the Weibull distribution for the majority of the time horizon.

The EAG also considered how the different OS approaches impact on the expected life years (LY) gained with BVd vs KRd, as shown in Table 3. The expected LYs in the progressed disease state is considerably longer than the benefit in terms of progression-free disease, across all but one modelled approach. This suggests that the survival benefit of BVd treatment is accrued largely beyond disease progression, under all but the most pessimistic survival assumptions. The plausibility of these estimates should be discussed and validated with clinical experts.

Table 3 Expected LY gained for BVd vs KRd with alternative survival extrapolations (undiscounted)

–	BVd: OS and PFS exponential (MAIC weighted curves) KRd: PFS exponential			BVd: OS and PFS exponential (unweighted curves)	
	KRd: OS generalised gamma	KRd: OS Weibull	KRd: OS exponential	KRd MAIC adjusted HR (without R-ISS)	KRd MAIC adjusted HR (with R-ISS)
Progression Free disease (on and off treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.1.2 Time to treatment discontinuation

The company updated the approach taken to model TTD for KRd compared to its previous one, which required using the BVd TTD as a baseline curve.[2] This approach can introduce bias into the cost-effectiveness analysis by overestimating discontinuation for patients receiving KRd. Due to unavailability of published data to inform a MAIC for TTD, the company had to make assumptions to fit a TTD curve for KRd. The company provides details of the alternative approaches explored in Table 15 of the additional evidence document (July 2025).

The company's base-case approach consisted of estimating a HR between PFS and TTD based on DREAMM-7 IA2 ITT data for DVd and applying this HR to the KRd extrapolated curve to derive the corresponding curve. The company considered this approach consistent with assuming the PFS HR for DVd vs. non trial comparators (i.e., selinexor with bortezomib and dexamethasone and high-dose carfilzomib) in the original company submission as a proxy for the corresponding TTD HRs, and deriving their TTD curves by applying these proxy HRs to a DVd TTD baseline. In scenario analysis, the company assumed that KRd TTD was equal to KRd PFS. This approach was deemed lacking in

clinical plausibility by the company, given a proportion of patients would discontinue treatment with KRd while remaining progression-free. Finally, the company used summary data (median treatment duration and median PFS) duration from the KRd arm of the ASPIRE trial, with the source of KRd efficacy included in the MAIC, to estimate the HR between PFS and TTD for KRd and derive the TTD curve by applying this HR to the KRd PFS curve. In this approach, the median duration of the lenalidomide component of KRd was used as a proxy for all treatments within KRd. The company justified using the median duration for lenalidomide (85 weeks)[4] as opposed to carfilzomib (72 weeks)[4] due to the median duration of the latter reflecting the stopping rule at 18 (4-weeks) cycles for carfilzomib, which does not apply to the remaining components of treatment. Furthermore, the separated TTD extrapolation curves for lenalidomide and carfilzomib in TA695 closely align up to the point where the carfilzomib stopping rule truncates the respective curve (Figure 10 of the company response to clarification questions).[5] The company's justification for not including this scenario assumptions in its base case pertain to *"uncertainty around the shape of the curve for carfilzomib discontinuation, given the shape of median duration is masked by the carfilzomib stopping rule"* and the use of a lenalidomide-naïve and bortezomib exposed subpopulation of ASPIRE in TA695. The company also adds that there is uncertainty on whether lenalidomide and carfilzomib are either closely aligned (Figure 10 of the company response to clarification questions).[5] or more patients discontinued lenalidomide than carfilzomib (based on Figure 23, TA695).[5] Due to this uncertainty on the trends of lenalidomide and carfilzomib the company considers this scenario conservative. Figure 2 illustrates the KRd TTD curves for the company's base case and the scenario considered conservative (but not necessarily implausible) by the company. Corresponding cost-effectiveness results for these two analyses are presented in Table 4.

Figure 2 Selected KRd TTD curves in the company's model

Table 4 Deterministic results of the company's base-case analysis and key KRd TTD scenario

Option	Costs	LYs	QALYs	Inc. Costs	Inc. LYS	Inc. QALYs	ICER, /QALY
Company's base-case analysis: KRd TTD based on DVd HR (PFS and TTD) as a proxy							
KRd	[redacted]	[redacted]					
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£165
Company's TTD scenario: KRd TTD based on ASPIRE PFS vs. median treatment duration							
KRd	[redacted]	[redacted]					
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,949

Abbreviations: BVd, belantamab mafodotin with bortezomib and dexamethasone; KRd, carfilzomib plus lenalidomide and dexamethasone.

The EAG notes that the company's TTD scenario above requires the use of a Microsoft Excel *goalseek* function to estimate the HR between PFS and TTD for KRd; this function does not provide a single solution to the formula it satisfies (see below). Therefore, the cost-effectiveness estimates when using this approach, are not completely reproducible when the *goalseek* function is rerun. This is a limitation of the approach.

$$(median\ PFS\ in\ ASPIRE - median\ treatment\ duration\ in\ ASPIRE)$$
$$= (median\ modelled\ PFS - median\ modelled\ TTD)$$

Points for critique

The EAG agrees with the company's decision to not use the BVd TTD curve as the baseline to estimate the corresponding TTD KRd curve, given that the BVd treatment scheduling and duration is impacted by the need to manage eye related ocular events that are specific to belantamab mafodotin.

The EAG is, however, concerned that the company's preferred approach to modelling the KRd TTD curve using DVd TTD data from DREAMM-7 is inconsistent with the data sources informing the clinical effectiveness in the model. Unlike the survival data used to inform the effectiveness of BVd, the DREAMM-7 DVd survival data that is used to derive the HR for TTD vs. PFS (which is applied to the KRd PFS curve to derive the corresponding TTD curve) has not been adjusted for the ASPIRE population characteristics. Given this limitation and the availability of summary treatment duration data for components of KRd treatment in the ASPIRE trial, the EAG considers that the use of these data would have been preferable to ensure consistency between evidence sources in the model.

The EAG is also concerned that this approach may overestimate the costs associated with KRd, in light of the available ASPIRE trial data on treatment duration for the KRd and TTD data used in the previous NICE appraisal of KRd (TA695).[5] In Table 5, the EAG reports the landmarks for the modelled KRd TTD curves over time and median TTD in the company's base-case and the scenario using ASPIRE trial data; these are contrasted with the corresponding values extracted from TA695's committee papers for validation. The EAG acknowledges that it is difficult to ascertain the level of overlap between the extrapolated TTD carfilzomib and lenalidomide components in TA695 committee papers. The EAG considers that both the company's preferred approach in the current appraisal and the ASPIRE trial informed scenario that uses KRd TTD curves have good alignment with the TA695 carfilzomib and lenalidomide TTD curves in the initial period, but beyond one year the company's preferred KRd curve lies above both curves in TA695. The median duration of treatment according to the different sources also suggest that the company's preferred approach may overestimate the TTD for KRd, particularly for the lenalidomide component.

The EAG preferred assumptions for modelling KRd TTD correspond to those of the scenario relying on ASPIRE trial PFS vs. median treatment duration data (henceforth referred to as the company's TTD scenario). In Section 3.2, the EAG presents additional analyses combining the alternative survival approaches described 3.1.1 with the company's TTD scenario.

Table 5 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
Company KRd TTD Base-case: DVd HR (PFS and TTD) as a proxy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company KRd TTD scenario: ASPIRE median PFS to median treatment duration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TA695 Lenalidomide TTD extrapolation[5] (Figure 10, response to PfCs and Figure 23, CS)*	~80%	~65%	~45%	30%	20%	~15%	<10%	~5%	<5%	<5%	<5%	~91 weeks (~1.75 years)
TA 695 Carfilzomib TTD extrapolation[5] (Figure 23, CS)*	~85%	70%	0%	0%	0%	0%	0%	0%	0%	0%	0%	72 weeks
Lenalidomide treatment duration ASPIRE trial[4]												85 weeks
Carfilomib treatment duration ASPIRE trial[4]												72 weeks

*manually extracted from TA695 ACM1 committee papers
Abbreviations: CS, company's submission; PfC, points for clarification

3.2 EAG additional analyses

The EAG presents in Table 6 additional analyses assuming PH, i.e., using the HRs from the unanchored MAIC to derive the KRd survival by applying these MAIC HRs (adjusting for all relevant covariates, with and without R-ISS) to the BVd unweighted extrapolation curves (exponential for both OS and PFS). Table 7 presents analysis combining the EAG preferred approach to modelling KRd TTD (i.e., using ASPIRE trial PFS vs. median treatment duration data to inform KRd) with key survival scenarios: a) using independently extrapolated survival curves and b) assuming PHs.

Table 6 Deterministic cost-effectiveness results – EAG PH scenarios

Option	Costs	LYs	QALYs	Inc. Costs	Inc. LYs	Inc. QALYs	ICER, /QALY
Company's base-case analysis							
KRd	[redacted]	[redacted]					
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£165
EAG Scenario 1.1: MAIC HRs for KRd PFS & OS adjusting for all TEMs and PFs except R-ISS							
KRd	[redacted]	[redacted]					
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
EAG Scenario 1.2: MAIC HRs for KRd PFS & OS adjusting for all TEMs and PFs including R-ISS							
KRd	[redacted]	[redacted]					
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

Abbreviations: BVd, belantamab mafodotin with bortezomib and dexamethasone KRd, carfilzomib plus lenalidomide and dexamethasone.

Table 7 Deterministic cost-effectiveness results – EAG combined survival and KRd TTD scenarios

Option	Costs	LYs	QALYs	Inc. Costs	Inc. LYs	Inc. QALYs	ICER, /QALY
Company's TTD scenario: KRd TTD based on ASPIRE PFS vs. median treatment duration							
KRd	[redacted]	[redacted]					
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,949
EAG Scenario 2.1: Company's TTD scenario + KRd OS extrapolated with Weibull							
KRd	[redacted]	[redacted]					
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,442
EAG Scenario 2.2: Company's TTD scenario + KRd OS extrapolated with Exponential							
KRd	[redacted]	[redacted]					
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£507
EAG Scenario 2.3: Company's TTD scenario + MAIC HRs for KRd PFS & OS adjusting for all TEMs and PFs except R-ISS							
KRd	[redacted]	[redacted]					
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£350

EAG Scenario 2.4: Company's TTD scenario + MAIC HRs for KRd PFS & OS adjusting for all TEMs and PFs including R-ISS							
KRd	[redacted]	[redacted]					
BVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

Abbreviations: BVd, belantamab mafodotin with bortezomib and dexamethasone KRd, carfilzomib plus lenalidomide and dexamethasone.

The EAG notes the magnitude of the BVd treatment benefit compared to BVd varies between [redacted] expected QALYs, when PH are explicitly assumed to hold. When applying independently fitted extrapolations and assuming a time varying treatment effect, the expected QALY gain varies between [redacted] and [redacted].

The EAG considers that, given the uncertainty associated with i) using an unanchored MAIC to inform the treatment effectiveness, ii) whether the MAIC can successfully adjust for the population differences between the ASPIRE and DREAMM-7 trials, and iii) the potential violation of the PH assumption (particularly for OS), the results of all the analyses in Table 7 are relevant to inform decision making but subject to considerable uncertainty.

4 REFERENCES

1. GlaxoSmithKline. *[Data on file]: Belantamab mafodotin with bortezomib and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6212] - Additional evidence for BVd versus KRd based on IA2-updated DREAMM-7 results*; 2025.

2. GlaxoSmithKline. *[Data on file]: ID6212 - Belantamab mafodotin with bortezomib and dexamethasone: Technical appendix, February*; 2025.

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