Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from GlaxoSmithKline**
   a. Technical appendix

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Myeloma UK
   b. UK Myeloma Society
   c. Menarini Stemline

3. **External Assessment Group critique of company comments on the Draft Guidance**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Thursday 17 July 2025**. 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):	GlaxoSmithKline Ltd
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:	Not applicable

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• 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.	
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	GSK does not receive funding from the tobacco industry
Name of commentator person completing form:	[redacted]

Comment number	**Comments**
Overview	GSK appreciates the opportunity to comment on the draft guidance document. The draft guidance decision not to recommend Blenrep® (belantamab mafodotin, 'belamaf') in combination with pomalidomide and dexamethasone (BPd) is disappointing as it prevents clinician and patient access to an efficacious treatment option in the 2L relapsed/refractory multiple myeloma (RRMM) lenalidomide unsuitable setting where there is considerable unmet need for new, more effective options with new mechanisms of action. In response to Committee's 'preferred assumptions' and requests (in 'areas needing clarification'), we provide an updated base case analysis that supports access to BPd for patients with 2L RRMM for whom lenalidomide is unsuitable. A technical appendix to this document provides further details of new analysis.
(i)	**Comments on draft guidance** On later lines of treatment GSK is seeking reimbursement at the 2L RRMM setting for patients for whom lenalidomide is not suitable. This has been the focus of our efforts to ensure rapid access for patients in the UK. The company is pursuing reimbursement in this setting for 3 key reasons: (1) As previously mentioned, there is a significant unmet need at 2L for lenalidomide unsuitable patients. This group has limited treatment options, and available data suggests poor corresponding outcomes. Therefore, there is an urgent need for more effective therapies with novel mechanisms of action at 2L;[1] (2) In myeloma, there is a well-established principle of utilizing the most effective therapy as early as possible, due to patient attrition across subsequent lines of therapy [2]; (3) All patients in the DREAMM-8 trial were lenalidomide exposed, with 81% being lenalidomide refractory. Therefore, a

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	lenalidomide unsuitable population would be the most clinically appropriate population for reimbursement consideration. In addition to these points the BPd combination offers several advantages that improve accessibility and reduces treatment burden for patients: • Convenient administration: Pomalidomide and dexamethasone are oral treatments that can be administered at home, while belamaf has a median dosing interval of 8.7 weeks [3], less frequent than every two months. Belamaf is administered via a short 30min infusion and does not require routine hospitalisation or post-infusion monitoring beyond standard clinical practice. This streamlined care reduces hospital visits and improves convenience for patients. • Introducing novel treatment in 2L: If approved, BPd combination will bring pomalidomide into the 2L setting which offers patients access to another effective class (immunomodulatory agents) in 2L, where the current options are proteasome inhibitor based (e.g. daratumumab in combination with **bortezomib** and dexamethasone (D**V**d), **carfilzomib** and dexamethasone (**K**d), **carfilzomib** in combination with lenalidomide and dexamethasone (**K**Rd), etc) [4]. • Flexibility and personalization: A unique feature of BPd is that, if approved, healthcare professionals (HCPs) will be able to combine belamaf with a backbone therapy of their choice. This clinical flexibility allows treatment to be tailored to individual patient needs, accounting for different side effect profiles and patient preferences. This synergy of backbone options ensures comprehensive care and improved outcomes for 2L patients with RRMM. GSK recognizes the unmet need in the third line (3L) setting and sincerely thanks the committee, clinical, and patient experts for their feedback on this matter. While our current focus is ensuring optimal outcomes in the 2L setting, we remain open to exploring options to address the 3L setting in the future. We are committed to ensuring patients receive the most effective treatments at the right time and welcome continued dialogue to meet the needs of all patients effectively.
(ii)	**Comments on draft guidance** On DREAMM-8 data The company wishes to address committee comments on the maturity of data from the DREAMM-8 trial. “The company explained that in DREAMM-8, the primary endpoint of median progression-free survival had been met only in the Pom-Bor-Dex group” (Section 3.7, page 19) • Since the appraisal committee meeting in January 2025, updated results published at the European Haematology Association (EHA) congress in June 2025 (median follow-up of 28 months) reported BPd mPFS as 32.6 months compared to 12.5 months for PVd (HR, 0.49; 95% CI, 0.35-0.68) [5]. • BPd continued to demonstrate statistically significant and clinically meaningful PFS benefit in patients with RRMM with ≥1 prior LOT. PFS benefit was maintained across key subgroups, including patients with high-risk cytogenetics and those with anti-CD38– and lenalidomide-refractory disease. The safety profile of BPd was manageable and consistent with the known safety profile of the individual agents. These data further support BPd as a

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	potential standard of care (SOC) option at first relapse to robust efficacy, manageable safety, and ease of administration. "The DREAMM-8 data, particularly for overall survival, was immature (see section 3.7)." (Section 3.6, page 15) • The company wishes to reiterate that the trial is event driven. [redacted]
(iii)	**Comments on draft guidance** The committee requested comment on whether the following technologies in the treatment pathway for multiple myeloma are still used in the NHS: On the RRMM treatment pathway **Bortezomib monotherapy for relapsed multiple myeloma (TA129)** • Bortezomib monotherapy was not included as a comparator in the final scope of this appraisal because clinical expert advice to the company suggested that this treatment is rarely used in clinical practice [6]. • Also worth noting that in ID6212 the EAG noted the following 'The EAG agreed, based on its own clinical advice, that bortezomib monotherapy is not a relevant comparator' [7] . **Bortezomib and thalidomide for the first-line treatment of multiple myeloma (TA228)** Based on the clinical feedback we have gathered, we would like to report the following: • Bortezomib and thalidomide under TA228 appears to be significantly diminished in the current NHS treatment landscape. For newly diagnosed transplant ineligible patients, the standard of care has shifted with the introduction on Revlimid (lenalidomide) and dexamethasone (Rd) in June 2019 that was widely adopted [8]. • This shift was further accelerated by the more recent introduction of Daratumumab in combination with Revlimid (lenalidomide), and Dexamethasone (DRd) on October 2023, which is emerging as the predominantly preferred regimen [9]. Clinical feedback indicates new adoption rates of DRd ranging from **70% to 85%** [10]. • It is worth noting that due to relative recent timing of 1L DRd access in the NHS, most patients on DRd remain progression-free at the time of writing, so the proportion who are daratumumab-refractory at first relapse is low. As selinexor in combination with bortezomib and dexamethasone (SVd) is approved for patients who are refractory to both lenalidomide and daratumumab, it may not be the most relevant comparator for this appraisal. **Lenalidomide plus dexamethasone for previously untreated multiple myeloma (TA587)** • Lenalidomide plus dexamethasone (Rd) is recommended by NICE as an option for previously untreated multiple myeloma in adults who are transplant ineligible [8]. • Clinician feedback indicates that DRd has emerged as the preferred regimen and SOC for transplant ineligible patients. While DRd is gaining popularity and is projected to be the dominant 1L regimen for this population, its impact on 2L daratumumab exposure will remain limited in the short term due to its extended median progression-free survival (mPFS). The MAIA trial demonstrated that DRd delivers an impressive mPFS of 61.9 months [11]. This means patients starting on DRd in 1L will remain on this regimen for ~5.2 years before progressing to 2L.

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	• Rd is a less relevant option in 1L treatment.
The committee's preferred assumption	

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1	**The committee's preferred assumption –** **To use the starting age based on the SACT data set (see Section 3.10 of NICE DG)** In the updated company base case, a baseline age of 70 years was used in line with the SACT source used to model daratumumab plus bortezomib and dexamethasone (DVd) overall survival (OS) (Lawton, 2024) [12]. This has been implemented in the model via a simple toggle included for the baseline age ('Settings' sheet, cell G20). The impact of including the baseline age change alone on the new base case is a small decrease to the cost-effectiveness of BPd versus comparators. Belamaf provides an OS advantage compared to DVd, selinexor plus bortezomib and dexamethasone (SVd) and carfilzomib plus dexamethasone (hKd), so the respective ICERs increase as the general mortality rate increases in the population.

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2	**The committee's preferred assumption –** for overall-survival benefit, to use the overall-survival data from SACT for Dar-Bor-Dex to estimate the absolute baseline curve, with the relative effects of the comparators applied from an updated network meta-analysis that addresses the methodological issues highlighted (in particular, the approach used for subsequent treatments; see sections 3.6 and 3.11 of NICE DG) A summary of the company's approach to an updated OS analysis is provided below. Full details are provided in the accompanying technical appendix. **Use of the adjusted OS HR from OPTIMISMM** The company maintains its position that using adjusted OS HR from the OPTIMISMM trial within the OS network of evidence remains an appropriate approach for evaluating relative OS benefits. This perspective is supported by the fact that 58.3% patients on the Vd arm received pomalidomide as subsequent treatment, introducing bias into the OS comparison between the treatment arms if unadjusted [13]. The high rates of unintended crossover dilute the observed OS benefit of PVd relative to Pd; therefore, an adjustment for subsequent treatment is necessary to account for this unintended crossover [14]. The company recently elicited advice from clinical experts to query these challenges and provide feedback on the company's base-case approach. The experts were supportive of the adjustment of OS, emphasising that true OS benefit of PVd over Vd may not be apparent due to confounding effects of crossover in OPTIMISMM [4]. The company is aligned to the committee's commitment to methodological transparency. However, the company do not own or have access to the detailed information regarding the adjustment method used in OPTIMISMM. To help mitigate this uncertainty in relative OS benefits between BPd and other comparators, the company have explored alternative methods. The committee noted their preference for scenario analyses using matching-adjusted indirect comparisons (MAIC) for all comparators (Section 3.11, page 25). However, a feasibility assessment was conducted and demonstrated that MAIC analyses are unlikely to resolve OS uncertainty due to a paucity of lenalidomide-exposed patient data in relevant trials. In recognition of the committee's preference for an updated network meta-analysis (NMA) that addresses the methodological limitations, the company proposes to adopt IPTW as an alternative method to link the DREAMM-8 trial to the broader network of evidence. *"For overall-survival benefit, to use the overall-survival data from SACT for Dar-Bor-Dex to estimate the absolute baseline curve, with the relative effects of the comparators applied from an updated network meta-analysis that addresses the methodological issues highlighted."* In response to the committee's request above, the IPTW methodology was implemented to estimate the relative OS benefit of BPd versus DVd, a key comparator and the current standard of care for the indicated patient population. This analysis utilized individual patient data (IPD) from the DVd arm from DREAMM-7 and BPd arm from DREAMM-8. Unified inclusion and exclusion criteria were applied to ensure a robust analysis population was reflective of UK clinical practice and suitable for comparing the two treatment arms. The IPTW approach has been recognised for its methodological strengths in NICE TSD 17 and 18, including its ability to provide symmetric adjustments across trial populations, thereby reducing selection bias and improving the reliability of comparative treatment effect estimates [15, 16]. The identified baseline prognostic factors were adjusted using propensity scores derived from the IPTW average treatment effect on the treated (ATT) method, ensuring balanced comparison between treatment arms. The results demonstrated statistically significant PFS (HR: 0.41 [0.25-0.65], p = 0.0002) benefit for BPd versus DVd. Although the OS data remains immature, the IPTW analysis demonstrated BPd

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	is associated with favourable OS ([redacted]) over DVd [17-19], demonstrating broad consistency with the OS analysis from the original NMA ([redacted]). In clinical expert validation, the rationale, methodology and results of the IPTW analysis were respectively deemed appropriate and plausible within the UK setting [4]. To further strengthen the evidence base and resolve perceived OS uncertainty, the IPTW was integrated into the 'ITT + len exposed' NMA from the original company submission. This approach connects BPd to DVd through IPTW, linking to the broader evidence network composed of 11 comparator studies. The fixed-effects model was utilized for the primary analysis, given the limited number of studies per link in the network. The results consistently demonstrated BPd OS benefit versus all relevant comparators with hazard ratios below 1: hKd (HR: [redacted]) and SVd ([redacted]). Again, these results demonstrated broad consistency with the OS analysis from the original NMA: hKd (HR: [redacted]) and SVd ([redacted]). Validation from statistical experts confirmed the methodological robustness of this approach, providing confidence in the results elicited. Moreover, this approach has precedence in NICE decision-making, as demonstrated in TA1015, where IPTW-integrated NMA was deemed appropriate for evaluating treatments within the RRMM landscape [20]. In response to the committee's request to anchor RCT data to UK clinical practice using RWE, SACT data for DVd was incorporated to estimate the absolute baseline curve for OS. Following a similar approach used in ID6212 evaluating belantamab mafodotin in combination with bortezomib and dexamethasone (BVd), a KM curve for OS was digitised from an appropriate SACT publication ([Lawton, 2024] a retrospective analysis of 2L lenalidomide exposed patients receiving DVd) and clinically validated against IPTW-derived DVd OS curve, demonstrating good agreement between IPTW-derived results and UK clinical practice [12]. Pseudo-individual patient data (IPD) was reconstructed, and parametric survival models were fitted to the SACT data, with the Weibull distribution selected as the base case on the account of internal and external validity. The relative effect of BPd versus DVd derived from IPTW analysis was applied to SACT DVd baseline as a HR to adjust OS accordingly, the resulting BPd OS curve was validated by external clinical experts to be plausible within a UK setting, and even a conservative estimate for the OS benefit of BPd [4]. The findings show that implementing SACT data improves the cost-effectiveness estimates for BPd, by both improving incremental costs and incremental QALYs, in favour of BPd in comparisons against all comparators (DVd, SVd, Kd).

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3	**The committee's preferred assumption –** to model a maximum dose interruption interval of 6 months for belantamab mafodotin (see section 3.12 of NICE DG) GSK acknowledges the committee's stance on permitting a 6-month treatment-interruption break for eye-related adverse events associated with BPd. However, GSK respectfully disagrees with the proposed 6-month cap for treatment breaks, based on the following considerations: **Clinical evidence from DREAMM-8 trial:** [redacted] of patients in the BPd arm experienced dose holds of ≥ 6 months (≥ 24 weeks). Despite the limited sample size, corresponding PFS data suggests that PFS outcomes for this group were not negatively impacted when compared to the data from the ITT population: [redacted] [redacted] **Impact on Patient Equity**: If affixed 6-month treatment breaks were implemented this could unfairly penalize [redacted] of patients who are still benefiting from therapy despite a prolonged break. This approach risks excluding patients who might otherwise continue to achieve disease control and improve outcomes, which is not equitable. Given the potentially necessary frequency and duration of treatment breaks during therapy with belamaf, the company requests that BPd be exempt from any treatment break policy. In cases where disease progression occurs during a treatment break from belamaf, therapy should be discontinued. This proposed criteria for use aligns with published blueteq criteria for belantamab mafodotin in combination with bortezomib and dexamethasone (BVd) from NHS England [23].

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4	**The committee's preferred assumption –** to use the acquisition cost of pomalidomide from the Medicines Procurement and Supply Chain framework (see section 3.13 of NICE DG) GSK welcomes the use of the confidential acquisition cost of pomalidomide from the Medicines Procurement and Supply Chain framework. In our updated base case, we have maintained the assumed price of generic pomalidomide from the original company submission in August 2024 and remain confident that this closely resembles the cost paid by the NHS.

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5	**The committee's preferred assumption –** to include the cost of monitoring eye-related adverse events using hospital-based ophthalmology services (see section 3.16 of NICE DG) GSK acknowledges the committee's request to include the cost of monitoring eye-related adverse events using hospital-based ophthalmology services in the base-case analysis. However, GSK does not believe this approach accurately reflects the costs that will be incurred in real-world practice, where most of the eye monitoring is expected to take place in the community. **Split between community and hospital eye care monitoring** GSK conducted an advisory board to understand the eye care pathway for patients on belamaf. The advisory board included consultant haematologists, consultant ophthalmologists and optometrist with direct experience in managing patients on belamaf. Feedback received was very clear: **community-based optometrists are fully capable of conducting eye assessments** (including visual acuity and slit lamp examinations) for patients on belamaf. This means that the vast majority of patients can have their eye examinations and management of side effects handled entirely within the community optometrist setting. This approach not only reflects clinical feasibility but also aligns with current NHS priorities, such as keeping patients closer to home/in the community [24, 25]. [redacted] Recognising the challenges of care coordination between secondary haematology and primary eyecare, as well as the potential cost burden on NHS services, GSK has developed the [redacted] [redacted] **Details of modelling** There is significant interest from various NHS trusts in adopting [redacted]. However, GSK has conservatively modelled an 80% community, and 20% hospital split for eye care costs, [redacted]

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	[redacted] while accurately reflecting real-world practice. The updated base case assumes [redacted] eye examinations per patient, based on DREAMM-8's January 2024 data cut-off: [redacted]. • **Median dosing interval:** 8.7 weeks (1 dose every 60.9 days) [See belamaf SmPC Table 12] [3]. This translates to [redacted] **÷ Dosing Interval (1 dose/60.9 days)** [redacted] Eye examinations are assumed to occur before every belamaf dose (i.e. number of eye examinations = number of belamaf doses). Therefore, each patient is expected to undergo 4 SmPC-mandated eye examinations followed by an [redacted] eye tests as clinically indicated. This assumption is conservative and may overestimate costs for several reasons. First, not all patients will require additional eye examinations beyond the first four SmPC-mandated ones. Second, feedback from haematologists and eye care professionals (ECP) suggests that while eye visits will initially be scheduled before every dose, this frequency is likely to decline over time as the haemato-oncology and ECP community gains confidence in managing eye-related side effects [25]. Lastly, individual patient data (IPD) trends show that dosing intervals lengthen as patients remain on treatment longer, and so accounting for these trends is likely to reduce the number of required eye examinations below the median value used from the SmPC. In summary, GSK has modelled the cost of eye monitoring for belantamab mafodotin patients using an 80% community and 20% hospital split, reflecting real-world practice where community optometrists will handle most routine eye care, [redacted] The model assumes [redacted], based on DREAMM-8 data, including 4 SmPC-mandated tests and [redacted] as clinically indicated. This conservative modelling accounts for variability in NHS trust participation [redacted] and may overestimate costs, as dosing intervals lengthen and the frequency of eye visits declines with growing clinician confidence in managing eye related side effects.

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6	**The committee's preferred assumption –** to assume no vial sharing (see section 3.17 of NICE DG) In alignment with the committee's conclusion, the company maintains its original base case setting of no vial sharing, given the lack of information on its extent in clinical practice.
7	**The committee's preferred assumption –** to exclude wastage of tablets (see section 3.17 of NICE DG) In the updated base case, the company has aligned to committee preference to exclude wastage of tablets. In its original base case, the company took a conservative approach in assuming there may be some wastage of tablets (i.e. forgetting to take medication, patients losing blister packets, tablets remaining after treatment stoppage, etc.). However, the company recognises that these situations are not guaranteed and aligns with the EAG, agreeing that tablet wastage is plausibly avoidable and can be excluded from the model. The company wishes to note that there was an error in the EAG implementation of excluding wastage for tablets which has been corrected in the updated model. "In its base case, the EAG considered that wastage of tablets (pomalidomide, selinexor and dexamethasone) should be excluded" (Section 3.17); however, in including wastage for tablets, the EAG had incorrectly assumed no wastage for bortezomib vials also. Full details are provided in the model change log.

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8

The committee's preferred assumption –
to apply the EAG's approach that used the same utilities derived from a wholly second line population, regardless of treatment (see section 3.18 of NICE DG).

The EAG's approach "preferred to use the company's scenario that applied utility values from one of the comparators, Dar-Bor-Dex (see TA897)" (Section 3.18, page 31). The draft guidance includes no mention of where TA897 utilities are derived from – the ENDEAVOR trial (Carfilzomib and dexamethasone [hKd] versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma).

The known gold standard approach is to use generic validated instruments directly included within the clinical trial (such as the EQ-5D-3L included in DREAMM-8), as outlined in the NICE methods [27], to minimise the ambiguity of outcomes included in the economic model. Not only are the ENDEAVOR trial utilities drawn from a separate trial, but in addition, no EQ-5D data was directly elicited (and a mapping algorithm was used instead) [28]. This indirect approach introduces additional uncertainty and may compromise the accuracy of the utility values. The methodology employed in ENDEAVOR therefore carries a high risk of underestimating utility values for the patient population included, potentially leading to a less reliable representation of health outcomes.

To align to the committee's request, the company's updated base case includes a baseline utility of [redacted] applied for the PFS state, independent of treatment and elicited directly from the DREAMM-8 trial (PFS on-treatment utility) [21]. For the progressed disease (PD) state, the meta-regression study from Hatswell et al. (2019) [29], was used to elicit a decrement to apply to PFS. This has been implemented in the model by including a switch to adjust the PD utility source ('Quality of Life' sheet, Cell D12). It is important to note that comparisons using an external source may be useful to ensure that the utilities from DREAMM-8 are robust, and clinically plausible given the drop in utility expected across subsequent treatment lines.

In alignment with the approach accepted by Committee in ID6212, the updated company base case uses Hatswell et al., (2019) [7][29], utility meta-analysis to estimate an alternative value for the utility decrement between the PFS and PD health state for all treatments under comparison in the company's cost-effectiveness analysis. In summary, this calculation took an average of the health state utility across lines of treatments from the meta-analysis (3L, 4L and 5L), including a weighting since less patients would be in each subsequent treatment line for less time (due to attrition). The company assumed that the utility decrement associated with disease progression would be equal to the difference between the 2L health state utility and the estimated average health state utility for 3L+.

The updated utility values used in the updated model base case are presented in Table 2.

Table 2: Progression-free and progressed disease treatment independent health state utilities used in the updated model base case

Health state	Utility	Source
PFS (on-treatment/off-treatment)* - DREAMM-8	[redacted]	DREAMM-8 [21]
PD - Hatswell et al.	[redacted]	DREAMM-8 [21] Hatswell et al. 2019 [29]

Notes: *PFS off-treatment utility values are assumed to be the same as on-treatment.
Abbreviations: DREAMM, DRiving Excellence in Approaches to Multiple Myeloma; PD, Progressed disease; PFS, progression-free survival

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9	**Areas needing clarification-** the adjustment method undertaken in OPTIMISMM and where relevant, approaches to subsequent treatment for all other trials in the network (see section 3.6 of NICE DG) In the original company submission, unintended crossover in the OPTIMISMM trial (PVd vs Vd) was accounted for in the 'ITT + len-exposed' network of evidence using an adjusted OS HR derived from a preplanned OS analysis [13, 14, 30]. In this original network, the OPTIMSIMM trial is a point of direct relevance as it provides the sole link from the DREAMM-8 trial to the rest of the network to inform relative effects versus all relevant comparators in this appraisal. Utilising this preplanned OS analysis using a Cox proportional hazard model with subsequent therapy as a time-dependent covariate and adjusting for stratification factors (including age, number of prior antimyeloma regimens and β2-microglobulin) produces a more accurate estimate of the relative effect of PVd vs Vd [30]. The company is aligned to the committee's commitment to methodological transparency. However, GSK do not own or have access to the detailed information regarding the adjustment method used in this analysis. To resolve the uncertainty in relative OS benefits between BPd and other comparators, the company has explored other methods (as described in Comment 2) including an IPTW analysis and its integration into the company's originally proposed network of evidence.

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10

Areas needing clarification-
the evidence of clinical effectiveness of Bel-Pom-Dex in the company's target second-line population (see section 3.7 of NICE DG)

The most appropriate available evidence that closely characterises the company's target population of 2L lenalidomide unsuitable patients is the 2L lenalidomide refractory subgroup from the DREAMM-8 trial.

The clinical effectiveness of patients in this population has been demonstrated through robust evidence from subgroup analyses. These findings were presented at the 66th ASH Annual Meeting (December 2024) and provide strong support for the use of BPd in this challenging patient population.

Below, is a summary of the key clinical efficacy outcomes for the target 2L population:

Table 3: key clinical efficacy outcomes (DREAMM-8 subgroup analysis) [31]

mPFS		
	ITT	**2L lenalidomide refractory subgroup**
BPd	NR (20.6 – NR)	NR (21.1–NR)
PVd	12.7 (9.1 – 18.5)	13.1 (9.1–19.8)
HR	0.52 (0.37,0.73)	0.43 (0.25,0.75)
mOS		
	ITT	**2L lenalidomide refractory subgroup**
BPd	NR (33.0 – NR)	NR (NR–NR)
PVd	NR (25.2 – NR)	NR (22.2 – NR)
HR	0.77 (0.51, 1.14)	0.72 (0.37 – 1.41)

Abbreviation: BPd – belamaf in combination with pomalidomide and dexamethasone; HR, Hazard Ratio; ITT, Intent-to-Treat; mOS, Median Overall Survival; mPFS, Median Progression-Free Survival;; PVd – pomalidomide in combination with bortezomib and dexamethasone [31]

The 2L and Lenalidomide refractory population, which closely aligns with the company's target population, demonstrated clinical outcomes consistent with the ITT population. BPd offers a robust progression-free survival benefit and promising overall survival trends, reinforcing its clinical effectiveness and suitability for use in this challenging patient group.

For full PFS and OS Kaplan-Meier curves of 2L lenalidomide refractory subgroup, please refer to Figure 1 and 2:

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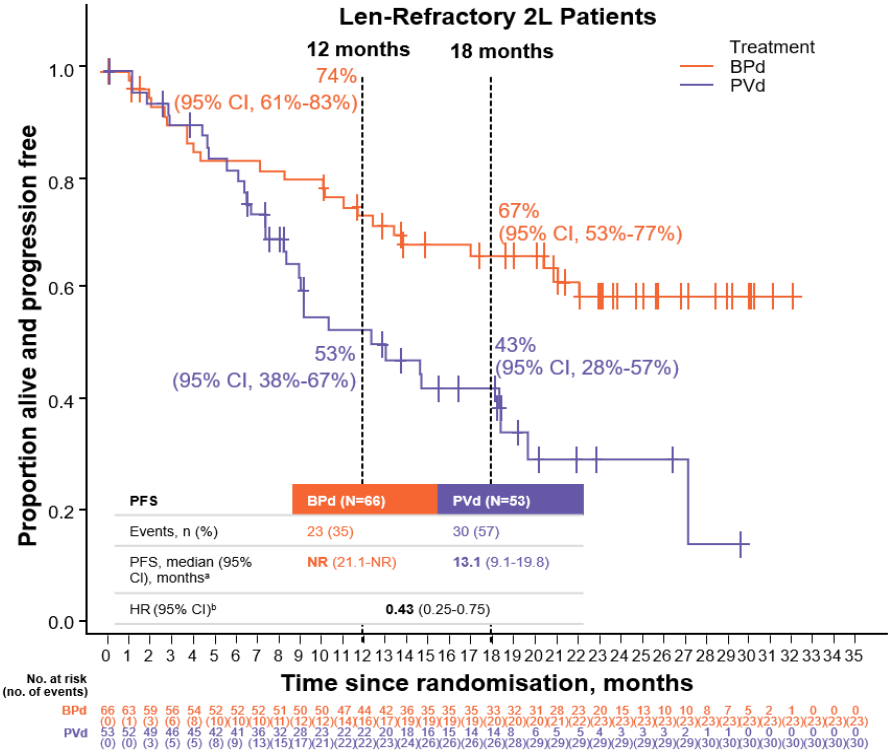
Figure 1: PFS in patients who are lenalidomide refractory in 2L only



Abbreviations: BPd, Belamaf in combination with Pomalidomide and Dexamethasone; HR, Hazard Ratio; Len, Lenalidomide; PFS, Progression-Free Survival; PVd, Pomalidomide in combination with Bortezomib and Dexamethasone [31].

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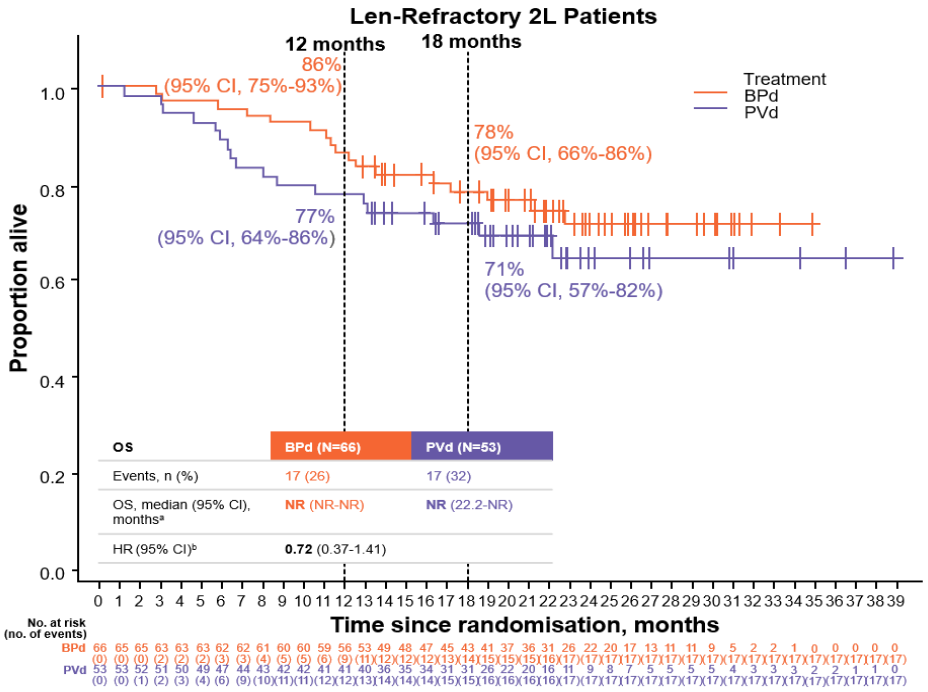
	Figure 2: OS in patients who are lenalidomide refractory in 2L only  Abbreviations: BPd, Belamaf in combination with Pomalidomide and Dexamethasone; HR, Hazard Ratio; OS, Overall Survival; PVd, Pomalidomide in combination with Bortezomib and Dexamethasone [31].

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11

Areas needing clarification-
the impact of dose modifications (reductions, delays or interruptions because of eye-related adverse events) of belantamab mafodotin on its clinical effectiveness (see sections 3.7 and 3.8 of NICE DG)

The DREAMM-8 study demonstrates that frequent dose modifications of BPd do not negatively impact clinical effectiveness.

Eye related adverse events necessitated frequent dose reductions, delays and interruptions, with 99% of BPd group experiencing at least one dose delay lasting a median of 53 days. Furthermore, 74% of patients required 3 or more dose delays, and 70% had dose reductions from once every four weeks (Q4W) to once every eight weeks (Q8W) [32]. [Note: Full details on belamaf dose exposure in DREAMM-8 is available in the SmPC Section 5.1 Table 12] [3].

Despite the high frequency of dose modifications in the DREAMM-8 trial, belamaf demonstrated consistent efficacy.

- Before patients' first dose delay, 87% of patients achieved a response (≥ PR).
- Among those who had not yet achieved a response (≤ PR) prior to the first dose delay:
  - 92% went on to achieve a best response of partial response or better (≥ PR), and
  - 73% went on to achieve a very good partial response (≥ VGPR) or better.
- Patients already achieving ≥ VGPR before the delay maintained or improved their responses, with 98% sustaining or deepening their responses during or following the delay.

These findings are summarized in Table 4:

Table 4: (Post hoc analysis) Summary of best response before and during/after first belamaf dose delay of ≥2 cycles[a]

Best response before first dose delay of >8 weeks (n =83)		**Best response during/after first dose delay of > 8 weeks**	
Response	**n (%)**	**Response**	**N(%)**
≤ PR [b]	37 (45)	≥ VGPR	27 (73)
		≥ PR	34 (92)
≥ VGPR	46 (55)	CR/sCR	36 (78)
		≥ VGPR	45 (98)

Abbreviations: CR – complete response; PR – partial response; sCR – stringent complete response; VGPR – very good partial response. [a] Dose delays are derived when the time between belamaf dose administration or the time from last dose to death, decision to discontinue treatment, treatment discontinuation date, start of new antimyeloma therapy, or last contact date is >31 days. [b] Includes 3 patients who had non-evaluable response [32]

Additionally, as discussed in detail in Comment 3 and Comment 14 in this document, PFS remained consistent with the ITT population even for patients who experienced extended dose delays (≥8 weeks, ≥12 weeks and ≥24 weeks). To facilitate easy comparison, a summary table has been provided in Table 5.

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	[redacted]
	These findings affirm that belamaf delivers durable clinical benefits, even with frequent dose modifications/delays.

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12	**Areas needing clarification-** the company's statement that it is exploring the option of supporting people with access to community-based ophthalmology at the point of recommendation (see section 3.16 of NICE DG). Recognising the challenges of care coordination between secondary haematology and primary eyecare, as well as the potential cost burden on NHS services, GSK has developed the [redacted] [redacted] For full details on the rationale, methodology, and cost modelling assumptions, please refer to Comment 5 in this document.

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13

Areas needing clarification-
network meta-analyses using data specific to the company's target second-line population (see section 3.7 in NICE DG)

Due to the paucity of data in the public domain that characterises the 2L lenalidomide unsuitable population the requested NMA is not feasible.

In the original submission, the company explained that the use of the ITT population from the DREAMM-8 trial is the most suitable approach for the current appraisal, as it ensures the inclusion of a large population (i.e., ~81% patients in the DREAMM-8 trial are lenalidomide refractory) and it is aligned with the populations of the other comparator studies that were included to conduct the NMA (CS Document B, Section B.2.9.3).

The lenalidomide refractory and 2L only subgroups are associated with a high degree of uncertainty as there is limited data available from the literature for indirect treatment comparisons (Table 6). No eligible studies of the three relevant comparators (DVd, SVd and hKd) reported PFS or OS outcomes for the '2L only' subgroup or OS outcomes for 'lenalidomide refractory' subgroup. Outcomes for lenalidomide-exposed patients were adequately reported; however, a key outcome of OS was not available for DVd or SVd.

Therefore, with limited information available for lenalidomide-refractory and/or 2L population, the ITT population from the DREAMM-8 trial and only the lenalidomide-exposed populations from the comparator studies were used for conducting the primary analysis (Table 6). Since primary analysis was not sufficient to populate all inputs for the economic model, a secondary NMA analysis of a 'lenalidomide-exposed + ITT population' was also conducted.

In summary, the NMA hazard ratios (HRs) for PFS and OS that were used as inputs in the economic model for hKd were sourced from the analysis of the lenalidomide-exposed population (primary analysis). The PFS HR inputs for DVd and SVd were based on the analysis on the lenalidomide-exposed population (primary analysis), whereas the OS HRs were derived from the lenalidomide-exposed plus ITT population (secondary analysis).

Table 6: Overview of possible comparisons in the NMA for PFS and OS for BPd versus relevant comparators of interest

Outcome and population	BPd vs DVd	BPd vs SVd	BPd vs hKd
PFS: Len-exposed	✓	✓	✓
OS: Len-exposed	X	X	✓
PFS: Len-refractory	✓	X	✓
OS: Len-refractory	X	X	X
PFS: 2L	X	X	X
OS: 2L	X	X	X

Notes: ✓: Comparison possible in the NMA for this population; X: Comparison not available for this specific population in the NMA
Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib, and dexamethasone; hKd, high dose carfilzomib and dexamethasone; Len, Lenalidomide; OS, overall survival; PFS, progression-free survival; SVd, selinexor plus bortezomib, and dexamethasone

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14	**Areas needing clarification-** analyses including Kaplan–Meier plots comparing progression-free survival in people having Bel-Pom-Dex treatment at 8 and 12 weekly intervals, to assess the impact of dose interruptions (see section 3.8 in NICE DG) Dose modifications in DREAMM-8 were effective in managing eye related side effects (ERSE) by tailoring the dosing schedule (dose reduction and dose hold) to individual patient tolerability, allowing patients to remain on treatment and benefit from its efficacy. Notably, 91% of patients remained on treatment by dose modifying belamaf, with only 9% discontinuing due to ERSEs [3]. Due to the nature of dose delays, which is primarily side-effect driven, and the fact that period of delays is not always consistent when they occur more than once, we have presented Kaplan–Meier analyses for patients who experienced at least one dose delay of ≥8 weeks and at least one dose delay of ≥12 weeks. This approach ensures consistency in evaluating the impact of dose interruptions. The analyses included patients with a minimum of 6 months of treatment, categorized as follows [33]: [redacted] [redacted] Abbreviations: PomDex, Pomalidomide and Dexamethasone [33] [redacted]

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	 Abbreviations: PomDex, Pomalidomide and Dexamethasone [33] The median progression-free survival (mPFS) for patients experiencing dose delays of ≥8 weeks and ≥12 weeks remains not reached (NR), closely mirroring the mPFS observed in the ITT population [NR (20.6 – NR)]. These findings indicate that extended dose interruptions or delays do not have adverse impact on PFS outcomes for patients on BPd treatment, highlighting the regimen's effectiveness despite treatment modifications.

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15	**Areas needing clarification-** a base-case analysis using overall-survival data from SACT for Dar-Bor-Dex to estimate the absolute baseline curve, with the relative effects of the comparators applied from an updated network meta-analysis that addresses the methodological issues highlighted; in particular, the approach used for subsequent treatments (see sections 3.6 and 3.11 of NICE DG) Please refer to Comment 2 for preferred assumptions
16	**Areas needing clarification-** a scenario analysis using the unadjusted overall-survival HR of 0.94 from OPTIMISMM in the network meta-analysis (see sections 3.6 and 3.11 of NICE DG) The company maintains its position that using adjusted OS HR from the OPTIMISMM trial within the OS network of evidence remains a highly appropriate approach for evaluating relative OS benefits. This perspective is supported by the fact that 58.3% patients on the Vd arm received pomalidomide as subsequent treatment, introducing bias into the OS comparison between the treatment arms if unadjusted [13]. The high rates of unintended crossover dilute the observed OS benefit of PVd relative to Pd, therefore an adjustment for subsequent treatment is necessary to account for this unintended crossover [14]. A clinical expert validated this approach, emphasising that true OS benefit of PVd over Vd may not be apparent due to confounding effects of crossover in OPTIMISMM [4]. To resolve the uncertainty in relative OS benefit between BPd and other comparators, the company have explored other methods (as described in Comment 2), including an IPTW analysis and its integration into the company's originally proposed network of evidence.

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17	**Areas needing clarification-** a scenario analysis in which all available IPD is used to estimate medication use and costs for all treatments (see section 3.14 of NICE DG) The company agrees that if IPD was available for all comparators, this would be supportive in reinforcing the cost-effectiveness results presented in the company base-case regarding treatment cost. However, IPD dosage is often scarcely reported, and mean or median RDI commonly reported in its place. This creates a challenge, as belamaf costs are vastly overestimated when using mean RDI dosage (as pointed out within the draft guidance; treatment costs increased significantly above what is seen in the trial). This is due to the crucial time varying factors of dose delays and dose reductions, which when accounted for using IPD, heavily impacts belamaf costs both within and beyond the trial period. A key criticism is that using mean RDI for comparators poses issues, given the discrepancy in approach versus IPD for belamaf which may lead to uncertain relative comparisons between treatments. To address this concern the company has shared additional evidence to reassure the committee of the following; 1. Belamaf treatment is unique, in that dose reductions and dose delays are an expected and common practice, as outlined in the SmPC [3], and there is precedence of alternative methodology of dosing between comparators being accepted by NICE 2. Time varying trends do not impact comparator dosing, for patients on treatment, and therefore mean RDI is an appropriate method to accurately depict treatment costs **1. Belamaf treatment is unique** Within NICE ID6212 Draft Guidance [35] for belamaf treatment within a different combination, BVd, there is strong alignment between the company, clinicians, the NICE EAG, and the NICE committee in that belamaf dosing is unique compared to comparators and requires a unique method of approach to account for dose reductions and dose delays. The EAG noted; *"it is likely that RDI is appropriate to model the dosing of daratumumab and individual patient data would have a small impact on the cost-effectiveness result."* In addition, the committee agreed that; *"using individual patient data from DREAMM-7 to inform dosing of belantamab mafodotin and RDI to inform dosing for other comparators may be appropriate. But it noted the uncertainty of using different metrics to inform dosing for belantamab mafodotin and its comparators."* Given the consistency of comparators across ID6212 and this submission, this statement highlights that differential methods of dosing represent a reasonable amount of uncertainty within the submission. The uncertainty aspect is investigated in the section below. **2. Time varying trends do not impact comparator dosing** In line with the suggestion of the committee, the company have analysed the available IPD the company has access to, in order to reassure the committee as to the accuracy of using RDI to calculate comparator treatment costs. Pomalidomide Within DREAMM-8, PVd was available as a comparator. While PVd is out of scope for inclusion as a comparator, the IPD for pomalidomide dosing within DREAMM-8 is a useful source to substantiate the lack of time varying trends identified for treatment alternatives (even if PVd is not available in the UK).

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xxxxxx 5 illustrates the average dose over time for pomalidomide (PVd), summarised to Q3W for illustrative purposes (in line with the cycle length of PVd treatment within the DREAMM-8 protocol). A similar extrapolation to belamaf IPD is applied here, after data is only available for less than 50 patients on treatment. This approach takes an average dose for all remaining IPD data carried forward (further detail is available within CS Document B, Section B.3.5.1.3). This figure is overlaid with the average dose from the mean RDI approach (14 doses received per cycle* 4mg per dose admin * mean RDI of pomalidomide). Importantly, there is both strong alignment to the mean RDI approach, and no time varying trends identified given the curve remains flat for the duration of where the bulk of the available data lies.

[redacted]

Abbreviations: mg, miligrams; Q3W, Three week cycle length; kg, kilograms; RDI, relative dose intensity; PVd, Pomalidomide in combination with bortezomib and dexamethasone.
Source: DREAMM-8. (2025). Data on file [36].

Daratumumab

Incorporating the IPD data for daratumumab in the model was not possible due to time constraints. However, a similar curve was constructed to identify any key time varying trends for daratumumab dosage occurring across the available data for patients on treatment. Figure 6[redacted] below outlines the average dose, summarised for illustrative purposes to the differing cycle lengths of daratumumab from the DREAMM-7 protocol (Q3W, weekly - cycles 1-3, Q3W, once per cycle – cycles 4-8, Q4W, once per cycle – cycles 9+). Similarly to the analysis of Pomalidomide (PVd) shown in xxxxxx , the extrapolated average dose of daratumumab was explored. In addition, the mean RDI approach was overlaid to compare between these methods (16mg/kg dose * mean RDI).

Similar to the analysis of Pomalidomide (PVd) (xxxxxx), there is no clear time varying trends of dosage identified for patients on treatment receiving daratumumab. In addition, given the increase in dose for patients at the tail end of the available daratumumab IPD, the mean RDI approach is estimated to be conservative and underestimate daratumumab costs for patients remaining on treatment over the long run.

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	[redacted] [redacted] Abbreviations: mg, miligrams; kg, kilograms; RDI, relative dose intensity; DVd, Daratumumab in combination with bortezomib and dexamethasone. Source: DREAMM-7. (2025). Data on file [37]. In conclusion, the company acknowledges that using different metrics to inform dosing creates uncertainty. However, it should be emphasized that, given 1), there is agreement that other methods than the IPD approach heavily biases the cost-effectiveness analysis in favour of comparators and that IPD is a valid approach to mitigate this issue. Secondly, given 2), evidence suggests uncertainty regarding RDI versus IPD approach for comparators is limited in terms of how this would impact cost-effectiveness. Together, these findings provide reassurance that it is reasonable to estimate belamaf costs with IPD, and all other treatment costs with mean RDI. Using the IPD approach with comparators, if it were feasible, is unlikely to have a significant impact on cost-effectiveness, and therefore decision making.

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18	**Areas needing clarification-** a scenario analysis in which SACT data is used to inform the modelling of subsequent treatments (see section 3.15 of NICE DG) The company was not able to identify appropriate SACT data to fulfil this committee request for scenario analysis. However, in two clinical validation meetings undertaken in June and July 2025 the company elicited clinical expert opinion on proportion of patients receiving subsequent therapy at each line of the RRMM pathway. There was alignment from clinicians that there would be approximately 75% and 50% of patients receiving treatment at 3L and 4L respectively [4]. A scenario to reflect these proportions has been included in the updated model ('Cost inputs' sheet, cell D236.
19	**Areas needing clarification-** scenario analyses in which teclistamab is included as a fourth-line option for subsequent treatments (see section 3.15 of NICE DG) GSK notes that it is not strictly appropriate for the Committee to request this information given comparators for each line of therapy were specified at the time of scoping, and teclistamab was not listed amongst them. Nevertheless, GSK has provided the requested information. Teclistamab has been included as a treatment option in the fourth-line subsequent treatment. This has been implemented in the model via a toggle ('Cost Inputs' sheet, cell D249). The clinically validated assumption is that teclistamab will become the new standard of care at fourth-line assuming a 40% market share in the first subsequent treatment (given the potential for line-skipping from second line to fourth line, which can occur in clinical practice) and displacing all other subsequent treatments which are reweighted accordingly [4]. The impact of including the teclistamab change alone on the submission base case is a minor improvement to the cost-effectiveness of BPd against all comparators. GSK notes that teclistamab has a confidential PAS discount price which obscures the magnitude of this benefit. Nevertheless, given the only driver of incremental costs of subsequent treatment is delaying transition to subsequent treatment through PFS, and teclistamab is likely to be more expensive than the previous subsequent therapies it will displace, the conclusion that this change will lower the overall cost of BPd relative to comparators is likely to hold.
20	**Areas needing clarification-** a base-case analysis that includes the cost of monitoring eye-related adverse events using hospital-based ophthalmology services (see section 3.16 of NICE DG) The company has modelled an 80% community and 20% hospital split for eye care costs as this is assumed to reflect real-world practice, where most eye monitoring for patients on belamaf is expected to occur in community optometry settings. This approach aligns with NHS priorities to deliver care closer to home while effectively managing eye-related adverse events**.** For full details on the rationale, methodology, and cost modelling assumptions, please refer to Comment 5.

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21	**Areas needing clarification-** a scenario analysis in which the cost of monitoring eye-related adverse events is provided using the community-based ophthalmology services as proposed by the company (see section 3.16 of NICE DG) The company has modelled community-based eye examinations as requested. This was modelled as 80% community and 20% hospital split for eye care costs because it reflects real-world practice, where most eye monitoring for patients on belamaf is expected to occur in community optometry settings. This approach aligns with NHS priorities to deliver care closer to home while effectively managing eye-related adverse events. GSK has accounted for community-based eye examinations that is supported by the fully [redacted] For full details on the rationale, methodology, and cost modelling assumptions, please refer to Comment 5.

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22

Areas needing clarification-
a scenario analysis in which the disutility of eye-related adverse events is applied (see section 3.19 of NICE DG).

As described in the company submission, GSK believe it is inappropriate to add disutility for eye-related AEs in addition to reported utility scores from the trial. This is because eye-related AEs were common in the DREAMM-8 trial but were effectively managed through dose delays and modifications. As a result, the impact of these AEs will have been captured by conventional patient-reported outcome measures. Notably, in DREAMM-8, 91% (136/150) of patients did not discontinue treatment due to eye-related side effects [21]. Furthermore, committee also noted that "Based on feedback from the patient expert, the committee considered that the EQ-5D-3L in DREAMM-8 would have likely captured the impact of eye-related adverse events on health-related quality of life, given the frequency of assessments" (page 33).
In response to committee's request, GSK have included eye-related AE disutility in a scenario analysis. The updated model includes a setting in which the source of the disutility for ocular AEs is based on the disutility used in NICE TA369 [38], and the median time to resolution of first event to baseline (Bilateral worsening of BCVA, 20/50 or worse) from the SmPC [3]. Table 7 provides a summary of the inputs applied to the updated model for ocular AEs based on the NICE TA369 disutility values.

Table 7: Disutility inputs for ocular adverse events[a]

Ocular AEs	Disutility (QALYs)	One-off probability that patients receiving BPd will experience Ocular AE	Live expected disutility
Keratopathy (Grade 3+)	0.03	[redacted]	[redacted]
Blurred vision (Grade 3+)	0.03	[redacted]	[redacted]
Dry eyes (Grade 3)	0.03	[redacted]	[redacted]
Total:			[redacted]

Abbreviations: AE, Adverse Event; BPd, Belamaf plus Pomalidomide and Dexamethasone; QALY, Quality-Adjusted Life Year [a] Source of ocular AE disutilities: TA369 [38]

The inclusion of these disutilities results in a negligible impact on overall QALY for the BPd arm, amounting to [redacted]. It is important to note that some degree of double counting may occur, as the EQ-5D elicitation may already account for these effects.

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Factual inaccuracies

The company wish to clarify factual inaccuracies made in the draft guidance.

Description of problem	Description of proposed amendment	Justification for amendment
Section 2.1, page 5 'Belantamab mafodotin (**BlenRep**, GlaxoSmithKline)'	'Belantamab mafodotin (Blenrep, GlaxoSmithKline)'	Product brand name incorrect
Section 3.3, page 9 'most people would have a daratumumab-containing regimen at first line, which is…'	'most **newly diagnosed** people would have a daratumumab-containing regimen at first line, which is…'	Currently, the majority of NHS patients entering second-line (2L) treatment for multiple myeloma (MM) remain daratumumab-naïve. This observation holds true across both transplant ineligible and transplant-eligible populations. Among 1L transplant-ineligible patients, the majority continue to receive regimens that were approved prior to the introduction of daratumumab in combination with lenalidomide and dexamethasone (DRd) in October 2023 [9]. While DRd is projected to be the dominant 1L regimen for this population, its impact on 2L daratumumab exposure will remain limited in the short term due to its extended median progression-free survival (mPFS). The MAIA trial demonstrated that DRd delivers an mPFS of 61.9 months [11]. This means patient starting on DRd in 1L will remain on this regimen for ~5.2years before progressing to 2L. Recognizing the evolving landscape of 2L MM, it is worth noting that approximately ¼ of DREAMM-8 patients were daratumumab-exposed, and all were lenalidomide-exposed, reflecting the anticipated patient profile as daratumumab-based regimen gain traction in 1L and progress into the 2L.
Section 3.5, page 14	The company would suggest reconfirming with the clinical expert	

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"In terms of generalisability of the results, the clinical experts mainly had concerns about the lower proportion having had daratumumab in DREAMM-8 compared with about 50% who would have it in the NHS."	on % of exposure, the '50%' quoted does not align with the clinical expert's comment during the ACM.	
Section 1, page 4 'Indirect comparisons suggest that belantamab mafodotin plus pomalidomide and dexamethasone increases how long people have before their condition gets worse compared with: • carfilzomib plus dexamethasone • selinexor plus bortezomib and dexamethasone. They do not show that it increases how long people live compared with usual treatment.'	'Indirect comparisons suggest that belantamab mafodotin plus pomalidomide and dexamethasone increases how long people have before their condition gets worse compared with: • carfilzomib plus dexamethasone • **daratumumab plus bortezomib and dexamethasone** • selinexor plus bortezomib and dexamethasone. **They also show it** increases how long people live compared with these treatments.'	Indirect treatment comparisons presented in the original company submission (confirmed by the results of the company NMA) demonstrated *did* suggest BPd increases how long people have before their condition gets worse *and* how long people live, compared with these treatments. A PFS increase vs all relevant comparators: BPd over DVd (HR, [redacted], 95% CrI: [redacted]), SVd (HR, [redacted], 95% CrI: [redacted]0.83) and hKd (HR, [redacted], 95% CrI: [redacted]). An OS increase vs all relevant comparators: BPd over DVd (HR, [redacted], 95% CrI: [redacted]), SVd (HR, [redacted], 95% CrI: [redacted]) and hKd (HR, [redacted], 95% CrI: [redacted]). The current statement in the draft guidance only refers to an 'increase' where the original company NMA results did not span one. Without further context provided, the current statement is misleading and not factually correct.

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Section 3.7, page 25 'It had serious concerns about the credibility of the company's estimates of long-term overall survival and recalled that no overall-survival benefit for Bel-Pom-Dex over its comparators had been shown (see section 3.7).'	'It had serious concerns about the credibility of the company's estimates of long-term overall survival and recalled that no **statistically significant** overall-survival benefit for Bel-Pom-Dex over its comparators had been shown (see section 3.7).'	As above, the company's estimates of long-term overall survival *did* demonstrate an increase in overall survival vs all relevant comparators (with CrI's spanning 1). Please refer to Issue 3 of the company's factually accuracy check of the EAG report where the company made this same comment on the statistical inference was made.

Insert extra rows as needed

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- 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.
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Single technology appraisal

[ID6211]

Belantamab mafodotin with pomalidomide and dexamethasone for previously treated multiple myeloma

Technical Appendix

July 2025

File name	Version	Contains confidential information	Date
ID6211_Belantamab mafodotin with pomalidomide and dexamethasone_Technical Appendix_17Jul2025 [CON]	V1.0	Yes	17 July 2025

Contents

1. Updated methodology to resolve relative OS uncertainty

1.1. Inverse probability of Treatment Weighting (IPTW)

1.1.1. Background & rationale

The Inverse probability of Treatment Weighting (IPTW) analysis was explored in response to the Committee's preferences for an updated indirect treatment comparison (ITC) which addresses the highlighted methodological limitations.

"For overall-survival benefit, to use the overall-survival data from SACT for Dar-Bor-Dex to estimate the absolute baseline curve, with the relative effects of the comparators applied from an updated network meta-analysis that addresses the methodological issues highlighted." (Section 3.20, page 33 of NICE DG)

"To address the uncertainty in the relative estimates of overall survival, it would also have preferred to see scenario analyses using matching-adjusted indirect comparisons (MAIC) for all the comparators" (Section 3.11, page 25 of NICE DG)

"The committee considered that neither the company's modelling of overall survival nor the EAG's assumption of no differential overall-survival benefit were aligned with its preferred assumptions" (Section 3.11, page 25 of NICE DG)

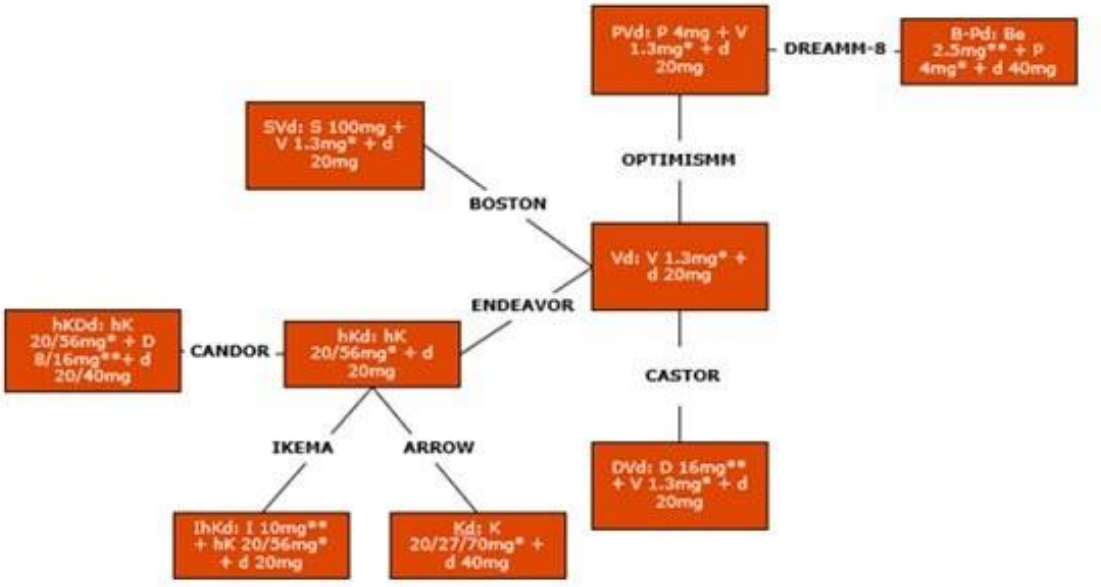
The IPTW analysis, detailed below, is proposed as an alternative ITC analysis to address the uncertainty in estimating the relative OS benefit of BPd. This approach serves to provide an alternative link for DREAMM-8 to the rest of the network of evidence, thereby mitigating the uncertainty resulting from the high rates of unintended cross-over in OPTIMISMM (Figure 1,
Figure **2**).

DVd is the current standard of care (SoC), and a key comparator in the 2L lenalidomide unsuitable RRMM treatment landscape. Due to the lack of direct evidence comparing BPd to DVd, the company utilises the available individual patient data (IPD) from DREAMM-7 (D7) and DREAMM-8 (D8) to evaluate the

relative treatment effect of BPd (D8 intervention arm) vs DVd (D7 comparator arm) with improved transparency.

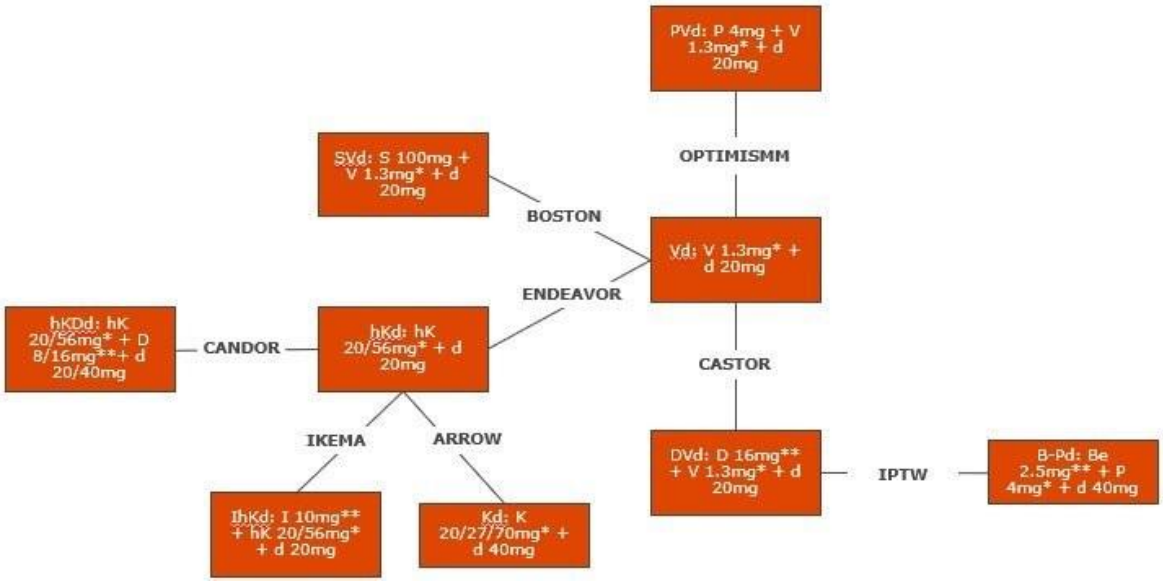
The IPTW method is prioritized over other techniques, such as Matching-Adjusted Indirect Comparison (MAIC) or Simulated Treatment Comparison (STC), due to its ability to symmetrically adjust both trial populations, ensuring a more balanced and comprehensive evaluation. Unlike MAIC and STC, which adjust only one arm to align with the other, IPTW facilitates a fairer comparison by accounting for differences across both groups. This balanced approach makes full use of the company's access to IPD across both submissions, enhancing the transparency and rigor of the analysis, and making it the preferred method for assessing relative treatment effects [1].

Figure 1. Original CS: Overall network of evidence



Abbreviations: BPd, Belantamab mafodotin, Pomalidomide, and Dexamethasone; CS, Company submission; DVd, Daratumumab, Bortezomib, and Dexamethasone; hKD, High dose Carfilzomib and Dexamethasone; hkDd, High dose Carfilzomib, Daratumumab, and Dexamethasone; IhKd, Isatuximab, High dose Carfilzomib, and Dexamethasone; Kd, Carfilzomib and Dexamethasone; PVd, Pomalidomide, Bortezomib, and Dexamethasone; SVd, Selinexor, Bortezomib, and Dexamethasone; Vd, Bortezomib and Dexamethasone.

Figure 2. New, alternative company approach: IPTW analysis integrated into overall network of evidence



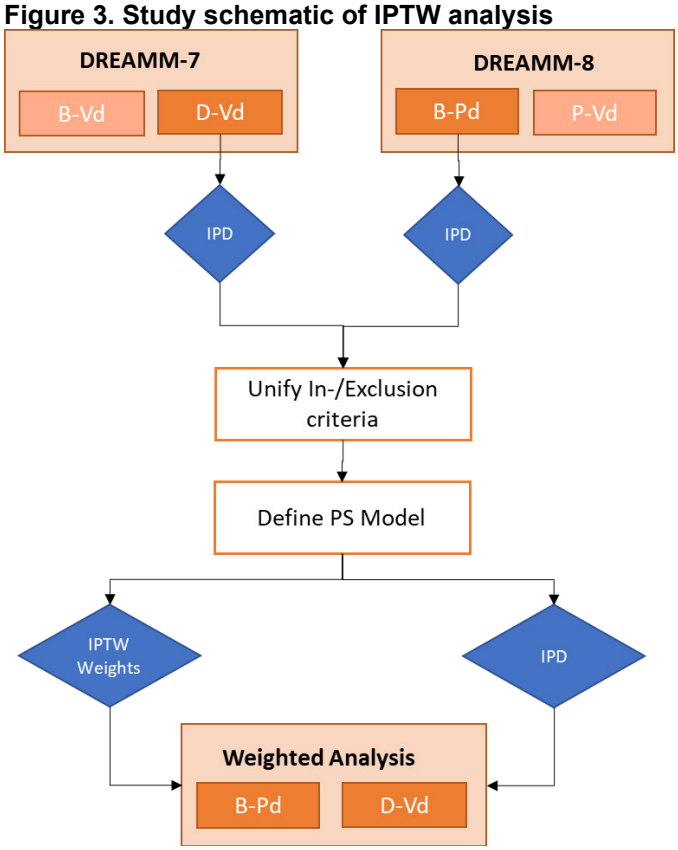
Abbreviations: BPd, Belantamab Mafodotin, Pomalidomide, and Dexamethasone; DVd, Daratumumab, Bortezomib, and Dexamethasone; hKD, High dose Carfilzomib and Dexamethasone; hkDd, High dose Carfilzomib, Daratumumab, and Dexamethasone; IhKd, Isatuximab, High dose Carfilzomib, and Dexamethasone; IPTW, Inverse Probability of Treatment Weighting; Kd, Carfilzomib and Dexamethasone; PVd, Pomalidomide, Bortezomib, and Dexamethasone; SVd, Selinexor, Bortezomib, and Dexamethasone; Vd, Bortezomib and Dexamethasone.

1.1.2. IPTW methods

Unifying Inclusion/Exclusion criteria

The primary goal of the IPTW analysis is to enable a robust comparison of the active treatment arm (BPd) from the DREAMM- 8 trial against a matched control arm (DVd) from the DREAMM-7 randomized control trial (Figure 3). To achieve this, patient level data from DREAMM-7 and DREAMM-8 – including study endpoints, treatment group and prognostic/treatment effect modifying variables – were selected for comparison.

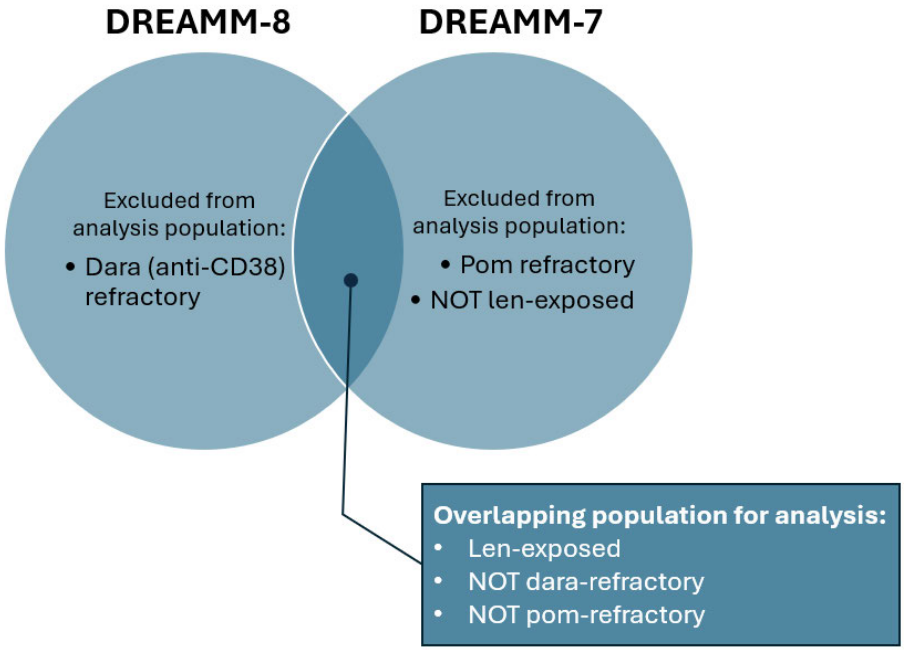
Figure 3. Study schematic of IPTW analysis



Abbreviations: BPd, Belantamab mafodotin in combination with pomalidomide, and dexamethasone; DVd, Daratumumab in combination with bortezomib, and dexamethasone; IPD, individual patient data; IPTW, inverse probability of treatment weighting; PS, propensity score.

Before conducting the analysis, inclusion and exclusion criteria were applied to ensure that the comparison population was appropriate and aligned with the eligibility criteria of both trials (Figure 4).

Figure 4. Venn diagram illustrating the overlapping population between DREAMM-7 and DREAMM-8



Abbreviations: CD-38, cluster of differentiation 38; Dara, daratumumab; Len, lenalidomide; Pom, pomalidomide.

Specifically:

- Patients from the DREAMM-7 trial who lacked prior exposure to lenalidomide or were refractory to pomalidomide were excluded (as per DREAMM-8 eligibility criteria).
- Patients from the DREAMM-8 trial who were refractory to daratumumab or other anti-CD38 therapies were excluded (as per DREAMM-7 eligibility criteria).

The inclusion/exclusion criteria summarized in (

Table **1**) were reviewed and validated by external clinical experts [2].

Table 1. Summary table of exclusion criteria applied to DREAMM-7 and DREAMM-8 for IPTW

Study	ITT population description	Exclusion criteria applied for IPTW study
DREAMM-7	Adult participants with RRMM	• Patients without prior exposure to len • Patients who are refractory to pom
	Previously treated with at least 1 prior LOT	
	No patients intolerant or refractory to dara	
	No more than 50% with 2+ prior LOT	
DREAMM-8	Participants with RRMM	Patients refractory to any anti-CD38 (including dara)
	Previously treated with len & at least 1 prior LOT	
	No patients refractory to pom	
	No more than 50% with 3+ LOT	

Abbreviations: CD-38, Cluster of Differentiation 38; Dara, Daratumumab; DREAMM-7, Driving Excellence in Approaches to Multiple Myeloma - Trial 7; DREAMM-8, Driving Excellence in Approaches to Multiple Myeloma - Trial 8; IPTW, Inverse Probability of Treatment Weighting; ITT, Intent-to-Treat; Len, Lenalidomide; LOT, Line of Therapy; Pom, Pomalidomide; RRMM, Relapsed/Refractory Multiple Myeloma.

Both experts agree that this step is necessary to ensure a robust evaluation of the relative treatment effect of BPd compared to DVd within the IPTW framework. Furthermore, one of the external clinical experts concluded that the resulting population is generalisable to the broader UK population [2]. Specifically, the exclusion criteria of 'no patient intolerant or refractory to daratumumab' aligns with current UK clinical practice, where daratumumab in combination with lenalidomide and dexamethasone (DRd) was approved for routine commissioning in Oct 2023 for 1L MM treatment. Given the median PFS of approximately 5 years [3, 4], most relapsed patients in 2L in the UK are unlikely to be refractory to anti-CD38 treatments.

The company's approach follows NICE's Technical Support Document (TSD) 18, which applies IPTW specifically in population-adjusted indirect treatment comparisons [5].

Prognostic factors, propensity score and reweighting

Baseline prognostic factors (PFs) between arms were identified from published review papers and previous belantamab mafodotin studies (DREAMM-2, DREAMM-3) and validated by external clinical experts (xxxxx 3) [2]. Propensity scores, estimated using logistic regression, were calculated to account for baseline difference between treatment arm BPd vs DVd for key characteristics.

Non-missing baseline data were reweighted using the IPTW method, with the average treatment effect on the treated (ATT) as the primary approach and the average treatment effect (ATE) as a sensitivity analysis, to adjust for selection bias, as advised in NICE's TSD 17 [6]. Further details of the IPTW method can be found in the IPTW report [7].

1.1.3. IPTW results

Subject disposition

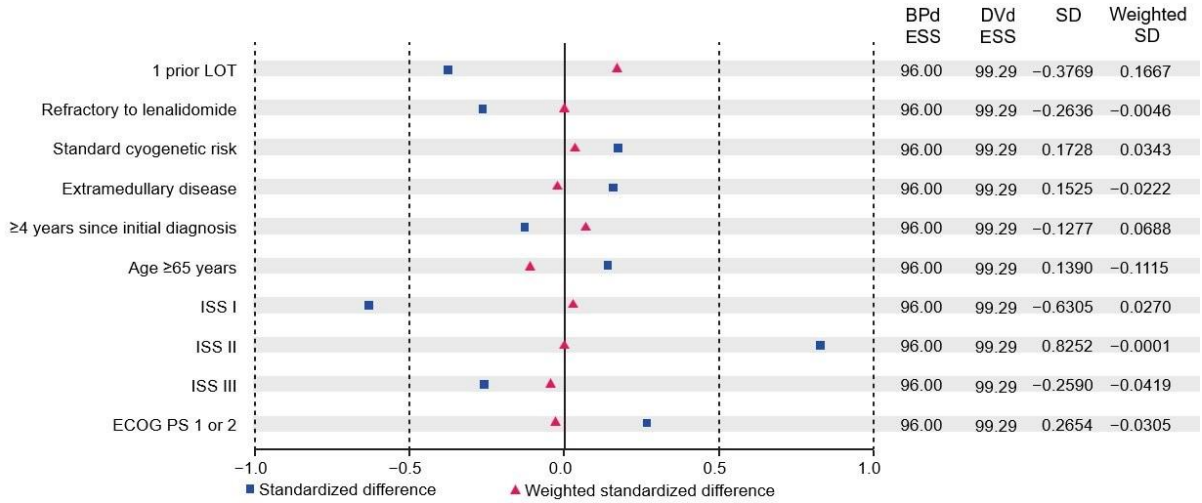
The disposition of patients included is summarized below, highlighting the patient numbers which meet the criteria. xxxxx 2 provides a breakdown of the DREAMM-7 (D-Vd) and DREAMM-8 (B-Pd) study populations when the criteria of the analysis are subsequently applied.

Abbreviation: BPd, Belantamab mafodotin, Pomalidomide, and Dexamethasone; CD-38, Cluster of Differentiation 38 (a protein targeted by monoclonal antibodies like Daratumumab); Dara, Daratumumab; DVd, Daratumumab, Bortezomib, and Dexamethasone; ITT, Intent-to-Treat; Len, Lenalidomide; Pom, Pomalidomide.

Baseline demographic and disease characteristics

After matching, the baseline Prognostic Factors (PFs) were well balanced between treatment arms (xxxxx 3), as illustrated by the weighted standardized differences (Figure 5). Clinical experts evaluated the adjusted population and determined it to be appropriate for comparative analysis between the treatment arms. Furthermore, the PFs align closely to what is expected for a 2-3L UK MM patient population [2].

Figure 5. Forest plot of stabilised IPTW standardised differences for analysis population

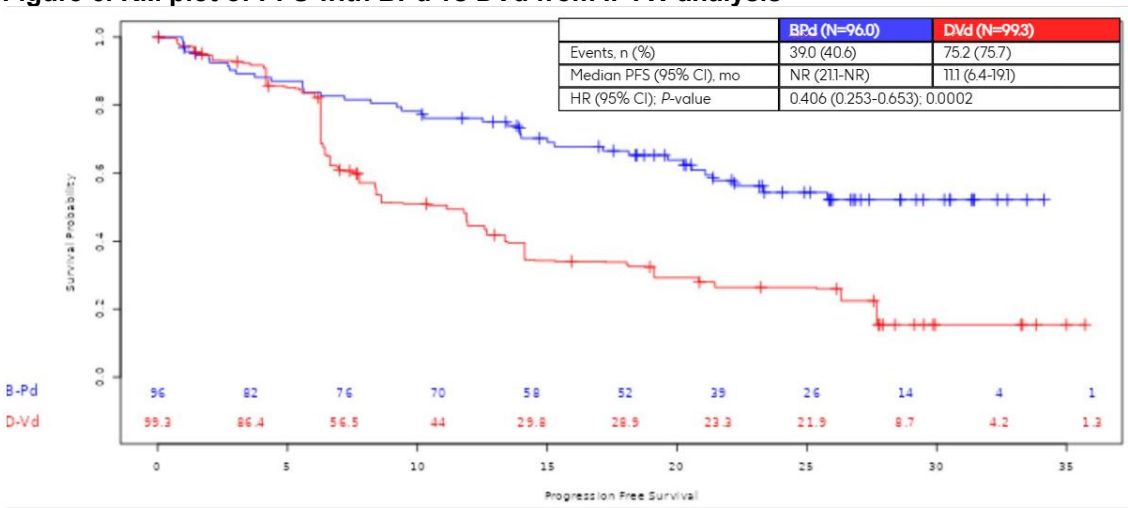


Abbreviation: BPd, Belantamab mafodotin, Pomalidomide, and Dexamethasone; DVd, Daratumumab, Bortezomib, and Dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESS, Effective Sample Size; ISS, International Staging System; LOT, Line of Therapy; SD, Standardized Difference.

Efficacy results

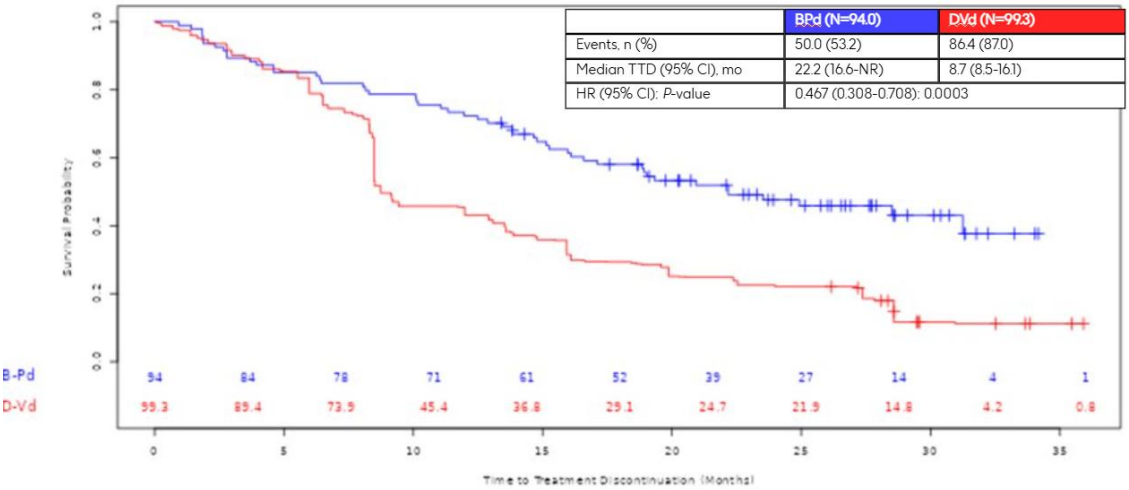
The results indicate that the BPd arm demonstrated a statistically significant PFS benefit compared to the DVd arm (HR= 0.41, 95% CI 0.25 – 0.65, p=0.0002; **Error! Reference source not found.**). Notably, the results are closely aligned to what was observed for BVd vs DVd in the DREAMM-7 NMA (HR= [redacted]), despite the IPTW-adjusted population in this analysis being composed entirely of lenalidomide-exposed patients – around 80% of whom were lenalidomide refractory - a population known to be more challenging to treat (while in the NMA only the ITT data was available from CASTOR for comparisons to DVd). Furthermore, patients in the BPd arm remained significantly longer on treatment compared to those in the DVd arm with a median TTD of 22.7 vs 8.7 months, respectively (p = 0.0003; Figure 7).

Figure 6. KM plot of PFS with BPd vs DVd from IPTW analysis



Abbreviations: BPd, Belantamab mafodotin, Pomalidomide, and Dexamethasone; DVd, Daratumumab, Bortezomib, and Dexamethasone; HR, Hazard Ratio; IPTW, inverse probability of treatment weighting; KM, Kaplan Meier; PFS, progression-free survival.

Figure 7. KM plot of TTD with BPd vs DVd from IPTW analysis



Abbreviations: BPd, Belantamab mafodotin, CI, Confidence interval; Pomalidomide, and Dexamethasone; DVd, Daratumumab, Bortezomib, and Dexamethasone; HR, Hazard Ratio; IPTW, Inverse Probability of Treatment Weighting; KM, Kaplan-Meier; TTD, Time to Discontinuation.

Acknowledging the notable drop observed in the PFS and TTD Kaplan-Meier curves of DVd around month 6-7 (Figure 6 and Figure 7), the company conducted a sensitivity analysis to exclude individuals assigned with high weight [1]. The full methodology is detailed in the IPTW NMA technical report [7]. The results obtained from the sensitivity analyses are consistent with those obtained from the initial analyses, indicating that the 4 subjects with high weights did not have meaningful impact on the PFS results. A clinical expert hypothesized that the noticeable drop in

PFS around the 6-month mark may be associated with the fixed duration of bortezomib and dexamethasone administration, which is limited to 8 cycles (~6 months) for the DVd combination. At this point, patients transition from a triplet therapy (DVd) to monotherapy consisting solely of daratumumab, potentially losing the initial PFS benefits from the triplet regimen [2].

The [redacted]; [redacted]) is [redacted]). While there is uncertainty, given immaturity of the OS data, the results are consistent with the previous CS approach in using adjusted OS HR from OPTIMISMM, resulting in an OS HR of 0.790 (CI 0.49-1.29) vs DVd. Additionally, clinical experts reviewed the MRD data and noted that the adjusted MRD negativity rate for the B-Pd group was [redacted] [2].

Figure 8. KM plot of OS with BPd vs DVd from IPTW analysis

Abbreviations: BPd, Belantamab mafodotin, CI, Confidence interval; Pomalidomide, and Dexamethasone; DVd, Daratumumab, Bortezomib, and Dexamethasone; HR, Hazard Ratio; IPTW, Inverse Probability of Treatment Weighting; KM, Kaplan-Meier; OS, Overall Survival.

Furthermore, the [redacted] These findings provide reassurance

and reduced uncertainty. A clinical expert suggested presenting sustained MRD negative rates as this will further reduce the uncertainty [2].

Taken together, these findings provide additional evidence that supports BPd as a more effective treatment option than DVd in patients with RRMM who received at least 1 prior line of therapy including lenalidomide. The time-to-event results have been validated by external clinical experts, agreeing that the findings are plausible within the context of UK clinical practice.

1.2. IPTW integrated NMA

1.2.1. Background & rationale

The IPTW integrated NMA (Figure 2) is provided as an alternative approach to the original NMA in the company submission (Figure 1), to estimate the relative of BPd vs other comparators.

This approach has previously been accepted by NICE for decision making, including TA1012, TA850, and specifically TA1015, which is within the context of RRMM treatment [8-10]. The committee concluded that the TA1015 IPTW-integrated NMA model structure is appropriate for decision making, despite identifying various methodological limitations, such as deviation from the guidance of TSD 17 or multiple unadjusted key PF [10]. The company has undergone extensive planning and validation to ensure the IPTW-integrated NMA provided is as robust as possible for this appraisal.

1.2.2. IPTW integrated NMA methods

The IPTW analysis provides a connection for BPd to DVd, linking it to the rest of the network composed of the 11 comparator studies (Figure 2). The IPTW connected network is anchored by four common treatments: DVd, Vd, hKd, and Kd. Full details for the NMA methodology can be found in the IPTW NMA technical report [1]. This method was validated externally with a statistical expert, who highlighted that a main

advantage of this approach is to provide a more direct path with less connections to reach main comparators of interest, especially DVd [1].

PFS and OS outcomes were derived from the IPTW integrated NMA for the len-exposed (lenalidomide exposed) + ITT population. This is to measure the comparative efficacy of BPd in the len-exposed population (a population equivalent to DREAMM-8 ITT). Similar to the original company submission, a population equivalent to len-exposed plus ITT was used to include comparator studies that did not report results for a len-exposed population [1].

The primary analysis for this IPTW integrated NMA utilises a fixed-effects model, given that there is only one study per link in the network and is insufficient to reliably estimate between study variances. However, the random-effects model was performed as a secondary analysis to account for heterogeneity in treatment effects between studies within the network.

The IPTW integrated NMA was reviewed and validated by two statistical experts, including a former NICE EAG member, confirming no methodological concerns with the approach [1]. The experts supported the use of IPTW as a credible method to reduce uncertainty and validate results from the original NMA.

1.2.3. Results

For the fixed effects model using the IPTW-integrated NMA, BPd demonstrated OS benefit versus all 12 comparator treatments in the len-exposed + ITT population with all HRs below 1 (xxxxxx 9).

[redacted]

Abbreviations: BPd, Belantamab mafodotin, Pomalidomide, and Dexamethasone; CI, Confidence interval; CyKd, Cyclophosphamide, high dose Carfilzomib, and Dexamethasone; CyVd, Cyclophosphamide, Bortezomib, and Dexamethasone; DVd, Daratumumab, Bortezomib, and Dexamethasone; EVd, Elotuzumab, Bortezomib, and Dexamethasone; hKd, High-dose Carfilzomib and Dexamethasone; hKDd, High-dose Carfilzomib, Daratumumab, and Dexamethasone; IhKd, Isatuximab, High-dose Carfilzomib, and Dexamethasone; Kd, Carfilzomib and Dexamethasone; PanoVd, Panobinostat, Bortezomib, and Dexamethasone; PVd, Pomalidomide, Bortezomib, and Dexamethasone; SVd, Selinexor, Bortezomib, and Dexamethasone; Vd, Bortezomib and Dexamethasone.

The OS HRs derived from IPTW-integrated NMA for BPd vs all comparators are marginally lower compared to those derived from the original NMA (Table 4). This difference arises from variations in how BPd is connected to the broader evidence network (Figure 1).

For the IPTW-integrated NMA, BPd is linked to DVd through IPTW (OS HR [redacted]), with DVd subsequently connecting to Vd through the CASTOR trial (OS HR 0.74) into the rest of the network (Figure 2). While in the original NMA, BPd is connected to PVd through DREAMM-8 (IA1 OS HR 0.77), with PVd linking to Vd through the OPTIMISMM trial (OS HR 0.76) into the rest of the network (Figure 1).

Table 4. Summary table for relative OS effect of BPd vs relevant comparators

Comparator	IPTW-integrated NMA	Global DREAMM-8 NMA
	BPd vs [95%CI]	BPd vs [95%CI]
hKd	[redacted]	[redacted]
SVd	[redacted]	[redacted]
DVd	[redacted]	[redacted]

Abbreviations: BPd, Belantamab Mafodotin, Pomalidomide, and Dexamethasone; CI, Confidence interval; DVd, Daratumumab, Bortezomib, and Dexamethasone; hKd, High-dose Carfilzomib and Dexamethasone; IPTW, Inverse Probability of Treatment Weighting; NMA, Network Meta-Analysis; OS, Overall Survival; SVd, Selinexor, Bortezomib, and Dexamethasone.

The IPTW-integrated NMA provides evidence that BPd is more efficacious in extending OS compared to all comparators. Additionally, the similarity in results derived from both the IPTW-NMA and the original company NMA offers an additional layer of confidence in the robustness of the findings.

1.3. DVd SACT baseline curve

1.3.1. Background & rationale

The company acknowledges the committee's preference in using real-world evidence (RWE) to complement RCT evidence to align to UK clinical practice. An analysis using systemic anti-cancer therapy (SACT) OS data for DVd to estimate the absolute baseline curve is provided to align with the committee's request:

"A base-case analysis using overall-survival data from SACT for Dar-Bor-Dex to estimate the absolute baseline curve." (Section 3.22, page 35)

1.3.2. Method

The company notes that a similar request was made by the committee for the evaluation of ID6212, an appraisal assessing the cost effectiveness of BVd, which has been accepted by the committee [11]. Here the company follows a similar approach to estimate the absolute baseline curve for DVd OS. While only treatment-free survival (TFS) data were available from the SACT data, a scenario analysis was explored which uses TFS from SACT as a proxy for PFS. This was incorporated into the scenario analysis with a similar method as that detailed below for OS.

SACT data was requested from NHS England, and a publication was identified which fit these criteria (RWE of DVd usage in the NHS 2L len-exposed setting) [12]. Real-

world data on patient outcomes was collected though the SACT database by the National Disease Registration Service (NDRS) for comparisons against CASTOR phase III clinical trial results.

The data used aligned with the current recommendation after the CDF exit of DVd in June 2023:

"Daratumumab with bortezomib and dexamethasone is recommended as an option for treating multiple myeloma in adults, only if they have had just 1 previous line of treatment and:

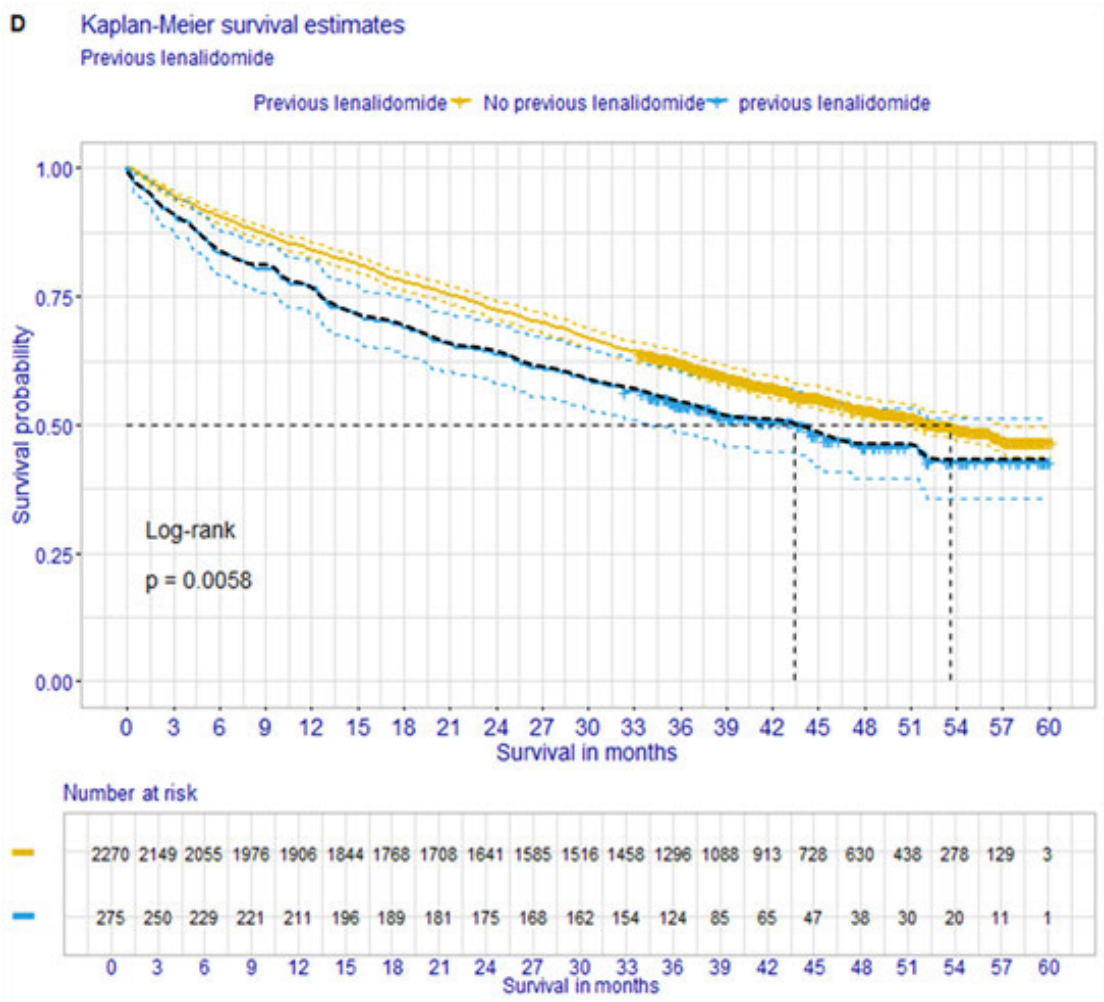
- *it included lenalidomide or*
- *Lenalidomide is unsuitable as a second-line treatment"*

A suitable proxy aligning for patients eligible to receive DVd was therefore identified in the publication; patients who have received previous lenalidomide.

Patients (n=275) treated with DVd via the CDF between March 2019 and June 2021 that were identified from the NHS England Blueteq system and the SACT dataset, with follow-up until 31 August 2023.

The KM curve for SACT DVd for patients treated with prior lenalidomide was extracted from the figures in the Lawton et al. (2024) publication using digitisation. Using the digitised KM data, pseudo-IPD was reconstructured using the algorithm from Guyot et al., (2012) [13], enabled by the "IPDfromKM" package in R [14]. This enables estimation of events and censoring time to align with the published KM data by Lawton et al., (2024). Figure 10 below shows the overall survival Kaplan Meier from Lawton et al., the black line overlaid onto the figure illustrates the digitised KM curve generated from the reconstructed digitised curve [12]. This resulting KM curve was then incorporated into the economic model.

Figure 10. Digitised OS KM curve overlaid on KM curve from Lawton et al., (2024) publication



To validate the resulting KM curve, it was overlaid on the IPTW DVd OS curve. Clinical experts noted that while general differences between RWE and RCT population can be observed, the SACT OS KM curve generally tracks the IPTW curve (

) [2]. The good agreement between the OS curves also implies that the results derived using the IPTW method are reflective of NHS clinical practice.

Figure 11. Digitised SACT data overlaid with the IPTW DVd curve

Abbreviations: DVd, Daratumumab, Bortezomib, and Dexamethasone; IPTW, Inverse Probability of Treatment Weighting; KM, Kaplan-Meier; SACT, Systemic Anti-Cancer Therapy.

Six standard parametric distributions (Exponential, Weibull, Gompertz, log-logistic, log-normal and Generalised Gamma) were fitted to the DVd SACT KM data using the “flexsurv” package in R. Model parameters were estimated by maximum likelihood. Goodness-of-fit was assessed using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). The choice of the most appropriate extrapolation method was based on clinical expert opinion, and the assessment of how well each model predicts the 5-, 10-, and 15-year clinical expert PFS and OS landmark estimates.

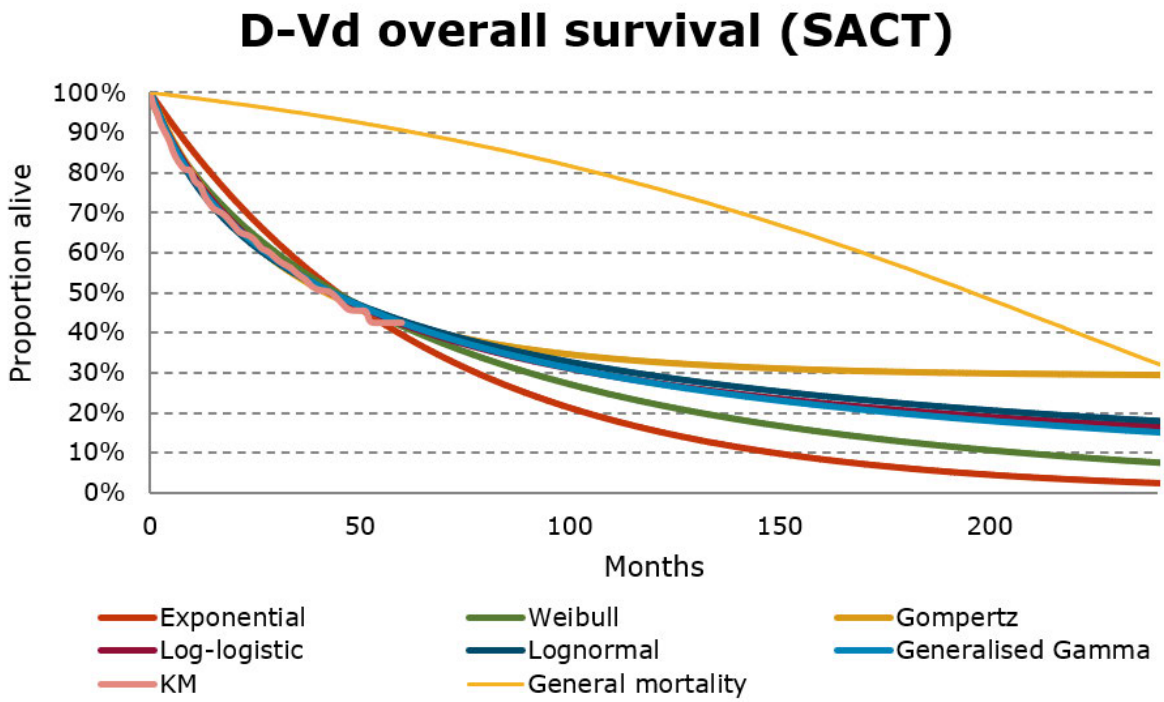
The SACT DVd OS KM curve and extrapolated OS data were added to the CEM. Table 5 displays the numerical outputs of this exercise, while **Error! Reference source not found.** visually displays these extrapolations on a graph overlaid with the SACT OS data. Note that negative AIC / BIC have the same interpretation as positive AIC / BIC, in that smaller absolute magnitudes indicate better fit.

Table 5. DVd parametric distribution coefficients and goodness-of-fit statistics

Function	Parameter	Coefficients	SE	Covariance	AIC	BIC
Exponential	Rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Scale	[redacted]	[redacted]	[redacted]		
Gompertz	Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Rate	[redacted]	[redacted]	[redacted]		
Log-logistic	Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Scale	[redacted]	[redacted]	[redacted]		
Lognormal	meanlog	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	sdlog	[redacted]	[redacted]	[redacted]		
Generalised Gamma	mu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Sigma	[redacted]	[redacted]	[redacted]		
	Q	[redacted]	[redacted]	[redacted]		

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; SE, Standard Error.

Figure 12. Summary of parametric extrapolations of DVd SACT OS data



Abbreviations: DVd, Daratumumab in combination with bortezomib and dexamethasone; KM, Kaplan-Meier; SACT, systemic anti-cancer therapy.

The Weibull curve was selected for the base-case for the following reasons:

- Best alignment to external clinical expert validation, given extensive experience of DVd in 2L treatment [15].
- Good visual fit in the region with known KM data, and a conservative extrapolation in the region beyond KM data.
- The exponential curve was considered but not pursued, given the visual fit to the KM was poor and there was a lack of alignment with external clinical expert expectation

Table 6 below highlights the clinician validation from ID6212 versus the DVd SACT analysis against the two closest fits to the clinician landmark estimates (exponential and Weibull). While only the clinical validation from the ID6212 were available (reflective of DVd OS outcomes from DREAMM-7), the landmarks elicited are broadly reflective of clinical plausibility of DVd OS outcomes in the mid to long-run. The Weibull curve was chosen as the closes fitting curve to the values elicited by the clinicians, given the disparity between the external expert landmarks and the exponential extrapolation from 5- to 10-years.

Table 6: DVd SACT OS extrapolation versus DREAMM-7 DVd clinician validation

Parametric curve (DVd)	Survival – 5 years	Survival – 10 years	Survival – 15 years
DREAMM-7 clinical validation (Average of 3 EE's, most likely %)	[redacted]	[redacted]	[redacted]
DVd SACT – Weibull	[redacted]	[redacted]	[redacted]
DVd SACT – Exponential	[redacted]	[redacted]	[redacted]

Abbreviations: DVd, Daratumumab, Bortezomib, and Dexamethasone; OS, Overall Survival; SACT, Systemic Anti-Cancer Therapy.

The generated parametric survival curves for DVd were incorporated into the updated economic model. In the company response to the Committee's request, the relative effect of BPd vs DVd baseline was incorporated by applying the OS HR from the IPTW analysis. The relative effect of other comparators (SVd and hKd) was incorporated by applying the OS HR from the IPTW integrated NMA (Table 4). A

toggle was included in the model ('Clinical inputs' sheet, cell D10) to select the IPTW + integrated NMA.

Technical considerations:

- While the OS for DVd has incorporated SACT data to align to Committee request, all other clinical data (including PFS and TTD) remain aligned to the original CS NMA (PFS NMA), where HRs are applied to the PVd baseline.
- This is due to only treatment-free survival being available from the SACT publication (introducing uncertainty on the validity of using TFS as a proxy for PFS). However, alternative methods using TFS were employed within the scenario analysis in order to consistently anchor all available outcomes to the DVd SACT data.

1.3.3. Results

Figure 13 illustrates the relative effect of BPd vs the SACT DVd baseline (Weibull) by applying the OS HR ([redacted]) from the IPTW analysis.

Figure 13. OS using IPTW HR for BPd (DVd- Weibull)

Abbreviations: BPd, Belantamab Mafodotin, Pomalidomide, and Dexamethasone; CS, Company Submission; DVd, Daratumumab, Bortezomib, and Dexamethasone; HR, Hazard Ratio; IPTW, Inverse Probability of Treatment Weighting; NMA, Network Meta-Analysis; OS, Overall Survival.

Figure 13 was validated by two external clinical experts, confirming the findings are clinically plausible within a UK setting. One clinical expert suggested that the BPd vs DVd IPTW OS results appear to be a conservative estimate at 10% difference at 5 years (Figure 13), noting that they would expect a 15% difference in OS favouring BPd [2].

1.4 Updated base case

Please refer to the 'change log' sheet in the model for full detail of the model changes (made from the EAG model) to derive the company's updated base case.

1.4.1. Background

In line with the committee's preference, the updated company base case incorporates DVd SACT baseline for OS, estimating relative effects for BPd using IPTW HR and other comparators (SVd and hKd) using IPTW-integrated NMA HRs (

Table **7**).

Apart from the company response to committee requests from the committee, no other changes to clinical input parameters have been made since CS. The company ensures the model is consistent and appropriate to facilitate efficient decision making by the committee to ensure timely access to patients.

In alignment with the Committee preferences and the respective company response (as outlined in the accompanying response document) further changes have been made in the updated company base case beyond the clinical parameters described above (Table 8). These include: baseline age, utilities, tablet wastage and ophthalmologist monitoring costs.

1.4.2. Clinical parameters

To further strengthen the evidence base and reduce the uncertainty in the relative OS benefits between BPd and comparators (DVd, SVd and hKd) raised by committee and EAG, the company has provided an updated base case (

Table **7**). A summary of changes from the original base case are highlighted in green cells.

Table 7: Summary of clinical parameters in the updated base case

Treatment	Clinical parameter	Original CS	Updated company base case	Reference for context and justification
DVd	**PFS**	NMA HR applied vs PVd baseline	NMA HR applied vs PVd baseline	Original CS
	OS	NMA HR applied vs PVd baseline	OS SACT baseline (Weibull)	Section 1.3. DVd SACT baseline curve
	TTD	NMA HR applied vs PVd baseline	NMA HR applied vs PVd baseline	Original CS
BPd	**PFS**	D8 ITT	D8 ITT - Weibull	Original CS
	OS	D8 ITT	IPTW HR applied vs DVd baseline	Section 1.1. Inverse probability of Treatment Weighting (IPTW)
	TTD	D8 ITT	D8 ITT - Weibull	Original CS
SVd	**PFS**	NMA HR applied vs PVd baseline	NMA HR applied vs PVd baseline	Original CS
	OS	NMA HR applied vs PVd baseline	IPTW NMA HR applied vs DVd baseline	Section 1.2. IPTW integrated NMA
	TTD	NMA HR applied vs PVd baseline	NMA HR applied vs PVd baseline	Original CS
hKd	**PFS**	NMA HR applied vs PVd baseline	NMA HR applied vs PVd baseline	Original CS
	OS	NMA HR applied vs PVd baseline	IPTW NMA HR applied vs DVd baseline	Section 1.2. IPTW integrated NMA
	TTD	NMA HR applied vs PVd baseline	NMA HR applied vs PVd baseline	Original CS

Abbreviations: PFS, Progression-free survival, OS, Overall survival; TTD, Time-to-treatment discontinuation; hKd, high-dose carfilzomib plus dexamethasone; SVd, Selinexor plus bortezomib and dexamethasone; BPd, Belamaf plus pomalidomide and dexamethasone; DVd, Daratumumab plus bortezomib and dexamethasone; PVd, pomalidomide plus bortezomib and dexamethasone; IPTW, inverse probability of treatment weighting; NMA, network meta analysis; HR, hazard ratio; SACT, systemic anti-cancer therapy

1.4.2. Committee preferred assumptions

In acknowledgement of the committee preferred assumptions, the company has provided an updated base case to reflect its response.

Table 8 Summary of committee preferred assumptions and company responses

Committee preferred assumptions	Status / updated company base case	Reference for context and justification
"To use the starting age based on the SACT dataset (see section 3.10 of NICE DG) "	Included in the base case.	See Comment 1 in DG Comments Form
"For overall-survival benefit, to use the overall-survival data from SACT for Dar-Bor-Dex to estimate the absolute baseline curve, with the relative effects of the comparators applied from an updated network meta-analysis that addresses the methodological issues highlighted (in particular, the approach used for subsequent treatments; see sections 3.6 and 3.11 of NICE DG)"	DVd SACT baseline for OS, estimating relative effects for BPd using IPTW HR and other comparators (SVd and hKd) using IPTW-integrated NMA HRs.	See Comment 2 in DG Comments Form
"To model a maximum dose interruption interval of 6 months for belantamab mafodotin (see section 3.12)"	Analysis provided to demonstrate maintenance of efficacy in BPd patients and potential for negative impact on patient equity.	See Comment 3 in DG Comments Form
"To use the acquisition cost of pomalidomide from the Medicines Procurement and Supply Chain framework (see section 3.13)"	Use of pomalidomide acquisition from the Medicines Procurement and Supply Chain framework is welcomed by the company.	See Comment 4 in DG Comments Form
"To include the cost of monitoring eye-related adverse events using hospital-based ophthalmology services (see section 3.16)"	Number of estimated ophthalmology visits needed [redacted] explained as well as proportional split between hospital and community services for such visits.	See Comment 5 in DG Comments Form
"To assume no vial sharing (see section 3.17)"	Aligned to the original company base case	See Comment 6 in DG Comments Form

Committee preferred assumptions	Status / updated company base case	Reference for context and justification
"To exclude wastage of tablets (see section 3.17 on NICE DG)"	Included in the base case.	See Comment 7 in DG Comments Form
"To apply the EAG's approach that used the same utilities derived from a wholly second-line population, regardless of treatment (see section 3.18 of NICE DG)."	DREAMM-8 utility applied for all treatments in the PFS state, independent of treatment. Hatswell et al. weighted approach applied for all treatments in the PD state.	See Comment 8 in DG Comments Form

Abbreviations: DG, draft guidance; SACT, systemic anti-cancer therapy; PFS, Progression-free survival; OS, overall survival; NMA, network meta analysis

1.4.5. Cost-effectiveness results using the company's updated base case (PAS vs list)

Please note that due to a minor rounding error in the belamaf confidential discount, the total costs for BPd are £17 higher for the base-case within the updated cost-effectiveness model where this error has been rectified [redacted]). Due to time constraints, the below results have not been updated. However, given this discrepancy is small, the conclusions are identical.

Total costs, LYG, QALYs, and the ICER for BPd versus hKd, SVd and DVd are presented in Table 9 and Table 10 below, for the DVd-eligible and DVd-ineligible populations. In the base-case, BPd resulted in the highest average QALYs ([redacted]) (no severity modifier was applied) and LYs ([redacted]) compared to all other treatments. BPd was also estimated to be a cost saving option compared to other treatments with average costs of £[redacted] over a patient's lifetime. A fully incremental analysis is not presented, as both hKd and SVd and DVd were dominated by BPd.

Table 9. DVd eligible subpopulation – pairwise cost-effectiveness results (PAS vs list, deterministic);

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER BPd vs. (£/QALY)
BPd	[redacted]	[redacted]	[redacted]				
hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib plus dexamethasone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 10. DVd ineligible subpopulation – pairwise cost-effectiveness results (PAS vs list, deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER BPd vs. (£/QALY)
BPd	[redacted]	[redacted]	[redacted]	-	-	-	
hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib plus dexamethasone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SVd, selinexor plus bortezomib and dexamethasone.

Results of the probabilistic analysis for both the DVd-eligible and DVd-ineligible subpopulations are presented in a tabulated form in Table 11 and Table 12. Results of the PSA were highly consistent with results from the deterministic base-case analysis, with hKd, SVd and DVd being dominated by BPd.

Table 11. DVd eligible subpopulation – pairwise cost-effectiveness results (PAS vs list, deterministic);

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER BPd vs. (£/QALY)
BPd	[redacted]	[redacted]	[redacted]	-	-	-	-
hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib plus dexamethasone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 12. DVd ineligible subpopulation – pairwise cost-effectiveness results (PAS vs list, deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER BPd vs. (£/QALY)
BPd	[redacted]	[redacted]	[redacted]	-	-	-	-
hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib plus dexamethasone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SVd, selinexor plus bortezomib and dexamethasone.

1.4.6 Scenario analysis (PAS vs list)

Two key scenarios were explored below to test the results against different applications of the IPTW analysis and include complete data from the SACT dataset for DVd. Note, for both scenarios the DVd OS SACT data is used as the baseline, consistent with the company base-case. In addition, multiple specific scenarios were listed in order to explore alternative settings to those updated in the model.

Full details of the results for the scenarios described in this section is provided in the 'Scenario manager' sheet of the updated model. Please note, that due to the numerous additional settings included, the best source of truth for how these settings are included in each scenario is within the 'Model Parameters' sheet. Columns AR and AS detail the precise settings used in each scenario below.

Scenario 1 – IPTW NMA used throughout the analysis, in place of the original company NMA

This scenario, exact settings detailed below, updates not only the OS analysis to include the evidence from the alternative IPTW NMA analysis, but all relative comparisons across the comparators for PFS and TTD. For SVd and hKd, BPd is used as the baseline and relative effects are applied from the IPTW NMA. For the OS analysis, the settings remain consistent as the base-case.

Table 13. Updated company base case and scenario settings for scenario 1

Treatment	Clinical parameter	Updated company base case	Scenario
DVd	**PFS**	NMA HR applied vs PVd baseline	IPTW HR vs BPd baseline
	OS	OS SACT baseline (Weibull)	OS SACT baseline (Weibull)
	TTD	NMA HR applied vs PVd baseline	IPTW HR applied vs BPd baseline
BPd	**PFS**	D8 ITT - Weibull	D8 ITT - Weibull
	OS	IPTW HR applied vs DVd baseline	IPTW HR applied vs DVd baseline
	TTD	D8 ITT - Weibull	D8 ITT - Weibull
SVd	**PFS**	NMA HR applied vs PVd baseline	IPTW NMA HR applied vs BPd baseline
	OS	IPTW NMA HR applied vs DVd baseline	IPTW NMA HR applied vs DVd baseline

Treatment	Clinical parameter	Updated company base case	Scenario
	TTD	NMA HR applied vs PVd baseline	IPTW NMA HR applied vs BPd baseline
hKd	PFS	NMA HR applied vs PVd baseline	IPTW NMA HR applied vs BPd baseline
	OS	IPTW NMA HR applied vs DVd baseline	IPTW NMA HR applied vs DVd baseline
	TTD	NMA HR applied vs PVd baseline	IPTW NMA HR applied vs BPd baseline

Abbreviations: PFS, Progression-free survival, OS, Overall survival; TTD, Time-to-treatment discontinuation; hKd, high-dose carfilzomib plus dexamethasone; SVd, Selinexor plus bortezomib and dexamethasone; BPd, Belamaf plus pomalidomide and dexamethasone; DVd, Daratumumab plus bortezomib and dexamethasone; PVd, pomalidomide plus bortezomib and dexamethasone; IPTW, inverse probability of treatment weighting; NMA, network meta-analysis; HR, hazard ratio; SACT, systemic anti-cancer therapy; TFS, treatment-free survival
Key: Green highlighted rows indicate that the OS analysis settings for the base case and scenario settings remain consistent.

The results of this scenario are largely consistent with the base-case results; however, the difference for incremental costs between BPd and all comparators has reduced.

Table 14. DVd eligible subpopulation – pairwise cost-effectiveness results (PAS vs list, deterministic); Scenario 1

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER BPd vs. (£/QALY)
BPd	[redacted]	[redacted]	-	-	-
hKd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
DVd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib plus dexamethasone; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 15. DVd ineligible subpopulation – pairwise cost-effectiveness results (PAS vs list, deterministic); Scenario 1

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER BPd vs. (£/QALY)
BPd	[redacted]	[redacted]	-	-	-
hKd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
SVd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib plus dexamethasone; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SVd, selinexor plus bortezomib and dexamethasone.

Scenario 2- DVd SACT data used as a baseline for both PFS (TFS proxy) and OS

This scenario, exact settings detailed below, applies all comparator efficacy relative to the DVd SACT data, including TFS from SACT (as a proxy for PFS) and OS. The

methodology used to digitise and extrapolate the SACT TFS data is aligned to the methods used for the OS SACT data, described in previous sections. While this scenario is not aligned to the committee request (investigating OS alone using SACT) this scenario was included to align as closely as possible to the DVd SACT dataset, for all available data.

Given no TTD data was available within the SACT publication, the BPd TTD remained the same and is used as a baseline for hKd and SVd, which all relative effects from the IPTW NMA (using PFS HR as a proxy) were applied. This also ensures that the dosing data for belamaf is synchronised to the DREAMM-8 data, ensuring the dosing remains reflective of the DREAMM-8 trial data. In addition, a hazard ratio from DREAMM-7 was elicited (comparing PFS with TTD) to use as a proxy in a bid to accurately depict DVd TTD (HR: 1.10) and align the likely treatment discontinuation relative to the PFS (SACT TFS proxy) used for DVd. While this value was based on the DREAMM-7 ITT, the relative differences between PFS and TTD are expected to hold within the len-exposed subpopulation.

Table 16. Updated company base case and scenario settings for scenario 2

Treatment	Clinical parameter	Updated company base case	Scenario
DVd	**PFS**	NMA HR applied vs PVd baseline	TFS SACT baseline (Weibull)
	OS	OS SACT baseline (Weibull)	OS SACT baseline (Weibull)
	TTD	NMA HR applied vs PVd baseline	D7 HR applied vs TFS SACT baseline
BPd	**PFS**	D8 ITT - Weibull	IPTW HR applied vs DVd baseline
	OS	IPTW HR applied vs DVd baseline	IPTW HR applied vs DVd baseline
	TTD	D8 ITT - Weibull	D8 ITT - Weibull
SVd	**PFS**	NMA HR applied vs PVd baseline	IPTW NMA HR applied vs DVd baseline
	OS	IPTW NMA HR applied vs DVd baseline	IPTW NMA HR applied vs DVd baseline
	TTD	NMA HR applied vs PVd baseline	IPTW NMA HR applied vs DVd baseline
hKd	**PFS**	NMA HR applied vs PVd baseline	IPTW NMA HR applied vs DVd baseline
	OS	IPTW NMA HR applied vs DVd baseline	IPTW NMA HR applied vs DVd baseline
	TTD	NMA HR applied vs PVd baseline	IPTW NMA HR applied vs DVd baseline

Abbreviations: PFS, Progression-free survival, OS, Overall survival; TTD, Time-to-treatment discontinuation; hKd, high-dose carfilzomib plus dexamethasone; SVd, Selinexor plus bortezomib and dexamethasone; BPd, Belamaf plus pomalidomide and

dexamethasone; DVd, Daratumumab plus bortezomib and dexamethasone; PVd, pomalidomide plus bortezomib and dexamethasone; IPTW, inverse probability of treatment weighting; NMA, network meta analysis; HR, hazard ratio; SACT, systemic anti-cancer therapy; TFS, treatment-free survival
Key: Green highlighted rows indicate that the OS analysis settings for the base case and scenario settings remain consistent.

The results of this scenario are largely consistent with the base-case results; however, the difference for incremental costs between BPd and all comparators has increased.

Table 17. DVd eligible subpopulation – pairwise cost-effectiveness results (PAS vs list, deterministic); Scenario 2

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER BPd vs. (£/QALY)
BPd	[redacted]	[redacted]	-	-	-
hKd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
DVd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib plus dexamethasone; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 18. DVd ineligible subpopulation – pairwise cost-effectiveness results (PAS vs list, deterministic); Scenario 2

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER BPd vs. (£/QALY)
BPd	[redacted]	[redacted]	-	-	-
hKd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
SVd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

Abbreviations: BPd, belamaf plus pomalidomide and dexamethasone; DVd, daratumumab plus bortezomib and dexamethasone; hKd, high-dose carfilzomib plus dexamethasone; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; SVd, selinexor plus bortezomib and dexamethasone.

Other scenarios

Additional scenarios are included to test the impact of the additional key requests by the committee with alternative methodologies. Table 19 includes the details of the different scenarios that were run, and Table 20, Table 21 and Table 22 includes the results of the scenario analyses for DVd, SVd and hKd respectively.

Table 19: Detail of the scenarios ran

Model setting	Updated company base case	Scenario analysis	Rationale and reference
Utilities	DREAMM-8 utility applied for all treatments in the PFS state, independent of treatment. Hatswell et al. weighted approach applied for all treatments in the PD state.	ENDEAVOR	Committee request. See comment 8 in the DG comments form.
Teclistamab subsequent treatment costs	Not included	Included	Committee request. See comment 19 in the DG comments form.
Proportion of patients receiving subsequent treatment	Raab et al. (in line with original CS)	Clinical expert opinion	Committee request (appropriate SACT data not identified). See comment 18 in the DG comments form.
ERSE disutilities	Excluded	Included	Committee request. See comment 22 in the DG comments form.
Ophthalmology test services	Ophthalmology test visits (80% community, 20% hospital)	100% community	Committee request. See comment 5 in the DG comments form.
Ophthalmology test services		100% hospital	Committee request. See comment 5 in the DG comments form.

Abbreviations: CS, company submission; DG, draft guidance; ERSE, eye-related side effects; PD, progressed disease; PFS, progression-free survival; SACT, systemic anti-cancer therapy

Table 20. Scenario analyses: ICERs for BPd vs. DVd (BPd discounted price, deterministic analysis results)

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	INMB* change from base case (£)
Updated base case	[redacted]	[redacted]	Dominating	[redacted]
ENDEAVOR utilities	[redacted]	[redacted]	Dominating	[redacted]
Teclistamab subsequent treatment costs included	[redacted]	[redacted]	Dominating	[redacted]
Proportion of patients receiving subsequent treatment – clinical expert opinion	[redacted]	[redacted]	Dominating	[redacted]

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	INMB* change from base case (£)
ERSE disutilities	[redacted]	[redacted]	Dominating	[redacted]
Ophthalmology test services – 100% community	[redacted]	[redacted]	Dominating	[redacted]
Ophthalmology test services – 100% hospital	[redacted]	[redacted]	Dominating	[redacted]

Abbreviations: BPd, belantamab mafodotoin in combination with pomalidomide and dexamethasone; DVd, daratumumab in combination with bortezomib and dexamethasone; ERSE, eye-related side effects; ICER incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; QALY, quality adjusted life years.

Table 21. Scenario analyses: ICERs for BPd vs. SVd (BPd discounted price, deterministic analysis results)

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	INMB* change from base case (£)
Updated base case	[redacted]	[redacted]	Dominating	[redacted]
ENDEAVOR utilities	[redacted]	[redacted]	Dominating	[redacted]
Teclistamab subsequent treatment costs included	[redacted]	[redacted]	Dominating	[redacted]
Proportion of patients receiving subsequent treatment – clinical expert opinion	[redacted]	[redacted]	Dominating	[redacted]
ERSE disutilities	[redacted]	[redacted]	Dominating	[redacted]
Ophthalmology test services – 100% community	[redacted]	[redacted]	Dominating	[redacted]
Ophthalmology test services – 100% hospital	[redacted]	[redacted]	Dominating	[redacted]

Abbreviations: BPd, belantamab mafodotoin in combination with pomalidomide and dexamethasone; ERSE, eye-related side effects; ICER incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; QALY, quality adjusted life years; SVd, selinexor in combination with bortezomib and dexamethasone.

Table 22. Scenario analyses: ICERs for BPd vs. hKd (BPd discounted price, deterministic analysis results)

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	INMB* change from base case (£)
Updated base case	[redacted]	[redacted]	Dominating	[redacted]
ENDEAVOR utilities	[redacted]	[redacted]	Dominating	[redacted]
Teclistamab subsequent treatment costs included	[redacted]	[redacted]	Dominating	[redacted]
Proportion of patients receiving subsequent treatment – clinical expert opinion	[redacted]	[redacted]	Dominating	[redacted]
ERSE disutilities	[redacted]	[redacted]	Dominating	[redacted]
Ophthalmology test services – 100% community	[redacted]	[redacted]	Dominating	[redacted]
Ophthalmology test services – 100% hospital	[redacted]	[redacted]	Dominating	[redacted]

Abbreviations: BPd, belantamab mafodotoin in combination with pomalidomide and dexamethasone; ERSE, eye-related side effects; hKd, high-dose carfilzomib and dexamethasone; ICER incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; QALY, quality adjusted life years.

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Thursday 17 July 2025**. 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):	Myeloma UK

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

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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. The funding received from the pharmaceutical industry in 2024 was approximately 4% of our annual income.

	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

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]

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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.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Myeloma UK are disappointed that NICE did not recommend belantamab mafadotin with pomalidomide and dexamethasone for myeloma patients who have received one previous treatment.** Belantamab mafadotin has a **novel mechanism of action** and due to the highly individual nature of myeloma and its response to treatment, **a range of treatment options with different mechanisms of action is needed for patients.** There is a high unmet need for effective and safe treatments, especially at later lines. We ask the Committee to recommend belantamab mafadotin with pomalidomide and dexamethasone for myeloma patients who have received one previous treatment to give these patients an effective option at second line. ***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.* ***"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."***
2	**We are concerned that the Committee did not fully consider the significant patient benefit of increased progression-free survival.** As shown in the committee meeting and the DREAMM-8 trial data, belantamab mafadotin with pomalidomide and dexamethasone delivered significant benefit, with 71% of patients still in remission after 12 months. We understand the data for overall survival was immature, however we believe the company have submitted recent DREAMM-8 trial data to reduce uncertainty of the clinical data. We believe that this new data together with the progression-free survival data shows the clinical benefit of belantamab mafadotin with pomalidomide and dexamethasone for patients. ***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***

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	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.* ***"Whilst I know Myeloma is a relapsing cancer, I was actually quite shocked that I had relapsed. Having been in remission for over 4 years I had convinced myself I was cured. So, it took me some time to come to terms with the fact it was back. Emotionally this was quite tough."***
3	**We are concerned that the Committee did not fully consider the significant patient benefit of taking an oral treatment rather than spending time in hospital for a sub-cut injection.** As discussed in the Committee meeting, the choice of belantamab mafadotin and a bortezomib plus dexamethasone backbone or a pomalidomide plus dexamethasone backbone will be based on a person's clinical history. We feel it is also important to consider patient preference in these decisions. Most patients we speak with prefer taking a tablet (pomalidomide) to having to travel for a hospital appointment for a sub-cut injection (bortezomib). We know from a Myeloma UK survey of 606 patients (Low et al. 2012), that 41.1% of patients would prefer to have a treatment that they could receive at home (preferably in tablet form) due to ease, convenience, the fact it reduces hospital visits and allows patients to avoid invasive procedures such as infusions. In patients who have multiply relapsed myeloma, using oral treatments such as pomalidomide allows them to spend more time at home with their families and to continue living as normal a life as possible according to their individual circumstances. This is particularly important for patients living in more rural areas who may not be able to regularly travel down to a cancer centre to receive IV treatment. One patient we spoke to about their experience of pomalidomide expressed, ***"From speaking to people at the Support Group I belong to, I feel particularly sorry for patients who have to travel from rural Wales to the hospital clinic to receive IV treatment – oral treatments such as pomalidomide are very useful for these patients in particular."***
4	**In answer to the consultation questions**, I. In the treatment pathway for multiple myeloma, are the following technologies still used in the NHS: − bortezomib monotherapy for relapsed multiple myeloma (TA129) – **No.** − bortezomib and thalidomide for the first-line treatment of multiple myeloma (TA228) – **No.** − lenalidomide plus dexamethasone for previously untreated multiple myeloma (TA587)? – **Yes.** **II.** Has all the relevant evidence been considered? **We understand that GSK have submitted additional data, which provides more mature data in terms of overall survival and progression free survival. We ask that the committee specifically reviews the additional data and discusses whether this impacts cost-effectiveness considerations.**

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	III. Are there aspects of the recommendations that need particular consideration to avoid unlawful discrimination? **Whilst not protected characteristics, we believe that there is an inequity consideration if BPD is not commissioned for routine use. Patients who live in rural areas or have velcade intolerance will be denied access to a safe and effective triple regimen which clinical data suggests would provide superior clinical management and remission compared to standard of care. Similarly, the oral pomalidomide component may be particularly beneficial to older and frailer patients who have challenges in travelling to clinics.**
5	**We urge the committee to consider the requirement for clinician and patient choice in managing their myeloma disease. Having the ability to select the optimal combination regimen that provides each patient with the best outcomes, in consideration of their fitness, disease profile and life circumstances is our key ask.** • As committee participants, we are aware of the discord in discussion in regard the maturity of data, health economic modelling and consideration that an MTA would have been an 'ideal' committee scenario. We ask that patient well-being, clinical outcomes and the need for flexibility at second line of myeloma treatment be a priority consideration in the committee discussion. • The requirement for multiple treatment options, in the context of heterogeneity of frailty, disease progression, life circumstances and intolerance/resistance to currently available regimens is a priority patient consideration. • We encourage NICE and GSK to prioritise the need for flexibility in the pathway, to meet patient needs and to consider the detrimental impact that a negative recommendation will have on patients and carers who are not eligible for other belantamab-containing regimens or who will be restricted to sub-optimal standard of care.
6	**We are concerned about the restriction of this treatment to patients at 2nd line only.** Belantamab mafodotin with pomalidomide and dexamethasone is licensed for use at second line and beyond. We welcome consideration and discussions between GSK and NHSE to make belantamab available to those patients who may benefit from second line onwards. We believe that patients at 3rd line should benefit from this treatment as demonstrated by the DREAMM-8 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. ***'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.*

Insert extra rows as needed

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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 comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	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 disappointed that patients will be unable to access Belantamab Pomalidomide and dexamethasone combination for relapsed myeloma. Patients with neuropathy would not be clinically eligible to receive Belantamab mafodotin Bortezomib and dexamethasone which has received a positive Draft guidance.
2	In section 3.5 – Statement says clinical experts 50% of Patients in the NHS would have had by the time they get to second line. This is not factual as less than 25% of patients entering second line

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Thursday 17 July 2025**. Please submit via NICE Docs.

	therapy have had Daratumumab. This is evidenced by the predominant second line therapy is Daratumumab containing regimen - DVD
3	Patients and clinicians would prefer to use Bela Pom dex in both 2nd and 3rd line relapsed myeloma patients
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 comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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	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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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	In section 1 the draft guidance states '*selinexor plus bortezomib and dexamethasone, if the multiple myeloma has not responded to both daratumumab and lenalidomide'.* This is incorrect as patients may have responded and then progressed. As stated in TA974 in the committee

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	discussion refractory refers to multiple myeloma that shows no response to treatment or that has progressed on or within 60 days of the last treatment. We therefore request that this is amended.
2	
3	
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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.
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- 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.
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EAG critique of the company draft guidance response

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Belantamab mafodotin with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma after 1 or more treatments [ID6211] – EAG critique of the company draft guidance response

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 168481

Completed 24th October 2025

CONTAINS no CONFIDENTIAL DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 BACKGROUND

Following the National Institute for Health and Care Excellence (NICE) Appraisal Committee Meeting 1 (ACM1), NICE published draft guidance[1] in which the NICE Appraisal Committee (AC) recommended[1] that "Belantamab mafodotin plus pomalidomide and dexamethasone [BPd] should not be used to treat multiple myeloma in adults who have had at least 1 treatment including lenalidomide".

The company has produced a detailed response to the NICE draft guidance[1] and has provided a technical appendix that includes an updated base case, scenarios, additional clinical effectiveness evidence and statistical analyses to address clinical and economic issues raised during NICE ACM1.

In response to preferences stated by the NICE AC (see Section 2.1), the updated company base case included the following changes

- modelled overall survival (OS) for daratumumab plus bortezomib and dexamethasone (DVd) using Systemic Anti-Cancer Therapy (SACT) data from patients treated with DVd (see Section 2.1.1)
- modelled OS for BPd using a hazard ratio (HR) estimated from an inverse probability of treatment weighting (IPTW) analysis of DREAMM-8 trial[2] and DREAMM-7 trial[3] OS data applied to the DVd SACT modelled OS (see Section 2.1.2)
- modelled OS for selinexor plus bortezomib and dexamethasone (SVd) and high dose selinexor and dexamethasone (hKd) via a network meta-analysis (NMA) using the IPTW OS HR for BPd vs DVd in the network (see Section 2.1.3)
- changed the starting age of the model to the mean age of patients in the SACT dataset who were treated with DVd (see Section 2.1.4)
- a maximum dose interruption interval of 6 months for belantamab mafodotin (see Section 2.1.5)
- DREAMM-8 trial utility applied for all treatments in the progression-free survival (PFS) health state, independent of treatment. The Hatswell study[4] weighted approach applied for all treatments in the progressed disease (PD) health state (see Section 2.1.6)
- excluded wastage of tablets (see Section 2.1.7)
- used the acquisition cost of pomalidomide from the Medicines Procurement and Supply Chain framework (see Section 2.1.8)
- assumed no vial sharing (see Section 2.1.9)
- included the cost of monitoring eye-related adverse events using hospital-based ophthalmology services (see Section 2.1.10).

In addition, in response to NICE AC requests or comments in the NICE draft guidance (see Section 2.2), the company has produced, or considered, the following scenarios:

- using the unadjusted OS HR of 0.94 from the OPTIMISMM trial in the NMA (see Section 2.2.1)
- all available individual patient data (IPD) is used to estimate medication use and costs for all treatments (see Section 2.2.2)
- SACT data is used to inform the modelling of subsequent treatments (see Section 2.2.3)
- teclistamab is included as a fourth-line subsequent treatment option (see Section 2.2.4)
- the disutility of eye-related AEs is applied (see Section 2.2.5).

The company also responded to the NICE AC requests for the following additional evidence or statistical analyses (see Section 2.3):

- an NMA using data specific to the company's target second-line population (see Section 2.3.1)
- an analysis of Kaplan–Meier (K-M) plots comparing PFS for people being treated with BPd at 8 and 12 weekly intervals; the purpose of this analysis was to assess the impact of dose interruptions (see Section 2.3.2)
- evidence of the clinical effectiveness of BPd in the company's target second-line population (see NICE draft guidance, Section 3.7) (see Section 2.3.3)
- the impact of dose modifications (reductions, delays or interruptions because of eye-related AEs) on the clinical effectiveness of belantamab mafodotin (see Section 2.3.4)

This External Assessment Group (EAG) report includes brief summaries of the company responses and the EAG's critique of those responses. This report should be read in conjunction with the company response document and technical appendix.

2 EAG critique of the company response to NICE draft guidance

2.1 Company updated base case

2.1.1 Modelled DVd OS using SACT data from patients treated with DVd

The NICE AC asked the company to run an analysis using SACT data from patients treated with DVd to model OS for patients treated with DVd and to use HRs to estimate OS for patients treated with BPd, hKd and SVd.

The company extrapolated DVd OS SACT data; the EAG considers that this extrapolation was performed correctly and the distribution chosen was acceptable. However, in this analysis, PFS and time to treatment discontinuation (TTD) were modelled by extrapolating DREAMM-8 trial data. The EAG considers that, when available, clinical effectiveness (i.e., OS, PFS and TTD) should all be taken from the same data source, otherwise it is unclear exactly which population is being modelled. As such, the EAG does not recommend that extrapolated SACT OS data should be used in the base case, even if these data may more accurately represent OS for NHS patients.

The company has run a scenario in which SACT treatment-free survival (TFS) data collected from patients treated with DVd are used as a proxies for PFS and for TTD for these patients. This introduces uncertainty given that TFS is not the same measure as either PFS or TTD and that PFS and TTD were not equal in the DREAMM-8 or DREAMM-7 trials. As such, the EAG considers that results from this scenario are of limited value to decision makers.

2.1.2 Modelled BPd OS using a HR estimated from an IPTW analysis of DREAMM-8 and DREAMM-7 trial OS data applied to the DVd SACT modelled OS

The NICE AC asked the company to consider carrying out a matching adjusted indirect comparison (MAIC) to estimate the relative efficacy of BPd and DVd. As the company had IPD from both the DREAMM-8 trial (for patients treated with BPd) and the DREAMM-7 trial (for patients treated with DVd), the company was able to perform an IPTW analysis (essentially, a more robust form of a MAIC which can be carried out when patient level data are available and therefore the baseline characteristics of both populations can be adjusted).

Detail of the IPTW approach taken by the company was provided in the company a technical appendix to their draft guidance response. The company validated their approach with expert clinical and statistical advisors. The EAG considers that, after adjustment, the two populations appear to be well matched across the baseline characteristics included in the analysis (company response to NICE draft guidance technical appendix, Table 3).

The OS and PFS HRs, for the comparison of BPd versus DVd, sourced from the IPTW analysis are in line with original company NMA OS and PFS HRs; the OS HR remained statistically insignificant ([redacted]). However, the company did not test the proportional hazards (PH) assumption; the EAG considers that the OS K-M data after IPTW adjustment suggests that the HR changes over time (company response to NICE draft guidance technical appendix, Figure 8). The K-M data also highlight the immaturity of the data with robust data (i.e., not heavily censored) only available for around 24 months.

The EAG considers that the lack of statistical significance, the immaturity of the data and the potential for the PH assumption to be violated mean that conclusions on the relative OS efficacy of BPd and DVd are difficult to reach. Modelling any specific difference in OS between the two treatments is poorly supported by the current evidence.

2.1.3 Modelled OS for SVd and hKd via an NMA linked by the IPTW OS HR for BPd vs DVd

The company has used the IPTW analysis of OS to link BPd and DVd into the NMA previously performed by the company in their original submission.

The EAG highlights that the problems with this network highlighted by the EAG in their report on the company submission remains, notably the failure to be able to adjust for subsequent therapies received by patients in different trials and the centrality of the OPTIMISMM trial in linking BPd to SVd.

The EAG was concerned at the lack of methodological transparency on how the hazard ratio the company had chosen to use from the OPTIMISMM trial was produced and why it differed so much from the published hazard ratio. The NICE AC raised this as a specific concern in the NICE draft guidance (Section 3.6), alongside how

approaches to subsequent treatment had been accounted for across all trials in the network.

The company stated in their response to the NICE draft guidance that they did not have sufficient information to explain how the HR adjustment for OPTIMISMM was undertaken and did not address the issue raised on subsequent treatments received in different trials.

As was the case with the company original NMA, in the new NMA differences in OS between treatments do not approach statistical significance. Given this and the methodological concerns around OPTIMISSM and the failure to account for subsequent treatments received in trials in the network, the EAG maintains its base case position of no OS difference between BPd and any other treatment.

2.1.4 Changed the starting age of the model taken from the mean age of patients in the SACT dataset who were treated with DVd

The NICE AC asked the company to set the model start age to match the mean age of patients treated with DVd in the SACT dataset rather than the mean age of patients in the DREAMM-8 trial. The company has implemented this request correctly; however, the EAG considers that using a start age that differs from the start age of the population that provided the efficacy data used to populate the economic model is inappropriate. This is because it is unclear if DREAMM-8 trial outcomes would have been different if the age of patients aligned with patients in the SACT dataset.

2.1.5 A maximum dose interruption interval of 6 months for belantamab mafodotin

The NICE AC asked that a maximum dose interruption of 6 months for belantamab mafodotin be included in the base case. The company has not included this in their base case, arguing that only a small number of patients had dose interruptions and outcomes for these patients did not appear worse than outcomes for patients who had not had such breaks in treatment. Further, the company argued that it would be inequitable to limit treatment gaps to 6 months as the DREAMM 8 trial had showed patients could benefit even with such long treatment breaks.

The EAG does not consider that there is an equality issue with only allowing a 6 month treatment gap but does consider that the data used to support arbitrarily implementing

a maximum 6 month gap does not exist. Whilst costs in the model could potentially be adjusted so patients who have a 6 month treatment gap cannot restart treatment with belantamab mafodotin, it is unclear what impact this would have on efficacy as efficacy is drawn from the DREAMM-8 trial and, in this trial, some patients had treatment gaps of longer than 6 months. The EAG therefore agrees with the company that a maximum 6 month treatment break for belantamab mafodotin should not be modelled at this time.

2.1.6 Used DREAMM-8 utility applied for all treatments in the PFS state, independent of treatment. The Hatswell study[4] weighted approach applied for all treatments in the PD state.

The NICE AC utility values preference was the approach suggested by the EAG, i.e., use the same utility values (derived from a wholly second line population), regardless of treatment. The company has agreed with this preference, but suggested that the Hatswell study[4] PD health state utility value is more robust than ENDEAVOUR trial PD health state utility values (the EAG's preferred values). Whilst the EAG accepts that Hatswell 2020[4] utilities may be more methodologically robust than ENDEAVOUR trial PD health state utility values, the Hatswell study[4] PD utility value is only 0.034 lower than the PFS utility from the DREAMM-8 trail preferred by the company in their updated base case. This compares to a reduction in utility from the PFS to PD state of 0.081 in the EAG base case. The EAG considers that whilst effective treatments are available for third- and subsequent-lines of treatment, the small decrement in the entirety of the PD health state utility value that results from using the Hatswell study[4] may not be clinically plausible. As such, the EAG considers the utility values chosen in its base case to be more plausible.

2.1.7 Exclude wastage of Tablets

The company has excluded wastage of tablets in their updated base case analysis. This is in line with NICE AC preferences and the EAG base case analysis.

2.1.8 Used the acquisition cost of pomalidomide from the Medicines Procurement and Supply Chain (MPSC) framework

The company was not able to access the MPSC pomalidomide cost and so does not form part of their updated base case.

2.1.9 Assumed no vial sharing

The company has assumed no vial sharing in their updated base case analysis; the company did not include vial sharing in the original base case analysis.

2.1.10 Monitoring eye related adverse events for patients treated with BPd using hospital based ophthalmology services

The company has included the additional costs of monitoring eye-related AE in their updated base case analysis. The company has estimated that, on average, patients require 5 extra eye monitoring visits on top of the 4 visits mandated by the summary of product characteristics (SmPC).[5] The EAG considers the company evidence to support 5 additional visits is reasonable.

The company has set up a programme to fully fund the community based monitoring of eye-related AEs for patients treated with belantamab mafodotin. Details of the programme are provided in the company response to NICE draft guidance. [redacted]. The company has therefore assumed that 80% of the additional 5 visits will be free (to the NHS) and delivered in the community. The EAG considers that this is not unreasonable and notes that even if the visits were all hospital-based, it would only add about 1% to the total cost of BPd and so would have a minimal impact on incremental cost effectiveness ratios (ICERs) per QALY gained. Given that the costs are likely to be close to zero if the company fully funded programme is widely adopted, the EAG has not amended its base case analysis.

2.1.11 Company updated base case analysis results

The company updated base case analysis results were provided in a technical appendix. These results were generated by applying the following changes to the original company base case analysis:

- using the SACT dataset to model OS for DVd with the IPTW analysis and IPTW informed NMA to generate OS for BPd, hKd and SVd.
- utility values for PFS from DREAMM-8 and for PD from the Hatswell study[4]
- excluded tablet wastage
- start age based on SACT data
- an additional 5 eye related visits for patients treated with BPd, 80% in the community.

The company also provided results from two scenarios that altered the sources of PFS and TTD used in the model. In the first scenario (scenario 1), PFS was modelled using IPTW NMA HRs applied to the BPd PFS from the DREAMM-8 trial. TTD remained the same as the analysis and the original submission.

In the second scenario (scenario 2), PFS and TTD were modelled using SACT TFS data as a proxy for PFS and TTD for patients treated with DVd. Company IPTW analysis and IPTW NMA HRs were then applied to the DVd TFS curve to generate PFS and TTD for all other treatments.

Differences between OS, PFS and TTD sources between the company analysis and scenarios are provided in Table 1. Probabilistic results for the base case analysis and deterministic results for the scenarios that were provided by the company in their technical appendix to the NICE draft guidance are reproduced in Table 2 to Table 7.

The EAG attempted to produce a scenario that uses the IPTW NMA HR applied to the BPd baseline from the DREAMM-8 trial. However, in the company model this scenario produced implausible OS results with patients treated with Dvd having substantially longer OS than patients treated with Bpd.

The PAS price for belantamab mafodotin and list prices for all other drugs have been used by the company. Results using confidential prices for all drugs have been generated by the EAG and provided in a confidential appendix.

Table 1 Updated company base case analysis and scenario settings

Treatment	Clinical parameter	Updated company base case analysis	Scenario 1	Scenario 2
DVd	PFS	NMA HR applied vs PVd baseline	IPTW HR vs BPd baseline	TFS SACT baseline (Weibull)
	OS	OS SACT baseline (Weibull)	OS SACT baseline (Weibull)	OS SACT baseline (Weibull)
	TTD	NMA HR applied vs PVd baseline	IPTW HR applied vs BPd baseline	D7 HR applied vs TFS SACT baseline
BPd	PFS	D8 ITT – Weibull	D8 ITT - Weibull	IPTW HR applied vs DVd baseline
	OS	IPTW HR applied vs DVd baseline	IPTW HR applied vs DVd baseline	IPTW HR applied vs DVd baseline
	TTD	D8 ITT – Weibull	D8 ITT - Weibull	D8 ITT - Weibull
SVd	PFS	NMA HR applied vs PVd baseline	IPTW NMA HR applied vs BPd baseline	IPTW NMA HR applied vs DVd baseline
	OS	IPTW NMA HR applied vs DVd baseline	IPTW NMA HR applied vs DVd baseline	IPTW NMA HR applied vs DVd baseline
	TTD	NMA HR applied vs PVd baseline	IPTW NMA HR applied vs BPd baseline	IPTW NMA HR applied vs DVd baseline
hKd	PFS	NMA HR applied vs PVd baseline	IPTW NMA HR applied vs BPd baseline	IPTW NMA HR applied vs DVd baseline
	OS	IPTW NMA HR applied vs DVd baseline	IPTW NMA HR applied vs DVd baseline	IPTW NMA HR applied vs DVd baseline
	TTD	NMA HR applied vs PVd baseline	IPTW NMA HR applied vs BPd baseline	IPTW NMA HR applied vs DVd baseline

Key: Green highlighted rows indicate differences between the company new base case analysis and scenarios.
PFS=progression-free survival; OS=overall survival; TTD=time-to-treatment discontinuation; hKd=high-dose carfilzomib plus dexamethasone; SVd=selinexor plus bortezomib and dexamethasone; BPd=belantamab mafodotin plus pomalidomide and dexamethasone; DVd=daratumumab plus bortezomib and dexamethasone; PVd=pomalidomide plus bortezomib and dexamethasone; IPTW=inverse probability of treatment weighting; NMA=network meta-analysis; HR=hazard ratio; SACT=systemic anti-cancer therapy; TFS=treatment-free survival

Table 2 New company base case analysis: DVd eligible subpopulation – pairwise cost-effectiveness results (probabilistic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER BPd vs. (£/QALY)
BPd	[redacted]	[redacted]	[redacted]	-	-	-	-
hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
DVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

BPd=belantamab mafodotin plus pomalidomide and dexamethasone; DVd=daratumumab plus bortezomib and dexamethasone; hKd=high-dose carfilzomib plus dexamethasone; ICER=incremental cost-effectiveness ratio; LYG=life years gained; QALYs=quality-adjusted life years.
Source: company technical appendix, Table 11

Table 3 New company base case analysis: DVd ineligible subpopulation – pairwise cost-effectiveness results (probabilistic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER BPd vs. (£/QALY)
BPd	[redacted]	[redacted]	[redacted]	-	-	-	-
hKd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
SVd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

BPd=belantamab mafodotin plus pomalidomide and dexamethasone; DVd=daratumumab plus bortezomib and dexamethasone; hKd=high-dose carfilzomib plus dexamethasone; ICER=incremental cost-effectiveness ratio; LYG=life years gained; QALYs=quality-adjusted life years; SVd=selinexor plus bortezomib and dexamethasone
Source: company technical appendix, Table 12

Table 4 Company scenario 1: DVd eligible subpopulation – pairwise cost-effectiveness results (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER BPd vs. (£/QALY)
BPd	[redacted]	[redacted]	-	-	-
hKd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
DVd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

BPd=belantamab mafodotin plus pomalidomide and dexamethasone; DVd=daratumumab plus bortezomib and dexamethasone; hKd=high-dose carfilzomib plus dexamethasone; ICER=incremental cost-effectiveness ratio; QALYs=quality-adjusted life years
Source: company technical appendix, Table 14

Table 5 Company scenario 1: DVd ineligible subpopulation – pairwise cost-effectiveness results (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER BPd vs. (£/QALY)
BPd	[redacted]	[redacted]	-	-	-
hKd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
SVd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

BPd=belantamab mafodotin plus pomalidomide and dexamethasone; DVd=daratumumab plus bortezomib and dexamethasone; hKd=high-dose carfilzomib plus dexamethasone; ICER=incremental cost-effectiveness ratio; QALYs=quality-adjusted life years; SVd=selinexor plus bortezomib and dexamethasone
Source: company technical appendix, Table 15

Table 6 Company scenario 2: DVd eligible subpopulation – pairwise cost-effectiveness results (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER BPd vs. (£/QALY)
BPd	[redacted]	[redacted]	-	-	-
hKd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
DVd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

BPd=belantamab mafodotin plus pomalidomide and dexamethasone; DVd=daratumumab plus bortezomib and dexamethasone; hKd=high-dose carfilzomib plus dexamethasone; ICER=incremental cost-effectiveness ratio; QALYs=quality-adjusted life years
Source: company technical appendix Table 17

Table 7 Company scenario 2: DVd ineligible subpopulation – pairwise cost-effectiveness results (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER BPd vs. (£/QALY)
BPd	[redacted]	[redacted]	-	-	-
hKd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
SVd	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

BPd=belantamab mafodotin plus pomalidomide and dexamethasone; DVd=daratumumab plus bortezomib and dexamethasone; hKd=high-dose carfilzomib plus dexamethasone; ICER=incremental cost-effectiveness ratio; QALYs=quality-adjusted life years; SVd=selinexor plus bortezomib and dexamethasone
Source: company technical appendix Table 18

2.2 Company scenarios produced or considered

2.2.1 Using the unadjusted overall-survival HR of 0.94 from OPTIMISMM in the network meta-analysis

The company has not run this scenario, arguing that the high degree of crossover in the OPTIMISSM trial means that the unadjusted HR is biased. The EAG reiterates that it is unclear the methodology used to generate the adjusted HR and that previous OPTIMISMM trial reports concluded there was no statistical differences in OS between the treatments considered in the trial. Using a HR of 0.94 from the OPTIMISMM trial would produce HRs generated by the company NMAs for BPd versus other treatments that were closer to one than reported by the company (HRs that were already not statistically significantly different from 1) thus decreasing the survival gain and QALY difference between BPd and comparator treatments and therefore increasing the ICERs for BPd versus comparator treatments.

2.2.2 Using available IPD is to estimate medication use and costs for all treatments

The company has not run this scenario, arguing that dosing for belantamab mafodotin is unique and that whilst IPD data does not exist for all other treatments, where IPD data are available (for daratumumab and pomalidomide [DREAMM-7 trial]) the use of

Relative Dose Intensity (RDI) or IPD would make little difference. The EAG largely supports this position, but notes that the daratumumab dosing data provided by the company from the DREAMM-7 trial (in their response to the NICE draft guidance and reproduced below) suggests that the use of daratumumab IPD may result in slightly lower costs for daratumumab than when costing using RDI.

Figure 1 Average dose of patients on treatment in DREAMM-7 (daratumumab - DVd) - ITT population

RDI=relative dose intensity; DVd=Daratumumab in combination with bortezomib and dexamethasone
Source: company response to NICE draft guidance, Figure 6

2.2.3 SACT data is used to inform the modelling of subsequent treatments

The company was unable to identify SACT data to model subsequent treatments. However, the company, through validation meetings held in June and July 2025, gathered clinician evidence that 75% of patients would receive 3rd line treatment and 50% would receive 4th line treatment. They have used this data in a scenario analysis.

2.2.4 Teclistamab is included as a fourth-line option for subsequent treatments

The company has run a scenario in which the cost of teclistamab is included as a fourth-line therapy. The EAG considers that including the cost of teclistamab but not the benefits of treatment with teclistamab will result in biased model estimates that are of limited use to decision making.

2.2.5 The disutility of eye-related adverse events is applied

The company has run a scenario that includes eye-related disutilities. The values used in the model are reproduced in Table 8. The EAG considers these values have been appropriately calculated and appropriately included in the model.

Table 8 Disutility inputs for ocular adverse events

Ocular AEs	Disutility (QALYs)	One-off probability that patients receiving BPd will experience ocular AE	Live expected disutility[a]
Keratopathy (Grade 3+)	0.03	[redacted]	[redacted]
Blurred vision (Grade 3+)	0.03	[redacted]	[redacted]
Dry eyes (Grade 3)	0.03	[redacted]	[redacted]
Total:			0.0078

[a] Ocular AE disutilities were sourced from TA369[6]
AE=adverse event; BPd=belantamab mafodotin plus pomalidomide and dexamethasone; QALY=quality adjusted life year
Source: company response to NICE draft guidance, Table 7

2.2.6 Additional company scenarios

In addition to the scenarios requested by the NICE AC, the company has also run the following scenario analyses:

- ophthalmology tests 100% delivered in the community
- ophthalmology tests 100% delivered in hospital
- use of ENDEAVOR trial utilities in the PFS and PD health states.

2.2.7 Results of company scenario analyses

Deterministic results of company scenario analyses were provided in the company technical appendix. These are reproduced below using the PAS price for belantamab mafodotin and list prices for all other drugs.

Table 9 Scenario analysis results: BPd versus DVd

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	INMB* change from base case analysis (£)
Updated base case analysis	[redacted]	[redacted]	Dominating	[redacted]
ENDEAVOR utilities	[redacted]	[redacted]	Dominating	[redacted]
Teclistamab subsequent treatment costs included	[redacted]	[redacted]	Dominating	[redacted]
Proportion of patients receiving subsequent treatment – clinical expert opinion	[redacted]	[redacted]	Dominating	[redacted]
ERSE disutilities	[redacted]	[redacted]	Dominating	[redacted]
Ophthalmology test services – 100% community	[redacted]	[redacted]	Dominating	[redacted]
Ophthalmology test services – 100% hospital	[redacted]	[redacted]	Dominating	[redacted]

BPd=belantamab mafodotin in combination with pomalidomide and dexamethasone; DVd=daratumumab in combination with bortezomib and dexamethasone; ERSE=eye-related side effects; ICER incremental cost effectiveness ratio; INMB=incremental net monetary benefit; QALY=quality adjusted life years
Source: Company response to NICE draft guidance, Table 20

Table 10 Scenario analyses: BPd versus SVd

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	INMB* change from base case analysis (£)
Updated base case analysis	[redacted]	[redacted]	Dominating	[redacted]
ENDEAVOR utilities	[redacted]	[redacted]	Dominating	[redacted]
Teclistamab subsequent treatment costs included	[redacted]	[redacted]	Dominating	[redacted]
Proportion of patients receiving subsequent treatment – clinical expert opinion	[redacted]	[redacted]	Dominating	[redacted]
ERSE disutilities	[redacted]	[redacted]	Dominating	[redacted]
Ophthalmology test services – 100% community	[redacted]	[redacted]	Dominating	[redacted]
Ophthalmology test services – 100% hospital	[redacted]	[redacted]	Dominating	[redacted]

BPd=belantamab mafodotin in combination with pomalidomide and dexamethasone; ERSE=eye-related side effects; ICER incremental cost effectiveness ratio; INMB=incremental net monetary benefit; QALY=quality adjusted life years; SVd=selinexor in combination with bortezomib and dexamethasone
Source: Company response to NICE draft guidance, Table 21

Table 11 Scenario analyses: BPd versus hKd

Scenario	Inc. cost (£)	Inc. QALY	ICER (£ / QALY)	INMB* change from base case analysis (£)
Updated base case analysis	[redacted]	[redacted]	Dominating	[redacted]
ENDEAVOR utilities	[redacted]	[redacted]	Dominating	[redacted]
Teclistamab subsequent treatment costs included	[redacted]	[redacted]	Dominating	[redacted]
Proportion of patients receiving subsequent treatment – clinical expert opinion	[redacted]	[redacted]	Dominating	[redacted]
ERSE disutilities	[redacted]	[redacted]	Dominating	[redacted]
Ophthalmology test services – 100% community	[redacted]	[redacted]	Dominating	[redacted]
Ophthalmology test services – 100% hospital	[redacted]	[redacted]	Dominating	[redacted]

BPd=belantamab mafodotin in combination with pomalidomide and dexamethasone; ERSE=eye-related side effects; hKd=high-dose carfilzomib and dexamethasone; ICER incremental cost effectiveness ratio; INMB=incremental net monetary benefit; QALY=quality adjusted life years
Source: Company response to NICE draft guidance, Table 22

2.3 Additional evidence or statistical analyses requested by the NICE AC

2.3.1 A network meta-analyses using data specific to the company's target second-line population

The company did not provide this analysis, arguing that there was insufficient information about the lenalidomide-refractory and/or second-line population in comparator trials to undertake the analysis for all comparators, and where this was possible the analysis had already been undertaken in the submission. The EAG agrees with the company position that it is not possible to produce the NMA requested by the NICE AC.

2.3.2 An analysis of Kaplan–Meier plots comparing progression-free survival in people having Bel-Pom-Dex treatment at 8 and 12 weekly intervals, to assess the impact of dose interruptions

The company provided PFS K-M data from the DREAMM-8 trial for patients with dose interruptions of ≥8 weeks (Figure 2) and for those with dose interruptions of ≥12 weeks (Figure 3). It is not entirely clear to the EAG that this is what was requested by the NICE AC. The EAG agrees with the company that the plots do not suggest any meaningful difference in PFS for patients who had dose interruptions of ≥8 or ≥12 weeks.

Figure 2 Patients with at least one dose delays ≥ 8 weeks (n=110)

PomDex=pomalidomide and dexamethasone
Source: Company response to NICE draft guidance, Figure 3

Figure 3 Patients with at least one dose delays >=12 weeks (n=93)

PomDex=pomalidomide and dexamethasone
Source: Company response to NICE draft guidance, Figure 4

2.3.3 Evidence of clinical effectiveness of Bel-Pom-Dex in the company's target second-line population

The company provided evidence, at the 66th ASH Annual Meeting in December 2024, from the DREAMM 8 trial to support BPd being at least as effective as PVd in the second-line lenalidomide refractory population in the trial as it was in the ITT population in the trial. The results presented are reproduced below (Table 12). The EAG consider these results are informative for the efficacy of BPd versus PVd in the target population for PFS but of limited use for OS because of immature data.

Table 12 Key clinical efficacy outcomes (DREAMM-8 subgroup analysis)

	ITT	2L lenalidomide refractory subgroup
mPFS		
BPd	NR (20.6 – NR)	NR (21.1–NR)
PVd	12.7 (9.1 – 18.5)	13.1 (9.1–19.8)
HR	0.52 (0.37,0.73)	0.43 (0.25,0.75)
mOS		
BPd	NR (33.0 – NR)	NR (NR–NR)
PVd	NR (25.2 – NR)	NR (22.2 – NR)
HR	0.77 (0.51, 1.14)	0.72 (0.37 – 1.41)

BPd=belantamab mafodotin in combination with pomalidomide and dexamethasone; HR=hazard ratio; ITT=intent-to-treat; mOS=median overall survival; mPFS=median progression-free survival; PVd=pomalidomide in combination with bortezomib and dexamethasone
Source: company response to NICE draft guidance, Table 3

2.3.4 The impact of dose modifications (reductions, delays or interruptions because of eye-related adverse events) of belantamab mafodotin on its clinical effectiveness

The company has presented evidence from the DREAMM-8 trial on response rates and PFS for the ITT population and for patients who had had dose delays of ≥8 weeks, ≥12 weeks and ≥24 weeks. The PFS results are reproduced below (Table 13) and suggest that PFS was not affected by does delays. The EAG considers that results suggest that a dose delay may have been beneficial for patient outcomes, although this was not tested statistically, and that the ITT sample is biased towards those who died or progressed earlier as they will not have had as great a chance of experiencing a dose delay or reduction.

Table 13 Summary of Progression-Free Survival (PFS) Outcomes for ITT Population and Extended Dose Delay Subgroups

	ITT (n=155)	Extended dose delays subgroup		
		≥8 weeks (n=110)	≥12 weeks (n=93)	≥24 weeks (n =29)
Number of subjects progressed or died, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
first quartile PFS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

CI=confidence interval; ITT=intention to treat, PFS=progression free survival; NR=not reached, PFS=progression free survival
Source: Company response to draft guidance, Table 5; GSK data on file[7-9]

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